TRIM29 promotes progression of thyroid carcinoma via activating P13K/AKT signaling pathway

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Abstract. Thyroid cancer (TC) is a common malignancy of the endocrine system. Abnormal expression of tripartite motif-containing 29 (TRIM29) has been reported to promote tumorigenesis and predict poor prognosis in several human malignancies. The aim of this study was to assess the involvement of TRIM29 in the significance and prognosis of TC. Fifty-six tumor samples and their clinicopathological parameters were obtained from TC patients; the expression level of TRIM29 was detected by RT-qPCR and western blotting. TRIM29 expression was knocked down by small interfering RNA (siRNA) among TT, TPC-1, and K1 cells to investigate the biological role of TRIM29 in TC cells. The results showed that TRIM29 expression was significantly increased in TC tissue samples and cells compared to normal tissues and cells (P<0.01, respectively). Overexpression of TRIM29 was associated with TNM stage (P<0.01), extrathyroidal extension (P<0.01), lymph node metastasis (P<0.05), and distant metastasis (P<0.05). Furthermore, the overall survival and disease-free rates of patients with high TRIM29 expression were decreased significantly compared with those with low TRIM29 expression (P<0.01, respectively). Knockdown of TRIM29 obviously suppressed cell proliferation; enhanced chemosensitivity to cisplatin; inhibited cell invasion and migration; caused cell cycle arrest at G0/G1 phase by decreasing cyclin B1, cyclin D1 and CDK2, while increasing p21 and p27; and induced cell apoptosis by enhancing the activities of caspase-3, caspase-9, and Bax, while decreased Bcl-2. Notably, decreased TRIM29 expression significantly inhibited the activation of P13K/AKT signaling pathway as well. Taken together, our findings suggested that TRIM29 played a crucial role in the progression and malignancy of TC, and silencing of TRIM29 exerted its antitumor effect by blocking P13K/AKT signaling pathway. Thus, TRIM29 might be a potential therapeutic target for the treatment of TC.

Introduction

Thyroid cancer (TC) is the most common malignancy of the endocrine system, and the incidence of TC rapidly increases worldwide each year. Thyroid carcinoma can be divided into papillary, follicular, medullary and anaplastic types according to histological type (1). Papillary is the most common thyroid carcinoma, accounting for >83% of all such malignancies (2). In recent years, the prognosis of TC patients has shown improvement due to advances in chemotherapy and radiotherapy. However, growing evidence demonstrates that patients with advanced TC are resistant to uptake of radioiodine or surgical resection, which leads to the disease recurrence or even death (3). Therefore, it is urgent to investigate novel strategies for the diagnosis and treatment of TC in early stage.

Tripartite motif-containing 29 (TRIM29), also known as ataxia-telangiectasia group D-associated protein (ATDC), belongs to the TRIM family, TRIM family is composed of evolutionary conserved N-terminal tripartite motif, such as B-box, RING finger and coiled-coil (RBCC) domain (4,5). The TRIM family members have been proved to be involved in various physiological and biological processes including cell apoptosis, proliferation and oncogenesis, once altered, pathological conditions will occur (6). The structure of TRIM29 is di...
In the present study, to illustrate the underlying molecular mechanisms of TRIM29 in TC development, TRIM29 expression level was evaluated in TC tumor samples and cell lines. We found that overexpression of TRIM29 was correlated with clinicopathological parameters and poor prognosis in TC patients. TRIM29 knocking down by siRNA method led to the inhibition of cell proliferation by arresting the cell cycle and inducing cell apoptosis, and further confirmed that the P13K/AKT signaling pathway was involved in the mediation of TRIM29 in TC development.

Materials and methods

Collection of tissue samples. In this study, 56 thyroid cancer (TC) tissues and paired adjacent normal tissues were obtained from TC patients who underwent total thyroidectomy at the Department of General Surgery, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, between November 2009 and September 2014. All TC samples were separately diagnosed and confirmed by two pathologists. Tumor stage was performed according to the sixth edition of the TNM (tumor, node, and metastasis) classification of the International Union Against Cancer. The clinical characteristics of patients including gender, age, TNM stage, tumor size, extrathyroidal extension, regional lymph nodes and distant metastasis were collected. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University and accordance with the Declaration of Helsinki, and the informed consents were obtained from all patients. The expression level of TRIM29 in tissue samples lower than the median level were considered as the low TRIM29 expression group and vice versa. A five-year survival time and outcomes were recorded in follow-up. The median duration of follow-up was 38 months (range: 1-60 months).

Cell line and cell culture. The human TC cell lines TT, TPC-1, K1, and human normal thyroid cell line Nthy-Ori-3-1 were purchased from the Cell Bank of the Chinese Academy of Medical Science (Beijing, China). All cells were cultured in DMEM medium (Invitrogen, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (Gibco, Carlsbad, CA, USA) and 1% penicillin/streptomycin under an atmosphere of 5% CO₂ at 37°C.

Silencing TRIM29 expression in TC cells by siRNA. The siRNA (small interference RNA) method was employed to knock down TRIM29 expression in TC cell lines. The sequences for siRNA were design as follows: sense strand 5'-AGU AGU UGG AGU UCU UGU CGU-3'; antisense strand 5'-GAC AAG AAC UCC AAC UAC UUC-3'. The scramble siRNA was random sequences by Blast website. Then the recombinant plasmids (si-TRIM29) or scramble siRNA (si-NC) were transfected into TC cells using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. The efficacy of siRNA knockdown was determined by RT-qPCR and western blotting.

Real-time quantitative PCR analysis. Total RNA was extracted from either tissue samples or cells using TRIzol (Invitrogen) according to the manufacturer's protocol, and then the isolated mRNA were reversely transcribed into cDNA by M-MLV Reverse transcriptase kit (Promega, Madison, WI, USA) according to the manufacturer's protocol. RT-qPCR analysis was performed by SYBR-Green Master Mix kit (Takara, Otsu, Japan). The primer sequences were as follows: TRIM29 sense, 5'-AGT CTT GGT GGT CAC TTT GG-3' and antisense, 5'-GCA CTT CCC TTA CCA GCA TAG-3'; β-actin sense, 5'-CAG CAT CAT GAA GTG CGA CGA-3' and antisense, 5'-CTG CAG TGT GGT GCT TCA AC-3'. The mRNA expression of TRIM29 was normalized to the housekeeping gene β-actin, which was used as an internal control. In brief, the PCR conditions were as follows: 95°C for 3 min, 95°C for 15 sec, 65°C for 30 sec for 40 cycles. The relative quantification referred as relative expression level was calculated by the value of 2-ΔΔCt. Each experiment was performed in triplicate.

Western blot analysis. Tissue samples or cells were washed twice with ice-cold PBS and lysed with RIPA lysis buffer (Beyotime, Haimen, China). BCA assay was used to quantify the protein concentration of cell lysates. Total proteins were separated by 15% SDS-polyacrylamide (SDS-PAGE) and then transferred onto PVDF membranes (Pierce, Thermo Scientific, Rockford, IL, USA). After blocking with 5% BSA for 1 h, the membranes were incubated with appropriate primary antibodies at 4°C overnight. Next, the membranes were incubated with goat anti-rabbit HRP-conjugated secondary antibody (diluted at 1:2000) (Santa Cruz Biotechnology) at 37°C for 1 h. The protein bands were detected using the Enhanced Chemiluminescence Detection System (Pierce, Thermo Scientific). β-actin was used for normalization and the protein intensity was quantified by using Image-Pro Plus 6.0 software (Media Cybernetics, MD, USA).

Cell viability assay. Cell proliferation was determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (Beyotime) assay according to the manufacturer's protocol. Cells were seeded in 96-well plates at the density of 5x10³ cells/well after transfected with siRNA-TRIM29 or siRNA-NC for 48 h and incubate at 37°C, 5% CO₂ for 5 days. For chemotherapy drug sensitivity test, the transfected cells were incubated with cisplatin (Sigma-Aldrich, St. Louis, MO, USA) at the doses of 0, 5, 10, 15, 20 µg/ml for 24 h. At indicated time points, 20 µl MTT solution (5 mg/ml) was added into each well and incubated for 4 h at 37°C. Dimethyl sulfoxide (DMSO) (150 µl) was added into the well to dissolve the crystals for 10 min on a low-speed shaker. The OD (optical density) value was measured each day at 490 nm using a microplate reader (BioTek, Winooski, VT, USA).

Colony formation assay. Cells were seeded at the density of 500 cells/well in 6-well plate after transfected with siRNA-TRIM29 or siRNA-NC for 48 h, and then incubated at 37°C, 5% CO₂ for 14 days. Colonies were fixed with 95% ethanol for 10 min after washing with PBS twice, and then stained with crystal violet for 20 min, colonies with at least 50 cells were counted and photographed. Each experiment was performed in triplicate.

Cell cycle analysis. Cells were harvested after transfected with siRNA-TRIM29 or siRNA-NC for 48 h and fixed in 75%...
Ethanol overnight, and then washed with PBS, stained by propidium iodide (5 mg/ml) containing RNase A. Cell cycle distributions were analyzed by flow cytometer FACSCalibur (Beckman Coulter, Inc., Fullerton, CA, USA) according to the manufacturer's protocol. Each experiment was performed in triplicate.

Cell apoptosis analysis. Cells were harvested after transfected with siRNA-TRIM29 or siRNA-NC for 48 h, and then washed with cold PBS, and stained with Annexin V-FITC double staining kit (BD Bioscience, San Jose, CA, USA) and analyzed using flow cytometry FACSCalibur (Beckman Coulter, Inc.) according to the manufacturer's protocol. Each experiment was performed in triplicate.

Cell migration and invasion assay. Cells were harvested after transfected with siRNA-TRIM29 or siRNA-NC for 48 h, and then suspended with serum-free medium, then seeded in the upper chamber of Transwell (8 µm pore size, Corning Inc., Coring, NY, USA) at the density of 5x10^4 cells per chamber for invasion assay and 1x10^5 cells per chamber for migration assay, respectively. For invasion assay, the upper chambers were precoated with Matrigel (BD Bioscience). The lower chambers were filled with medium containing 10% FBS and incubated for 24 h. Cells remaining on the upper chamber were removed carefully, the migrating cells in the lower chamber were fixed with 100% methanol, and stained with crystal violet. The stained cells were imaged with an inverted microscope (Olympus), and counted at ten randomly selected visual fields for each experimental condition. Each experiment was performed in triplicate.

Statistical analysis. Statistical analyses were performed using SPSS-12.0 software. Each experiment was performed in triplicate, unless otherwise indicated. All data are presented as mean ± standard deviation (SD). Comparisons between groups were done using the unpaired Student's t-test. A P-value of <0.05 was considered to indicate a statistically significant difference.

Results

Elevated expression of TRIM29 in TC tissue samples and cell lines. RT-qPCR and western blot assays were used to detect the expression of TRIM29 in TC tissue samples and adjacent paired normal tissues. As shown in Fig. 1A, the mRNA expression of TRIM29 was significantly upregulated in TC tissue samples compared with the adjacent paired normal tissues. Consistent with RT-qPCR results, the western blot also revealed that TRIM29 was significantly upregulated in TC tissue samples compared with the adjacent paired normal tissues. Consistent with RT-qPCR results, the western blot also revealed that TRIM29 was upregulated at protein levels in TC tissue samples (Fig. 1B and C). Furthermore, the expression level of TRIM29 was evaluated among three TC cell lines (TT, TPC-1, K1) and normal thyroid cell line Nthy-Ori-3-1. The result showed that TRIM29 expression was remarkably increased in TT, TPC-1, and K1 cells when compared to Nthy-Ori-3-1 cell line (Fig. 1D-F).

TRIM29 expression correlates with clinicopathological parameters on the prognosis of TC patients. The correlation between TRIM29 expression and clinicopathological parameters of all patients were investigated by Pearson's Chi-square analysis. TC cases were subdivided into two groups according to the mRNA expression level of TRIM29 as described above. High TRIM29 expression was observed in 73.21% (41/56) of cases, while 26.79% (15/56) had low TRIM29 expression. The high TRIM29 expression was associated with TNM stage (P<0.01), extrathyroidal extension (P<0.01), lymph nodes metastasis (P<0.05), and distant metastasis (P<0.05),
but had no correlation with patient gender, age or tumor size (Table I). In addition, the survival time of the two groups was compared by Kaplan-Meier analysis, the cumulative 5-year overall survival rate (OS) was 21.95% in the high TRIM29 expression group whereas 80.00% in the low TRIM29 expression group (P<0.05); while the disease-free survival rate (DFS) was 34.15% in the high TRIM29 expression group which was lower than 86.67% in the low TRIM29 expression group (P<0.05) (Fig. 2). These findings demonstrated that the TRIM29 overexpression was correlated with poor prognosis in TC patients.

Knockdown of TRIM29 expression in TC cells inhibits cell proliferation. The expression of TRIM29 was knocked down in TT, TPC-1, and K1 cells by using siRNA method. The efficiency of TRIM29 knockdown was confirmed by RT-qPCR and western blotting (Fig. 3A). Next, the viability of cells with TRIM29 knockdown was detected by MTT assay. As shown in Fig. 3B, TRIM29 knockdown significantly decreased the viability of TT, TPC-1, and K1 cells (P<0.01, respectively) when compared with NC group. Furthermore, in agreement with MTT data, colony formation assays also illustrated that the numbers of colonies were significantly reduced in TT, TPC-1, and K1 cells with TRIM29 knockdown compared to corresponding NC groups (P<0.01, respectively; Fig. 3C). These results suggested that downregulated TRIM29 expression inhibited the proliferation of TC cells.

TRIM29 knockdown enhanced the sensitivity of TC cells to chemotherapy. The effect of TRIM29 knockdown on the sensitivity of TC cells to cisplatin was determined by MTT method. We transfected TT, TPC-1, and K1 cells with siRNA-TRIM29 or siRNA-NC and treated with cisplatin at various doses (0, 5, 10, 15, 20 µg/ml) for 24 h. As shown in Fig. 3D, compared with the control groups, TT, TPC-1, and K1 cells with siRNA-TRIM29 transfection significantly decreased cell viability by enhancing cell sensitivity to cisplatin under different-dose treatments (10, 15, 20 µg/ml, respectively). Thus, we concluded that the downregulation of TRIM29 by siRNA-TRIM29 enhanced cell sensitivity to cisplatin in TC development.

Silencing of TRIM29 expression reduces invasion and migration of TC cells. To investigate whether the knockdown of TRIM29 influences invasion and migration of TC cells,

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*P-value statistically significant.
when compared with control group, the number of migrated cells were significantly decreased in TT, TPC-1, and K1 cells with TRIM29 knockdown (P<0.01, respectively), which indicating that downregulation of TRIM29 suppressed TC cell invasion and migration. To further address the role of TRIM29 knockdown in cell invasion and migration, western blot result revealed that TRIM29 knockdown significantly decreased the hallmarks of cell invasion and migration including matrix metallopeptidases (MMP2 and MMP9).

**TRIM29 silencing causes cell cycle arrest at G0/G1 phases in TC cells.** The flow cytometry assay showed that knockdown of TRIM29 contributed to a remarkably increased in the G0/G1 phase in TT, TPC-1, and K1 cells compared to cells.
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Figure 4. The inhibition of cell invasion and migration on TC cells with TRIM29 knockdown. (A) Number of invasive cells with siRNA transfection was detected by invasion assay. (B) Number of migrated cells with siRNA transfection was detected by migration assay. (C) Expression levels of MMP-2 and MMP-9 proteins in TC cells with siRNA transfection were detected by western blotting. Data are shown as mean ± SD; all the experiments were in triplicate. **P<0.01, statistically significant, when compared to si-NC group.

Figure 5. TRIM29 knockdown in TC cells delays the cell cycle. (A) Cell distribution analysis of TC cell cycle with TRIM29 knockdown. (B) The expression levels of related cell cycle regulatory proteins cyclin E, cyclin B1, CDK2, p21 and p27 were detected by western blotting. Data are shown as mean ± SD; all the experiments were in triplicate. *P<0.05, statistically significant, when compared to siRNA-NC group.
in control group (P<0.01, respectively). While cells in S phase were reduced in TRIM29 knockdown cells compared to cells in control group (P<0.01, respectively; Fig. 5A). Furthermore, to deeply investigate the mechanism underlying the cell cycle arrest caused by TRIM29 knockdown in TC cells, the central cell cycle regulatory proteins such as cyclin D1, cyclin E, cyclin-dependent kinase 2 (CDK2), p21 and p27 were examined by western blotting. As shown in Fig. 5B, the expression levels of cyclin D1, cyclin E and CDK2 were significantly decreased; while the expression of cyclin-dependent kinase inhibitors such as p21 and p27 were increased in TC cells with TRIM29 knockdown. Thus, these findings indicated that knockdown of TRIM29 resulted in cell cycle arrest in TC cells.

Knockdown of TRIM29 induces apoptosis in TC cells. Flow cytometry was used to clarify the effect of TRIM29 knockdown on cell apoptosis of TC cells. TRIM29 knockdown significantly increased the percentages of cell apoptosis in TT, TPC-1, and K1 cells compared to control group (P<0.01, respectively, Fig. 6A and B). In addition, we also found that TRIM29 knockdown induced TC cell apoptosis by activating apoptosis-related protein expression. As shown in Fig. 6C, upregulation of TRIM29 remarkably increased the levels of cleaved caspase-3, cleaved caspase-9, Bax expression, while decreased the expression of Bcl-2 in TT, TPC-1, and K1 cells compared to control groups. Thus, these results suggested that inhibition of TRIM29 induced apoptosis of TC cells.
Knockdown of TRIM29 suppresses the P13K/AKT signaling pathway. The phosphoinositide 3-kinase (P13K)/AKT signaling pathway plays a crucial role in thyroid oncogenesis and affects proliferation, metastasis, apoptosis of TC cells (14). Since the inhibitory effect of TRIM29 knockdown on TC cell cycle and apoptosis has been clarified, to further determine whether P13K/AKT signaling pathway is involved in TRIM29-mediated TC tumorigenesis, the key molecules of the P13K/AKT pathway were detected in TT, TPC-1, and K1 cells with TRIM29 knockdown. Western blot results showed that the P13K, and phosphorylation of AKT expression levels were prominently decreased in TT, TPC-1, and K1 cells with downregulation of TRIM29 compared to vehicle-treated cells, though the total AKT levels were similar among different treated groups (Fig. 7). Our results illustrated that TRIM29 knockdown significantly inhibited the P13K/AKT signaling pathway in TC cells.

Discussion

TC is the most common endocrine malignancy, with increasing knowledge of its molecular pathogenesis (15,16). In order to increase the efficacy of the therapeutic treatment and to reduce side effects, the investigations on gene dysregulation during TC progression are becoming the novel subject of research in this field. The location of TRIM29 is at chromosome 11q23, and functions as a sensitive component of a protein kinase mediated signaling transduction pathway against ionizing radiation, which might aggravate tumorigenesis and progression (17,18). TRIM29 is involved in tumor proliferation and progression in a variety of cancer cells. However, among different tumor cell types, TRIM29 functioned either as tumor suppressor or oncogene according to the origin of the neoplasm (4). Recent analysis demonstrated that TRIM29 overexpression could promote tumor cell survival and growth in various types of cancers (19). To our knowledge, the investigation of the relationship between TRIM29 expression and TC tumorigenesis has not been previously reported.

In the present study, we found that TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression. Moreover, the high expression of TRIM29 mRNA and protein were significantly enhanced in TC tumor samples and cell lines, suggesting a pro-oncogenic role of TRIM29 in TC progression.
proteins into chromatin and then activated DNA damage response (20). Wang et al also indicated that TRIM29 played a crucial role in DNA damage signaling and radioreistance in human pancreatic cancer cells (21). Xu et al demonstrated that TRIM29 was a novel prognostic biomarker for prediction in aggressive cervical cancer patients that need postoperative adjuvant chemoradiotherapy (22). Liu et al suggested that silencing of TRIM29 enhanced chemosensitivity to cisplatin in human lung squamous cancer by increasing cell apoptosis (10). Cisplatin is a widely used chemotherapeutic drug against various types of cancers through DNA damage mechanism (23). The present study stated the association of TRIM29 expression with cisplatin cell resistance in TC cells and proved knockdown of TRIM29 made TC cells more sensitive to cisplatin treatment.

Studies have shown that TRIM29 is intimately associated with cell proliferation, cell cycle, invasion and cell apoptosis. Liu et al discovered that TRIM29 knockdown suppressed proliferation and invasion in human lung squamous cancer cells (10). Sun et al reported that TRIM29 promoted tumor cell proliferation and progression in pancreatic cancer (8). Yuan et al discovered that TRIM29 promoted cancer cell proliferation by suppressing p53 nuclear activities (24). To illustrate the function of TRIM29 on TC progression, siRNA approach was employed to silence TRIM29 expression in TC cell lines. Our data showed that TRIM29 knockdown significantly inhibited TC cell proliferation and reduced colony formation, caused cell cycle to halt at G0/G1 phase, accompanied by repressing the expression of cyclin D1, cyclin B1, and CDK2; while increasing the expression of p21 and p27, which resulted in cell growth inhibition. Cyclin D1 could phosphorylate Rb protein and accelerate cancer progression via G1-S phase of cell cycle (25). Furthermore, the activation of cyclin E-CDK2 complex has been proved as another crucial demand for the G1/S phase transition in cancer aggressiveness; conversely, p21 and p27 inhibit the activation of CDK-cyclin complexes during tumor development (26). Collectively, the alternations of cell cycle regulatory molecules may contribute to the phase distribution in TC cells.

In the present study, we found that the expression of TRIM29 was significant in lymph nodes metastasis, and distant metastasis in TC progression according to clinicopathological factor analysis. The abilities of invasion and metastasis of cancer cells are dependent on the degradation of the components of extracellular matrix and basement membranes, which is regulated by matrix metalloproteinase (MMP) family (27). Silencing of RTIM29 significantly reduced the invasive and migratory abilities of TC cells by inhibiting the activities of MMP-2 and MMP-9, which are implicated in dysregulation of tumor invasion and metastasis in numerous human malignancies (28). Furthermore, the imbalance between apoptosis-induced and -inhibited molecule expressions are responsible for the vulnerability of cells to apoptosis (29). Thus, in this study, the activation of caspase-3 and caspase-9, decreased ratio of Bax/Bcl-2 indicated that TRIM29 knockdown induced TC cell apoptosis in a caspase- and Bax/Bcl-2-dependent manner.

P13K/AKT pathway is a vital intracellular signaling pathway for regulating various bioprocesses in mammalian cells, including cell proliferation, metabolism, transformation, motility and tumorigenesis (30). P13K/AKT pathway could induce the development of tumor and promote tumor metastasis via various pathways. In order to enhance cell survival, activation of P13K/AKT pathway could in turn activate or inhibit a series of downstream target proteins, such as caspase-9, p21, Bax, MMP2, and mammalian target of rapamycin (mTOR) (14,31,32). Tan et al proved that TRIM29 overexpression promoted cell proliferation and survival through NF-κB signaling pathway in bladder cancer cells (19). Xu et al reported that TRIM29 overexpression enhanced tumor progression by activating Wnt/β-catenin pathway in cervical cancer (22). Furthermore, a recent study demonstrated that elevated TRIM29 expression contributed to the cell proliferation and metastasis of nasopharyngeal cancer by activating PTEN/AKT/mTOR signaling pathway (33). On the basis of references above, in our study, we found that the antitumor effect of TRIM29 silencing was associated with the inhibition of P13K/AKT signaling pathway, which might be the pivotal mechanism of TRIM29 knockdown-mediated proliferation suppression, chemosensitivity enhancement, the inhibition of invasion and migration, delayed cell cycle transition, cell apoptosis in TC (34). However, the deep molecular details still remained to be further elucidated.

In conclusion, this study highlighted the crucial role of TRIM29 overexpression in TC prognosis and progression, and subsequently demonstrated that TRIM29 knockdown resulted in the alternations of cell proliferation, chemosensitivity to cisplatin, invasion and migration, cell cycle arrest, and cell apoptosis via blocking the activation of P13K/AKT signaling pathway and the involved downstream target genes, which provide credible evidence for novel therapeutic target combined with the P13K/AKT signaling pathway for TC treatment.

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References


