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Original Article

The role of TAK1 expression in thyroid cancer

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Abstract: Objective: To investigate the expression, significance, and role of transforming growth factor β-activated kinase 1 (TAK1) in human thyroid cancer tissue. Methods: The data of 101 patients with thyroid cancer who underwent surgical treatment at our hospital from June 2001 to March 2010 were collected. All the patients were diagnosed with thyroid cancer by post-operative pathological examination. Immunohistochemistry staining was performed to detect the expression of TAK1 protein in thyroid cancer tissue and the adjacent tissues, and correlation analysis was performed to explore the relationships between TAK1 expression level and clinical and pathological features and the patient's prognosis. In addition, thyroid cancer cells (BCPAP) were cultured *in vitro* to investigate the role of TAK1 in the proliferation, invasion, and apoptosis of thyroid cancer cells and the possible mechanisms of its action. Results: The TAK1 expression rate was 78.2% in human thyroid cancer tissue, which was significantly higher than in the adjacent normal tissues (14.9%) ($P < 0.05$). The TAK1 expression level was unrelated to the patient's age, gender, and histological type ($P > 0.05$) and was closely related to the clinical stage and lymph node metastasis ($P < 0.05$). Moreover, the five-year survival rate of patients with TAK1 expression was significantly lower than those without TAK1 expression ($P = 0.019$). *In vitro*, 5Z-7-oxozeaenol, a selective TAK1 inhibitor, significantly inhibited the proliferation and invasion and promoted the apoptosis of thyroid cancer cells, possibly due to its inhibition of the activation of the nuclear factor-κB (NF-κB) signaling pathway. Conclusion: TAK1 may be an important factor involved in the pathogenesis of thyroid cancer, and targeted down-regulation of TAK1 may improve the prognosis of patients with thyroid cancer.

Keywords: Thyroid cancer, TAK1, proliferation, invasion, apoptosis

Introduction

Thyroid cancer is a common malignancy of the endocrine system and is more common in women than men. At present, surgery-based comprehensive treatment is the main clinical treatment [1], but it has yet to significantly improve the prognosis of thyroid cancer due to inadequate understanding of the pathophysiology of thyroid cancer and a lack of specific targeted therapeutic drugs in clinical treatment [2]. Therefore, it is important to develop a deep understanding of the specific molecular biological mechanisms of the development and progression of thyroid cancer and to develop targeted therapeutic drugs. Transforming growth factor β-activated kinase 1 (TAK1) is a member of the mitogen-activated protein-3 kinase (MAP3K) family that plays an important role in the development and progression of a variety of tumors [3]; however, there are few studies on the expression and role of TAK1 in thyroid cancer. In this study, we investigated the expression of TAK1 in thyroid cancer and its clinical significance, and we further investigated the role of TAK1 in the development and progression of thyroid cancer *in vitro* using 5Z-7-oxozeaenol, a selective TAK1 inhibitor. Our findings should provide new ideas and methods for the treatment of thyroid cancer.

Materials and methods

General data of the patients

The data of 101 patients with thyroid cancer who underwent surgical treatment at our hospital from June 2001 to March 2010 were collected. Specimens of resected tumor tissue and the corresponding adjacent normal thyroid tissue were collected. None of the patients

Table 1. Analysis of TAK1 expression level in thyroid cancer tissue and the adjacent normal tissues

Group	TAK1 expression		P
	Percentage of positive cells (%)	Percentage of negative cells (%)	
Cancer tissue	79 (78.2)	22 (21.8)	< 0.001
Adjacent tissue	15 (14.9)	86 (85.1)	

received radiotherapy, chemotherapy or biological therapy before surgery. All the patients were diagnosed with thyroid cancer by postoperative pathological examination. They all had complete clinical medical records. The patients' general data are summarized in **Table 2**. This study was approved by the Ethics Committee of our hospital. All the patients signed informed consent forms before surgery. The patients were followed up by phone or hospital visit every three months, for up to five years.

Immunohistochemistry and hematoxylin and eosin (HE) staining

The resected tissue specimens were fixed in 10% formalin, embedded in paraffin, and prepared into 4-micron sections. The slides were baked at 60°C for 8 hours for later use. Next, paraffin sections were deparaffinized and hydrated, followed by three washes in phosphate-buffered saline (PBS) for 3 minutes each. After soaking with distilled water, TAK1 (antigen) was repaired in EDTA buffer at 100°C for 20 minutes, and then cooled to room temperature. After washing with distilled water, the slides were washed with PBS, at 3 minutes per wash. Next, the peroxidase blocking solution was added, followed by incubation at room temperature for 10 minutes to block the activity of endogenous peroxidase. Then, the slides were washed with PBS three times for 3 minutes each. Next, non-immune serum of animal source was added then discarded after incubation at room temperature for 10 minutes. The primary antibody against caspase-1 (1:150, 1:300 and 1:400) was added, and the slides were incubated at room temperature for 1 hour. PBS was used in place of the primary antibody as a negative control. After PBS washing, the biotin-labeled secondary antibody (goat anti-rabbit IgG, Zhongshan Jinqiao Biotech Co., Ltd., China) was added, and the slides were incubated at room temperature for 10 minutes. After the PBS wash, the streptavidin-anti-biotin-peroxidase solution was added, and the slides were incubated at room temperature for 10 minutes. After another PBS wash, DAB chromogenic reagents were added. Then, the slides were washed with tap water, re-stained with hematoxylin, washed with tap water until the color turned blue, dehydrated and dried with ethanol, rendered transparent with xylene, and mounted with neutral resin. HE staining was performed according to the standard operating procedures. TAK1 expression was judged positive if brown precipitates were present in the cytoplasm. Two experienced pathologists (blinded to the group) observed the slides independently and counted 15 fields on each slide at high magnification (×400). The positive cell rate was calculated as the number of cells with TAK1 expression per 100 cells. The interpretation of positive immunohistochemical results (brown particles in the nucleus or cytoplasm) was taken from past literature [4], as follows. For judging the percentage of positive cells: 0 points: less than 1% positive cells; 1 point: 1-10%; 2 points: 10-30%; 3 points: 30-60%; 4 points: greater than 60%; and for judging the staining intensity of positive cells: 0 points: negative staining; 1 point: pale yellow; 2 points: yellow; 3 points: brown. The interpretation of the final result: negative: 0-2 points; positive: 3-7 points.

Cells and reagents

The human thyroid cancer cell line (BCPAP) was provided by Shanghai Branch, the Chinese Academy of Sciences. RPMI1640 medium was purchased from Gibco. 5Z-7-Oxozeaenol and a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (M2128) detection kit were purchased from Sigma-Aldrich Inc. (USA). Matrigel was purchased from Becton Dickinson & Co. An Annexin V-FITC Apoptosis Detection Kit was purchased from BD Biosciences. A total cellular protein extraction kit (P0013), nucleoprotein and plasma protein extraction kit (P0028) and ECL luminescence agent (P0018) were purchased from Nantong Biological Technology Co., Ltd. (Jiangsu, China). The primary antibodies against p65, H3, X-linked inhibitor of apoptosis protein (XIAP), cleaved caspse-3, matrix metallopeptidase 9 (MMP9) and β-actin (sc-7210) were purchased from CST (USA). The horseradish peroxidase (HRP)-

Table 2. The relation between TAK1 expression and the clinical and pathological features and the stage of thyroid cancer

Group		n	TAK1 expression		P
			Positive	Negative	
Gender	Male	29	23	6	0.87
	Female	72	56	16	
Age (years)	< 45	57	48	9	0.097
	≥ 45	44	31	13	
Histological type	Papillary cancer	61	47	14	0.861
	Follicular cancer	21	16	5	
	Medullary cancer	15	13	2	
	Undifferentiated cancer	4	3	1	
Clinical stage	I, II	81	52	29	0.008
	III, IV	30	27	3	
Lymph node metastasis	Yes	52	48	4	0.0004
	No	49	31	18	

labeled rabbit anti-mouse IgG secondary antibody (sc-2020) was purchased from Bioworld Biotechnology.

Culture of BCPAP human thyroid cancer cells

The human thyroid cancer cell line BCPAP was seeded in culture flasks after thawing, in RPMI1640 medium containing 10% FBS, where the final concentration of streptomycin, penicillin, and glutamine was 100 mg/L, 100 U/mL, and 2 mmol/L, respectively. The culture flasks were placed in an incubator at 37°C and 5% CO_2. The cells adhered to the flask wall and grew into a single-cell layer, and they were passaged every 2-3 days. Cells in the exponential growth phase were harvested for drug intervention experiments.

Drug treatment and groups

The cells were seeded into 96-well plates at 100 μL (5-9×10^4 cells)/well, and 100 μL of culture medium was added into each well. There were four experimental groups: the blank group (without any intervention), the control group (1% DMSO group), the low-dose 5Z-7-oxozeaenol group (3 μM), and the high-dose 5Z-7-oxozeaenol group (6 μM).

Annexin V-FITC detection of cell apoptosis

Cells were harvested at 24 hours, 48 hours and 72 hours of drug treatment. According to the procedure described in the instructions of the Annexin V-FITC kit, cells were resuspended with 100 μL of Annexin V-FITC/PI incubation solution (1:1000) and allowed to sit at room temperature for 15 minutes in the dark. Next, 400 μL of incubation solution was added to stop the reaction, followed by flow cytometry detection.

MTT colorimetric assay of cell proliferation

After the addition of drugs, cells plates were placed into an incubator for 24 hours, 48 hours or 72 hours. Next, 20 μL of MTT (5 g/L) solution were added into each well and the cells were incubated for 4 hours. Then, the supernatant in each well was aspirated and replaced with 150 μL of dimethyl sulfoxide (DMSO). The cell plates were placed on a shaker for 10 minutes at room temperature, and the optical density (OD) *(A)* of each well was measured at 690 nm in an enzyme-linked immunosorbent assay analyzer. The results of six duplicates were averaged, and the inhibition rate of cell proliferation was calculated for each drug treatment group. Growth inhibition rate = (1-OD values of the experimental group/OD value of the blank group)×100%.

Cell invasion assay

The Matrigel stock solution was placed on an ice bath in a refrigerator at 4°C overnight to allow it to thaw. Then, a pre-cooled tip was used to mix it. Next, thawed Matrigel stock solution and pre-cooled serum-free RPMI medium were prepared into the gel to coat the upper Transwell chamber at 80 μL per well. The chamber was then placed at 37°C for 2 hours to allow the gel to solidify. For each group, cells in the exponential growth phase were digested, centrifuged, and counted and then diluted to a cell suspension (1×10^9 cells/L) with serum-free RPMI1640 medium. Next, 150 μL of cell suspension was added to each upper Transwell chamber, and 500 μL of fresh RPMI medium containing 10% FBS was added to the lower chamber. For each group, nine duplicate wells were set up, and the

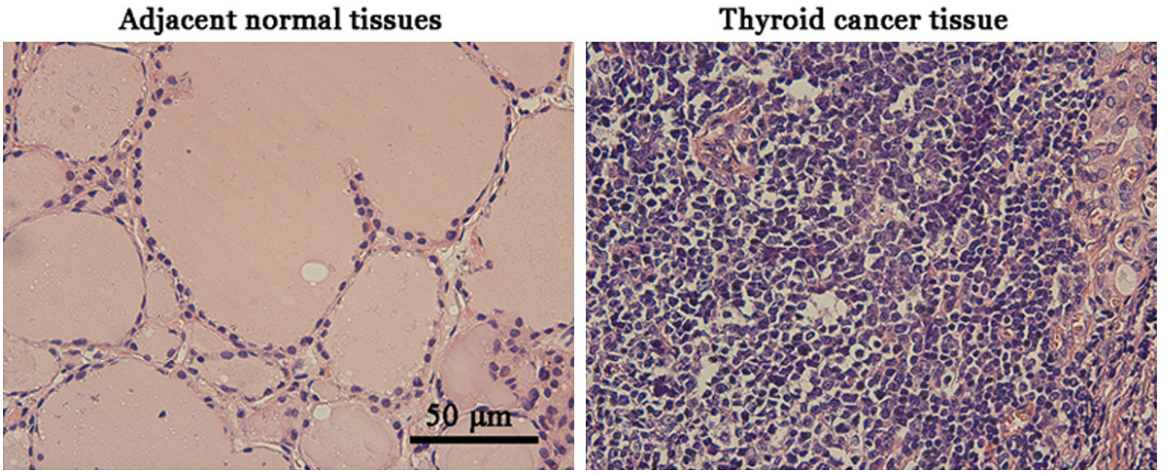

Figure 1. HE staining of thyroid cancer tissue and the adjacent normal tissues.

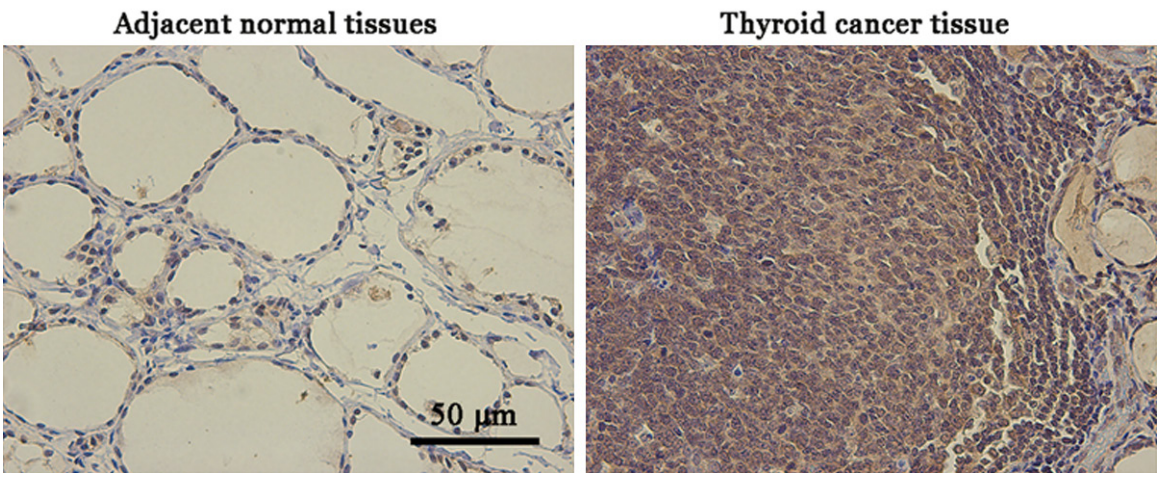

Figure 2. Immunohistochemical staining of thyroid cancer tissue and the adjacent normal tissues.

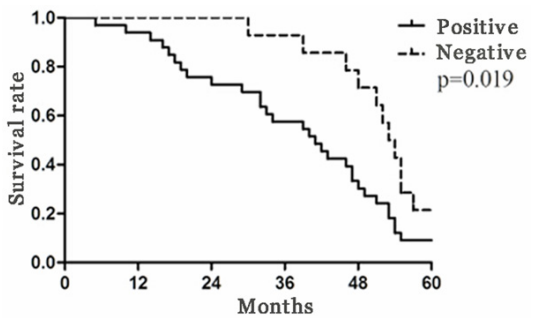

Figure 3. Correlation between TAK1 expression and 5-year survival rate.

cells were placed in an incubator at 37°C for 24 hours. Next, the Transwell chamber was removed from the incubator. After PBS wash, a cotton swab was used to gently remove cells on the upper side of the polycarbonate membrane, and the underside of the membrane was immediately fixed in 4% formaldehyde for 30 minutes, followed by PBS wash, air-drying, Giemsa staining for 5 minutes, a wash with distilled water, and observation and counting (mean: 10 fields) under a microscope (100×).

Western blot analysis of XIAP, cleaved caspse-3, and MMP9 in thyroid cancer cells

The thyroid cancer cell line BCPAP and control cells were harvested after 48 hours of 5Z-7-oxozeaenol treatment. After washing with PBS twice, the cells were centrifuged at 12,000× g for 15 minutes. Next, the total cellular protein extraction kit and nucleoprotein extraction

Table 3. The effect of a selective TAK1 inhibitor on the proliferation of thyroid cancer cells

		Inhibition rate (%)		
Group	n	24 h	48 h	72 h
Blank	10	0.04 ± 0.01	0.06 ± 0.01	0.05 ± 0.02
Control	10	0.02 ± 0.07	0.08 ± 0.01	0.02 ± 0.02
5Z-7-oxozeaenol (3 μM)	10	12.6 ± 2.56*	30.5 ± 5.79*	39.7 ± 5.62*
5Z-7-oxozeaenol (6 μM)	10	15.9 ± 3.34#,*	61.3 ± 10.2#,*	62.8 ± 10.9#,*

*P < 0.05, compared with the control group; #P < 0.05, compared with the 5Z-7-oxozeaenol (3 μM) group.

Table 4. The effect of a selective TAK1 inhibitor on the invasion of thyroid cancer cells

Group	n	72 h (cell number)
Blank	10	167.9 ± 14.9
Control	10	166.5 ± 15.6
5Z-7-oxozeaenol (3 μM)	10	123.5 ± 10.76*
5Z-7-oxozeaenol (6 μM)	10	95.6 ± 8.98#,*

*P < 0.05, compared with the control group; #P < 0.05, compared with the 5Z-7-oxozeaenol (3 μM) group.

reagents were used to extract nucleoprotein according to the manufacturer's instructions. The nucleoprotein was then used to detect p65, with H3 as the internal control. The total cellular protein extraction reagents were used to extract total protein, which was then used to detect the expression of XIAP, cleaved caspse-3, and MMP9. For quantitative measurement of protein using the BCA method, 30 μg of protein was used as the sample in sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to a membrane, followed by blocking with 5% skim milk for 1 hour. Then, diluted H3, p65, β-actin, XIAP, cleaved caspse-3, and MMP9 antibodies (1:200 in 5% milk) were added and the membrane was placed at 4°C overnight. After TBST wash, horseradish peroxidase-labeled rabbit anti-goat secondary antibody (diluted in 5% milk) was added, followed by incubation and washing. Next, according to the instructions of the ECL reagents, a 1:1 luminescence solution was prepared for gel imaging, and Image J software was used for densitometric analysis.

Statistical analysis

SPSS16.0 software was used for statistical analysis. Count data were analyzed with a χ^2 test, and Kaplan-Meier curves were used for survival analysis. One-way analysis of variance was performed for multi-group comparisons. P < 0.05 was considered statistically significant.

Results

TAK1 protein expression in thyroid cancer tissue and the adjacent tissues

In this study, all thyroid cancer tissue specimens and the adjacent normal tissue specimens were confirmed by HE staining (see **Figure 1** for typical histopathological findings). Immunohistochemistry showed that the cytoplasm of thyroid cancer cells with TAK1 expression was yellow or brown, in a diffuse pattern. TAK1 expression was significantly lower in the adjacent normal tissues (**Figure 2**). The TAK1 expression rate was 78.2% in thyroid cancer tissue and 14.9% in the adjacent normal tissues (P < 0.001, **Table 1**).

Relationships between TAK1 expression and clinical and pathological features and stage of thyroid cancer

TAK1 expression level was unrelated to the gender, age, and histological type of patients with thyroid cancer (P > 0.05), but it was significantly correlated with the clinical stage and lymph node metastasis of thyroid cancer (P < 0.05). TAK1 was higher in patients with more advanced clinical stage and lymph node metastasis (**Table 2**).

Relation between TAK1 expression and five-year survival rate of patients

The Kaplan-Meier survival analysis (**Figure 3**) showed that the median 5-year survival was 41 months in patients with TAK1 expression, which was significantly lower that of patients without TAK1 expression (53.5 months) (P = 0.019).

Effect of 5Z-7-oxozeaenol, a selective TAK1 inhibitor, on the proliferation and apoptosis of thyroid cancer cells

In vitro culture of BCPAP human thyroid cancer cells showed that 5Z-7-oxozeaenol significantly inhibited the proliferation (**Table 3**) and invasion (**Table 4**) of thyroid cancer cells in a dose-

Table 5. The effect of a selective TAK1 inhibitor on the apoptosis of thyroid cancer cells (%)

Group	n	Apoptosis rate (%)		
		24 h	48 h	72 h
Blank	10	1.2 ± 0.02	4.69 ± 1.38	5.96 ± 1.79
Control	10	1.3 ± 0.01	4.81 ± 1.45	5.89 ± 2.01
5Z-7-oxozeaenol (3 μM)	10	15.6 ± 2.56*	29.6 ± 3.56*	31.2 ± 7.56*
5Z-7-oxozeaenol (6 μM)	10	32.9 ± 4.39#,*	46.3 ± 7.98#,*	49.6 ± 8.91#,*

*P < 0.05, compared with the control group; #P < 0.05, compared with the 5Z-7-oxozeaenol (3 μM) group.

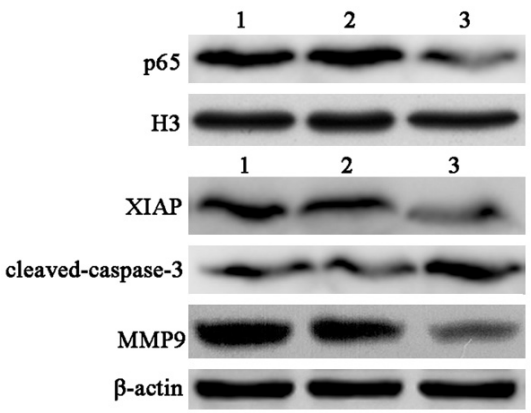

Figure 4. Western blot analysis (representative images: 1: blank group; 2: control group; 3: 5Z-7-oxozeaenol (6 μM)).

dependent manner (P < 0.05). In addition, compared with the control group, 5Z-7-oxozeaenol significantly promoted the apoptosis of thyroid cancer cells (P < 0.05) (**Table 5**).

Effect of 5Z-7-oxozeaenol, a selective TAK1 inhibitor, on the nuclear factor-κB (NF-κB) signaling pathway

The above experiments confirmed that high-dose 5Z-7-oxozeaenol (6 μM) effectively inhibited BCPAP invasion and proliferation and promoted apoptosis. Next, we used 6 μM 5Z-7-oxozeaenol to investigate the mechanism. The results (**Figure 4**; **Table 6**) showed that compared with the solvent group, the expression level of the pro-apoptotic protein cleaved caspase-3 was significantly higher in the 5Z-7-oxozeaenol group, while the expression level of nuclear p65, MMP9, and XIAP was significantly lower (P < 0.05).

Discussion

TAK1, a serine/threonine protein kinase, is a member of MAPK kinase kinase (MAPKKK) family. TAK1 plays an important role in transforming growth factor-β (TGF-β) signal transduction and osteogenesis. It mediates signal transduction and plays a key regulatory role in the stress responses, inflammation, immunity, and cancer development and progression [5]. It is highly expressed in a variety of tumor tissues and is closely related to tumor development, progression, and invasion [6-8]. It regulates the activation of MAPK and NF-κB signaling pathways. MAPK signaling is highly upregulated in thyroid cancer tissue, and inhibition of MAPK activity significantly inhibits the proliferation and promotes the apoptosis of thyroid cancer cells [9, 10]. NF-κB is also highly expressed in thyroid cancer tissue and is closely related to the prognosis of patients with thyroid cancer. Inhibition of NF-κB signaling significantly inhibits the proliferation and invasion and promotes the apoptosis of thyroid cancer cells [10], suggesting that NF-κB may become a new target for the treatment of thyroid cancer [11]. Comprehensive analysis of past studies suggest that TAK1 may play an important role in the development and progression of thyroid cancer. Therefore, in this study, we first investigated TAK1 expression in thyroid cancer tissue, and the results showed that TAK1 protein was significantly higher in thyroid cancer tissue than the adjacent normal tissues. Moreover, the expression level of TAK1 was closely related to lymph node metastasis and the clinical stage of thyroid cancer but was unrelated to the patient's gender, age, and histological type. Further study showed that the 5-year survival rate was significantly lower in patients with TAK1 expression than those without TAK1 expression. These results show that TAK1 may play an important role in the development, progression, and invasion of thyroid cancer. In addition, detection of TAK1 expression in resected thyroid cancer specimens may provide a reference for determining the patient's prognosis.

5Z-7-Oxozeaenol is a selective TAK1 inhibitor that significantly inhibits the proliferation and promotes the apoptosis of a variety of tumor cells by down-regulating TAK1 protein [12-15]. Hence, in this study, after confirming the high expression level of TAK1 in thyroid cancer tis-

Table 6. Western blot analysis

Group	n	p65	Cleaved caspase-3	XIAP	MMP9
Blank	10	0.96 ± 0.12	0.21 ± 0.09	0.81 ± 0.15	0.98 ± 0.14
Control	10	0.95 ± 0.11	0.26 ± 0.08	0.79 ± 0.11	0.94 ± 0.16
5Z-7-oxozeaenol (6 μM)	10	0.17 ± 0.02#	0.86 ± 0.13#	0.15 ± 0.06#	0.29 ± 0.09#

#P < 0.05, compared with the control group.

sue, we performed *in vitro* culture of BCPAP human thyroid cancer cells to further explore the role and possible mechanisms of TAK1 in the invasion and apoptosis of thyroid cancer cells. We referred to past literature for the dose of 5Z-7-oxozeaenol [15]. This TAK1 inhibitor significantly inhibited the invasion and proliferation and promoted the apoptosis of thyroid cancer cells. 5Z-7-oxozeaenol significantly reduces the expression of p65 protein in the nucleus, and cleaved caspase-3 and XIAP play important roles in the apoptosis of thyroid cancer cells [16]: cleaved caspase-3 promotes their apoptosis and XIAP inhibits their apoptosis. Both proteins are regulated by the NF-κB signaling pathway. This study showed that 5Z-7-oxozeaenol significantly increased the expression of cleaved caspase-3 protein while inhibiting the expression of XIAP protein in thyroid cancer cells. In addition, MMP9 plays an important role in the invasion of thyroid cancer cells [17]. MMP9 is also regulated by the NF-κB signaling pathway. Here, 5Z-7-oxozeaenol significantly inhibited the expression of MMP9. These effects may partly explain how 5Z-7-oxozeaenol promotes the apoptosis of thyroid cancer cells.

We only used one thyroid cancer cell line to explore the mechanisms of TAK1 function and 5Z-7-oxozeaenol action, so the results may have certain limitations. In the future, more thyroid cancer cell lines should be used to investigate these mechanisms. Furthermore, selective TAK1 inhibitors should be used in animal studies to investigate their role in the development and progression of thyroid cancer, in order to lay a solid theoretical foundation for their clinical application.

In summary, TAK1 expression level is significantly increased in thyroid cancer tissue and is correlated with the patient's prognosis. The use of 5Z-7-oxozeaenol, a specific TAK1 inhibitor, significantly inhibits the proliferation and invasion and promotes the apoptosis of thyroid cancer cells, suggesting that TAK1 may become a new target for the treatment of thyroid cancer and that 5Z-7-oxozeaenol may become a novel drug for the treatment for thyroid cancer.

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Disclosure of conflict of interest

None.

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