

# TRIM24 is upregulated in human gastric cancer and promotes gastric cancer cell growth and chemoresistance

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**Abstract** The tripartite motif protein tripartite motif-containing 24 (TRIM24) is involved in human cancer progression. However, the expression pattern and biological roles of TRIM24 in human gastric cancer have not been studied. Here, we report that expression of TRIM24 protein was upregulated in 65 of 133 gastric cancer specimens. TRIM24 upregulation positively correlated with clinical stage, local invasion, and poor patient prognosis. We overexpressed TRIM24 by transfection in SGC-7901 cells and used an siRNA strategy to knock down TRIM24 in MKN-1 cells. MTT and colony formation assays showed that transfection of TRIM24 plasmid accelerated, while its depletion inhibited cell proliferation rate. TRIM24 overexpression also induced chemoresistance to 5-FU in gastric cancer cells. Further analysis showed that TRIM24 overexpression upregulated cyclin D1 and Akt phosphorylation. Akt inhibitor LY294002 reversed the role of TRIM24 on chemoresistance. In conclusion, our study shows that TRIM24 is overexpressed in human gastric cancer and accelerates cell growth as well as induce chemoresistance, possibly through the Akt pathway.

**Keywords** TRIM24 · Gastric cancer · Proliferation · Chemoresistance

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## Introduction

Gastric cancer (GC) is the third most lethal cancer in male and the fifth in female individuals [1]. Despite improved prognosis resulting from earlier diagnosis, radical surgery, and development of adjuvant therapy, the 5-year survival rate still remains below 30 % [2]. Oncogenes and tumor suppressor genes have a vital role in the development and progression of gastric cancer, and genetic heterogeneity has been proven to influence the prognosis markedly. Therefore, it is important to identify novel molecular mediators conferring malignant potential to gastric cancer cells that may be used as tumor markers in predicting risk of gastric cancer progression [3–5].

TRIM24 is also known as transcription intermediary factor 1-alpha (TIF1 $\alpha$ ) and was identified as a coregulator of retinoid signaling [6–8]. Aberrant expression of TRIM24 might promote tumor development. TRIM24 is a target of chromosomal translocations to form oncogenic fusion proteins in acute promyelocytic leukemia, papillary thyroid carcinoma, and myeloproliferative syndrome [9–11]. TRIM24 was reported to bind chromatin and estrogen receptor to activate estrogen-dependent genes associated with cellular proliferation and tumor development [12, 13]. Elevated expression of TRIM24 promotes progression of prostate cancer and negatively correlates with survival of breast cancer patients [13, 14]. TRIM24 is overexpressed in nonsmall cell lung cancer, and its depletion inhibited cell growth [15]. TRIM24 accelerates malignant progression and serves as a prognostic factor in glioma [16]. These findings suggest that TRIM24 is an important oncogene in tumor development.

In the present study, we examined expression pattern of TRIM24 in 133 gastric cancer specimens and analyzed its correlation with clinicopathological factors. We also investigated its effects on proliferation and chemoresistance in gastric cancer cell lines.

## Materials and methods

### Patients and specimens

The study protocol was approved by the institutional reviewer board of China Medical University. Tumor tissue specimens of 133 cases of primary gastric cancer and 20 adjacent normal gastric tissue samples were obtained from patients diagnosed with gastric cancer who underwent resection in the First Affiliated Hospital of China Medical University between 2006 and 2010. The histological diagnosis was evaluated on sections stained with hematoxylin and eosin according to the World Health Organization (WHO) classification guidelines. Clinical and histopathological data including histopathological diagnosis and tumor grade were extracted from medical records. All cases in this study received radical total or subtotal gastrectomy with D2/D3 lymph node dissection. Pathological examination revealed no tumor involvement of the resection margins in surgical specimens (R0: no residual tumor based on R category in AJCC classification). None of our study patients had received preoperative chemotherapy or radiotherapy. After surgery, patients received four cycles or more of chemotherapy (chemotherapy regimens: FOLFOX4 program).

### Cell culture and transfection

MKN-1 and SGC-7901 cell lines were obtained from the American Type Culture Collection (Manassas, VA, USA). Cells were cultured in DMEM (Invitrogen, Carlsbad, CA, USA) containing 10 % fetal calf serum (Invitrogen), 100 IU/ml penicillin (Sigma, St. Louis, MO, USA), and 100 µg/ml streptomycin (Sigma). Cells were grown on sterilized culture dishes and were passaged every 2 days with 0.25 % trypsin (Invitrogen).

The plasmid of pCMV6-TRIM24 was purchased from Origene (Origene, Rockville, USA). Plasmid was transfected into cells using Attractene Transfection (Qiagen, Hilden, Germany). Empty vector was used as a negative control. Cells were harvested 48 h later after transfection.

On-TargetPlus SMARTpool small interfering RNA (siRNA) for TRIM24 (M-005387-03-0005) and ON-TARGETplus Non-targeting siRNA #1 (D-001810-01-20) were purchased from Dharmacon. The cells were transfected with siRNA using the DharmaFECT 1 (0.20 µl/well; ThermoFisher Scientific) according to the manufacturer's protocol.

### Immunohistochemistry

Surgically excised tumor specimens were fixed with 10 % neutral formalin and embedded in paraffin, and 4-µm-thick sections were prepared. Immunostaining was performed using the avidin–biotin–peroxidase complex method (UltraSensitive™, MaiXin, Fuzhou, China). The sections were deparaffinized in xylene, rehydrated with graded alcohol,

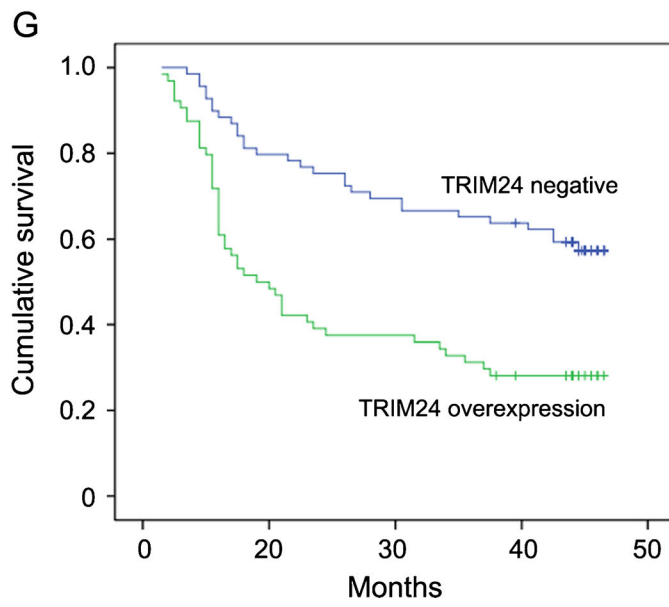
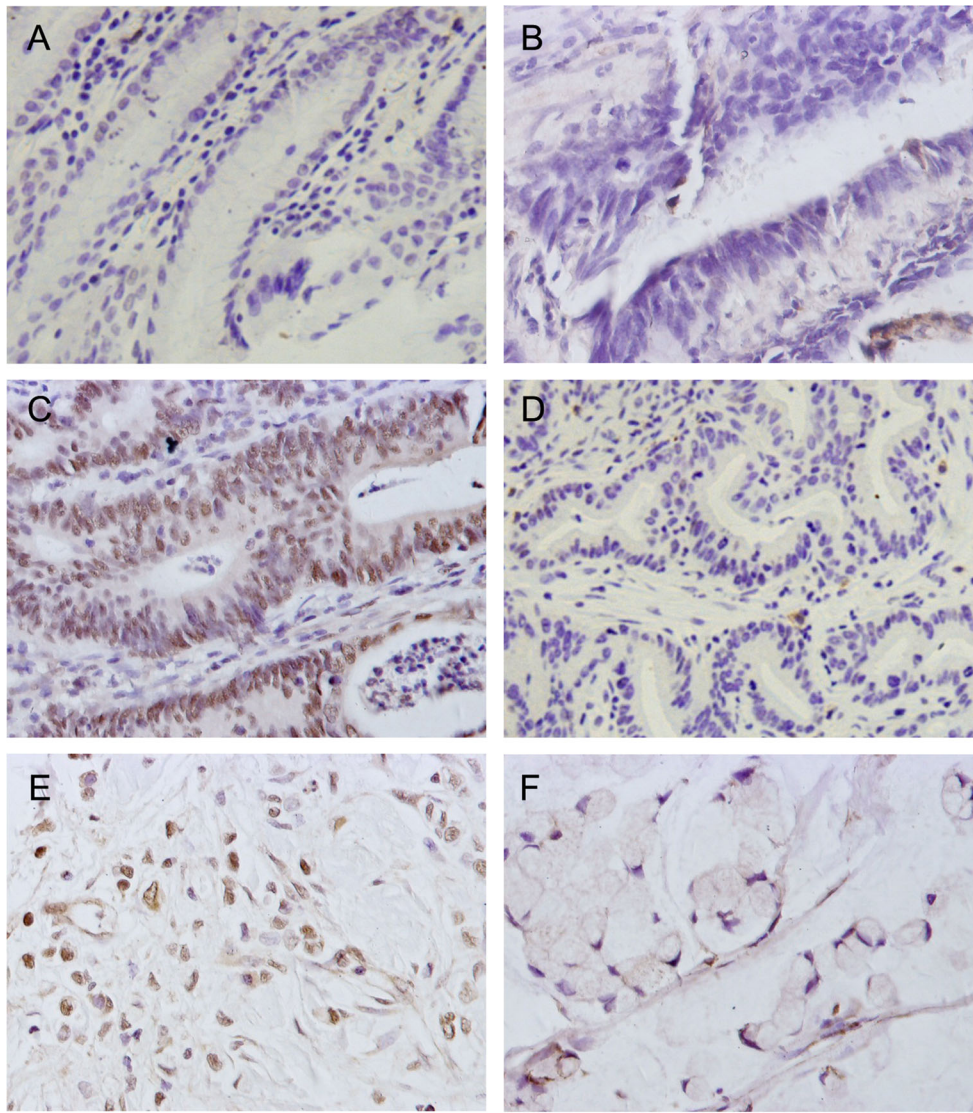
and then boiled in 0.01 M citrate buffer (pH 6.0) for 2 min in an autoclave. Hydrogen peroxide (0.3 %) was applied to block endogenous peroxidase activity, and the sections were incubated with normal goat serum to reduce nonspecific binding. Tissue sections were incubated with TRIM24 rabbit polyclonal antibody (1:150 dilution; Proteintech) at 4 °C overnight. Rabbit immunoglobulin (at the same concentration as for the antigen-specific antibody) was used as a negative control. Prostate cancer specimens were used as positive control, which were found TRIM24 staining positive in a previous study [15]. Biotinylated goat antirabbit serum IgG was used as a secondary antibody. After washing, the sections were incubated with streptavidin–biotin conjugated with horseradish peroxidase, and the peroxidase reaction was developed with 3, 3'-diaminobenzidine tetrahydrochloride. Counterstaining with hematoxylin was performed, and the sections were dehydrated in ethanol before mounting.

Two independent blinded investigators examined all tumor slides randomly. Five views were examined per slide, and 100 cells were observed per view at ×400 magnification. Immunostaining of TRIM24 was scored on a semiquantitative scale by evaluating the intensity and percentage of tumor cells according to previous studies [15]. Nuclear immunostaining in tumor cells was considered as positive staining. We counted 400 tumor cells and calculated the percentage of positively stained cells. The intensity of TRIM24 staining was scored as 0 (no signal), 1 (moderate), and 2 (strong). Percentage scores were assigned as 1, 1–25; 2, 26–50; 3, 51–75; and 4, 76–100 %. The scores of each tumor sample were multiplied to give a final score of 0–8; tumor samples scored 4–8 were considered as TRIM24 upregulated.

### Quantitative real-time PCR (SYBR green method)

Quantitative real-time PCR was performed using SYBR Green PCR master mix (Applied Biosystems) in a total volume of 20 µl on 7900HT Fast Real-Time PCR System (Applied Biosystems) as follows: 95 °C for 30 s, 40 cycles of 95 °C for 5 s, and 60 °C for 30 s. A dissociation step was performed to generate a melting curve to confirm the specificity of the amplification. B-Actin was used as the reference gene. The relative levels of gene expression were represented as  $\Delta\text{Ct} = \text{Ct gene} - \text{Ct reference}$ , and the fold change of gene

**Fig. 1** Expression pattern of TRIM24 protein in gastric cancer tissues. **a** Negative nuclear TRIM24 staining in normal gastric tissue. **b** Negative nuclear TRIM24 staining in a case of papillary adenocarcinoma. **c** Strong nuclear TRIM24 expression in a case of tubular adenocarcinoma. **d** Negative nuclear staining of TRIM24 in a case of tubular adenocarcinoma. **e** Positive TRIM24 expression in a case of poorly cohesive adenocarcinoma (signet ring cell carcinoma). **f** Negative TRIM24 expression in a case of mucinous adenocarcinoma (magnification, ×400). **g** TRIM24 upregulation correlated with poor prognosis of gastric cancer patients





expression was calculated by the  $2^{-\Delta\Delta Ct}$  method. Experiments were repeated in triplicate. The primer sequences are as follows: TRIM24 forward, 5' CGCCACCCAAGTTGGA GT 3', TRIM24 reverse, 5' GCTGGGAACCTCAGTAGTGT CCT 3';  $\beta$ -actin forward, 5' ATAGCACAGCCTGGATAG CAACGTAC 3',  $\beta$ -actin reverse, 5' CACCTTCTACAATG AGCTGCGTGTG 3'.

#### Western blot analysis

Total proteins from cells were extracted in lysis buffer (Pierce, Rockford, IL, USA), quantified using the Bradford method, and 50  $\mu$ g protein samples were separated by SDS-PAGE. Samples were transferred to polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA) and incubated overnight at 4 °C with antibody against TRIM24 (1: 500; Proteintech, Chicago, USA), p-Akt, Akt, cyclin D1 (1:1000, Cell Signaling Technology, Boston, USA), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1:1000; Santa Cruz, USA). After incubation with peroxidase-coupled antimouse/rabbit IgG (1:1000, Cell Signaling Technology, USA) at 37 °C for 2 h, bound proteins were visualized using ECL (Pierce) and detected using a DNR BioImaging System (DNR, Jerusalem, Israel). Relative protein levels were quantified using GAPDH as loading control.

#### Colony formation and MTT assays

For colony formation assay, cells were transfected with plasmid for 48 h and plated into three 6-cm cell culture dishes (1000 per dish). Cells were incubated for 12 days in medium containing 10 % FBS. Plates were washed with PBS and stained with Giemsa. The number of colonies with more than 50 cells was counted. The colonies were manually counted using a microscope.

For 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, 24 h after transfection cells were plated in 96-well plates at a concentration of approximately 3000 cells per well and cultured for 5 days. For quantitation of cell viability, 20  $\mu$ l of 5 mg/ml MTT (thiazolyl blue) solution was added to each well and incubated for 4 h at 37 °C. The medium was removed from each well, and the resulting MTT formazan was solubilized in 150  $\mu$ l of DMSO. Each solution was measured spectrophotometrically at 490 nm.

#### Statistical analysis

SPSS version 11.5 for Windows was used for all statistical analyses. A  $\chi^2$  test was used to examine possible correlations between TRIM24 expression and clinicopathological factors. The Kaplan–Meier method was used to estimate the probability of patient survival, and differences in the survival of subgroups of patients were compared using Mantel's log-rank

test. Student's *t* test was used to compare densitometry data on focus numbers between control and TRIM24-transfected cells. All *p* values are based on a two-sided statistical analysis, and *p*<0.05 was considered to indicate statistical significance.

## Results

### Expression pattern and clinical significance of TRIM24 in gastric cancer tissue

We examined TRIM24 protein expression in 133 gastric cancer specimens (including 110 tubular adenocarcinomas, 5 papillary adenocarcinomas, 12 mucinous adenocarcinomas, and 6 poorly cohesive adenocarcinomas) and 20 samples of normal gastric mucosa (Fig. 1). In normal gastric mucosa, cytoplasm of differentiated surface epithelia and mucosal glands showed

**Table 1** Distribution of TRIM24 status in gastric cancer according to clinicopathological characteristics

Characteristics	Number of patients	TRIM24 weak/negative	TRIM24 upregulation	<i>p</i> value
Age				
<60	68	35	33	0.9355
≥60	65	33	32	
Gender				
Male	101	50	51	0.5059
Female	32	18	14	
Differentiation				
Poor	60	27	33	0.1500
Well moderate	73	42	31	
Histologic classification				
Tubular	110	57	53	0.2444
Papillary	5	3	2	
Mucinous	12	8	4	
Poorly cohesive	6	1	5	
Tumor location				
Proximal	29	12	17	0.2006
Distal	104	57	47	
Tumor invasion (T)				
T1+T2	46	31	15	0.0092
T3+T4	87	38	49	
Lymph node metastasis				
Absent	49	28	21	0.3535
Present	84	41	43	
TNM stage				
I+II	61	39	22	0.0104
III	72	30	42	
Relapse				
Negative	59	41	18	0.0003
Positive	74	28	46	

weak or negative staining. Sixty-five of 133 primary gastric cancers showed TRIM24 upregulation, with immunoreactivity located in the nuclear compartment of carcinoma cells. Correlations between TRIM24 upregulation and clinicopathological characteristics are shown in Table 1. TRIM24 upregulation in the primary gastric cancer correlated significantly with advanced clinical stage ( $p=0.0104$ ). The rate of TRIM24 upregulation in the T3–T4 group was higher than that in the T1–T2 group ( $p=0.0092$ ). In addition, significant positive correlation was observed between TRIM24 upregulation and tumor relapse ( $p=0.0003$ ). There was no significant correlation between TRIM24 levels with other parameters as listed in Table 1. Kaplan–Meier analysis and the log-rank test were used to calculate the effect of TRIM24 expression on patient survival. The log-rank test showed that overall survival was significantly different between these two groups. Patients with low TRIM24 expression had longer overall survival, whereas those with high TRIM24 expression had shorter survival (Fig. 1g, log-rank,  $p<0.0001$ ).

#### TRIM24 overexpression accelerates cell growth in gastric cancer cell lines

We checked TRIM24 protein and messenger RNA (mRNA) expression in five gastric cancer cell lines (BGC-823, AGS, SGC-7901, MKN-1, and HGC-27) and found that TRIM24 expression was relatively low in SGC-7901 cells and relatively high in MKN-1 cells (Fig. 2a). Plasmid transfection was performed in SGC-7901 cells, and siRNA knockdown was carried out in MKN-1 cells. As shown in Fig. 2b, plasmid transfection significantly upregulated TRIM24 at both protein and mRNA levels, and siRNA treatment downregulated its expression. To investigate the impact of TRIM24 on cell proliferation, MTT and colony formation assays were performed. MTT assay showed that TRIM24 transfection caused

significant increase in proliferation rate of SGC-7901 cells, while siRNA depletion inhibited proliferation of MKN-1 cells (Fig. 3a). Consistent with the MTT results, colony formation assay showed that TRIM24 overexpression increased, while its depletion decreased colony formation ability (Fig. 3b).

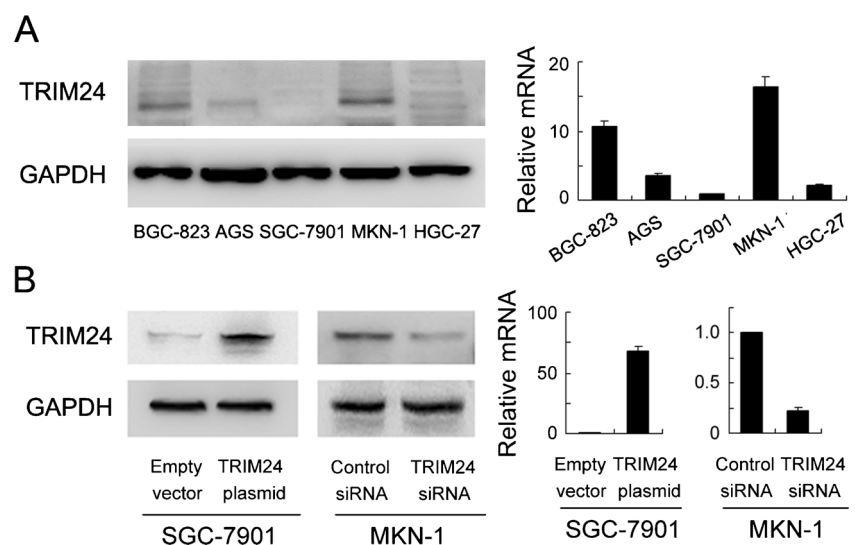
#### TRIM24 increases chemoresistance of gastric cancer cells

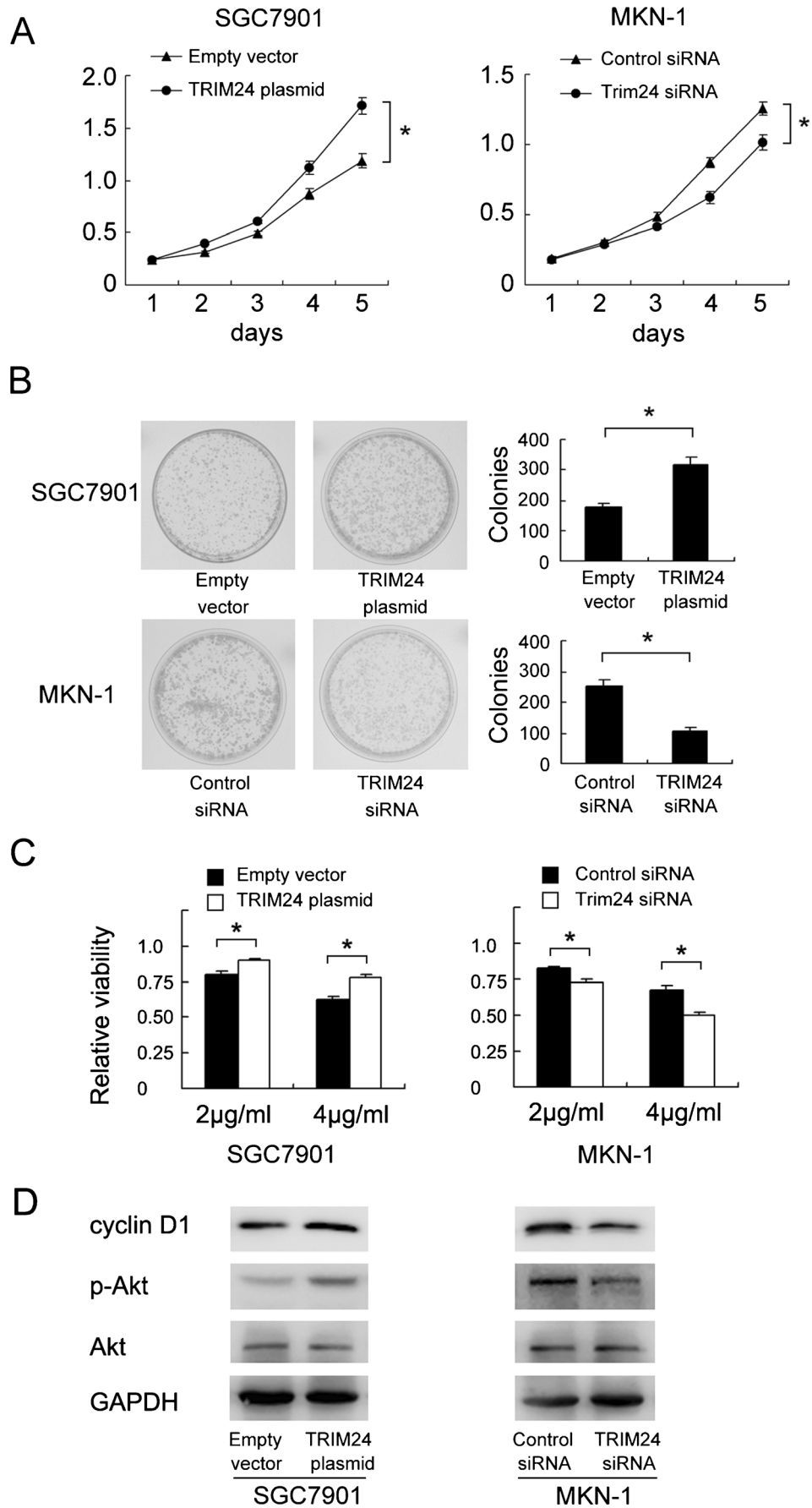
To investigate the role of TRIM24 on chemoresistance of gastric cancer cells, we treated TRIM24 overexpressed cells with different concentrations of 5-FU (2 and 4  $\mu\text{g/ml}$ , 48 h). Relative cell viability was determined by MTT assay. Compared with the control group, TRIM24 transfection increased viability of SGC-7901 cells. In contrast, TRIM24 siRNA treatment decreased cell viability (Fig. 3c). These data indicate that TRIM24 enhances resistance of gastric cancer cells against 5-FU.

#### TRIM24 regulates Akt signaling pathway

To investigate the possible mechanism of TRIM24 on proliferation and chemoresistance, we examined changes of cyclin D1 and Akt phosphorylation in TRIM24-overexpressed and depleted cancer cells. We found that the levels of cyclin D1 and p-Akt were upregulated after TRIM24 transfection and downregulated after siRNA depletion (Fig. 3d). To validate the involvement of Akt activation in TRIM24-mediated cell proliferation and chemoresistance, we used LY294002 (20  $\mu\text{mol/l}$ , 48 h after transfection), an Akt inhibitor, on SGC-7901 cells. Akt inhibitor treatment did not block the effect of TRIM24 on proliferation (Fig. 4b). As shown in Fig. 4c, Akt inhibitor significantly blocked the effect of TRIM24 on chemoresistance. These results indicate that inhibition of Akt counteracts the chemoresistance-enhancing effect of TRIM24.

**Fig. 2** Expression of TRIM24 in gastric cancer cell lines. **a** Protein and mRNA expression of TRIM24 in gastric cancer cell lines. MKN-1 cell line has relatively high expression and SGC-7901 cell line has relatively low expression. **b** Western blot and real-time PCR analysis showed that siRNA treatment markedly decreases TRIM24 levels in MKN-1 cells and plasmid transfection significantly increased its level in SGC-7901 cells



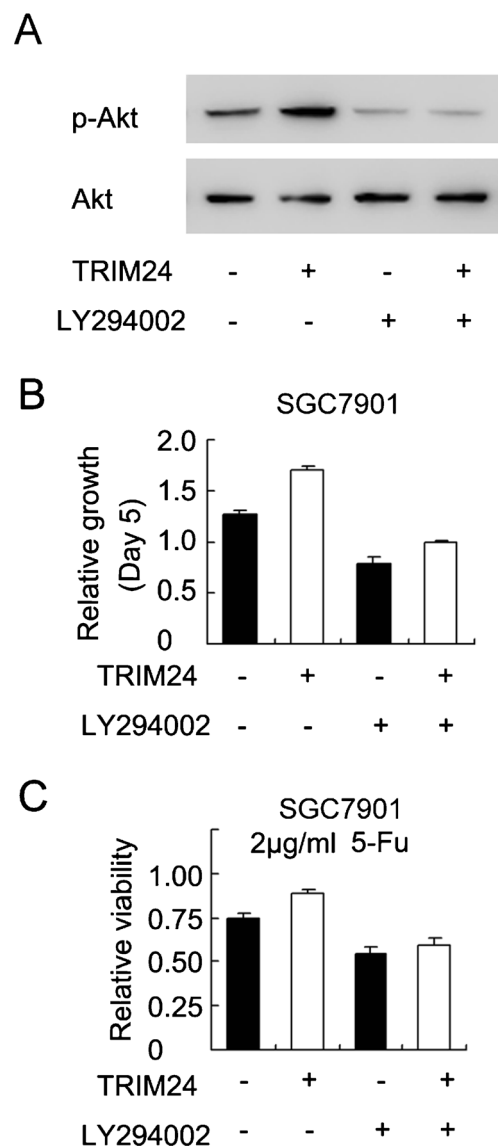


**Fig. 3** Biological roles of TRIM24 on gastric cancer cell proliferation and chemoresistance. **a** MTT assay showed that TRIM24 knockdown inhibited proliferation in MKN-1 cell line. TRIM24 overexpression promoted proliferation in SGC-7901 cell line ( $p < 0.05$ ). **b** TRIM24 knockdown decreased colony numbers while its overexpression increased colony formation ability ( $p < 0.05$ ). **c** MTT assay showed that TRIM24 overexpression enhanced cell viability and its depletion inhibited cell viability in gastric cancer cells treated with 5-Fu (2 and 4  $\mu\text{g/ml}$ , for 48 h). **d**. TRIM24 knockdown decreased while its overexpression upregulated cyclin D1 and p-Akt expression

## Discussion

Gastric cancer is one of the most common cancers worldwide, and it has been one of the most serious public health problems. Although researchers have found that many aberrantly expressed genes in gastric cancer contribute to the malignant behavior, novel molecular markers that can identify tumor progression and predict the aggressive phenotype at the level of the individual patient are still urgently needed [17, 18]. Upregulation of TRIM24 expression had been implicated in several human cancers. TRIM24 gene upregulation in breast cancer is associated with poor patient prognosis. TRIM24 overexpression was also reported in advanced head and neck squamous cell carcinoma and correlates with adverse overall survival. TRIM24 protein was found to be overexpressed in human lung cancer and correlated with TNM stage, poor differentiation, and Ki67 labeling index. TRIM24 is overexpressed in human malignant glioma and serves as an independent predictive factor for overall and progression-free survival [9–11, 13, 15]. To date, its expression pattern and clinical significance in human gastric cancer remain unexplored. Here, we examined TRIM24 in 133 gastric cancer specimens by immunohistochemistry. We found that TRIM24 expression is upregulated in almost 50 % of the cases and associated with local invasion and clinical stage, suggesting that its expression is correlated with malignant behavior. In addition, we demonstrated that TRIM24 upregulation is correlated with poor overall survival of gastric cancer patients. These data are in agreement with previous reports and suggest that overexpression of TRIM24 protein may be a common feature in gastric cancer and can serve as a prognostic marker to identify patients with poor clinical outcome.

Previous studies also suggested that TRIM24 siRNA knockdown inhibits cell growth and invasion. To further reveal the function of TRIM24 in gastric cancer, plasmid transfection and siRNA knockdown were performed in SGC-7901 and MKN-1 cells. MTT and colony formation assay were employed to assess its role on cancer growth. In agreement with previous studies, TRIM24 transfection promoted gastric cancer cell proliferation, and its depletion inhibited cell growth. In addition, TRIM24 overexpression increased the level of cyclin D1. In addition to its effect on cell proliferation, we found that TRIM24 overexpression modifies cancer cell



**Fig. 4** TRIM24 enhances gastric cancer chemoresistance via Akt. **a** Akt inhibitor LY294002 (20  $\mu\text{mol/l}$ , 48 h after transfection) blocked Akt phosphorylation in both control and TRIM24 transfected cells. **b** MTT assay showed that Akt inhibitor treatment did not block the role of TRIM24 on cell proliferation. **c** Effect of Akt inhibitor on chemoresistance. SGC-7901/Empty vector and SGC-7901/TRIM24 cells were treated with Akt inhibitor. Akt inhibitor treatment counteracts the upregulatory effect of TRIM24 on chemoresistance

survival upon 5-FU treatment, suggesting that TRIM24 might be a potential target for gastric cancer chemotherapy.

Chemoresistance of cancer cells involves a host of processes and interaction of multiple genes. Previous studies indicated that TRIM24 regulates Akt signaling in human glioma [16]. In this study, we examined how TRIM24 overexpression and knockdown changes Akt phosphorylation in gastric cancer cells. We found that TRIM24 overexpression increased Ser 473 phosphorylation of Akt, while its knockdown decreased phosphorylation. In addition, an Akt inhibitor partly reversed the enhancing effect of TRIM24 on chemoresistance.

Akt is involved in the regulation of chemoresistance to many drugs including 5-FU [19–21]. These data strongly suggest that TRIM24 regulates cancer cell chemoresistance through activation of the Akt pathway.

In summary, we show that TRIM24 expression is upregulated in human gastric cancer in association with local invasion, clinical stage, and poor prognosis. TRIM24 accelerates malignant cell growth and induces chemoresistance, possibly through the Akt pathway. We propose that TRIM24 upregulation might identify patients at high risk and serve as a novel therapeutic target for gastric cancer.

**Conflict of interest** No potential conflicts of interest were disclosed.

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