Observational Study

Medicine

OPEN

Katanin subunits p60 and p80, potential biomarkers for papillary thyroid carcinoma to distinguish nodular goiter: STROBE

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Abstract

Katanin subunits p60 and p80 are involved in microtubule-mediated cytoskeletal organization during cell division. Their aberrant expression has been found in prostate, breast, and non-small cell lung (NSCLC) cancers. It has recently been reported that compared with adjacent papillary thyroid carcinoma (PTC) tissues, both are highly expressed in tumor tissues. Here, we investigated whether katanin subunits p60 and p80 can be used as potential biomarkers for PTC to distinguish nodular goiter (NG).

Immunohistochemistry was performed to investigate the expression of katanin subunits p60 and p80 in the tissues of 97 cases of PTC and NG. This cohort included 87 cases with PTC (74 classical or conventional (CPTC) and 13 follicular (FVPTC) variants) and 10 cases with NG.

We found that katanin subunits p60 and p80 were expressed in PTC, but not in NG. The cutoff values of katanin p60 and p80 for PTC were 22.43% and 0.83%, respectively. The katanin subunit p60 was significantly associated with lymph node metastasis. Katanin subunit p80 was more highly expressed in CPTC than in FVPTC. The expression of the katanin subunit p60 was positively correlated with the expression of katanin p80 in PTC. Importantly, we found that overexpression of katanin p60 increased the expression of katanin p80 in a human papillary thyroid carcinoma KTC-1 cell line, which further supports the existence of katanin p60 and p80 feedback loops.

Our results indicate that katanin subunits p60 and p80 may be used as potential PTC biomarkers to distinguish NG and may be novel therapeutic targets for PTC.

Abbreviations: AAA = ATPase associated with diverse cellular activities, CPTC = classical or conventional of papillary thyroid carcinoma, FVPTC = follicular variant of papillary thyroid carcinoma, IHC = immunohistochemistry, MIT = microtubule interacting and trafficking, MTAs = microtubule targeting agents, NG = nodular goiter, NSCLC = non-small cell lung, PTC = papillary thyroid carcinoma.

Keywords: biomarker, immunohistochemistry, katanin p60, katanin p80, papillary thyroid carcinoma

1. Introduction

Thyroid nodules (NGs) and thyroid cancers are common thyroid diseases. In recent years, the incidence of thyroid nodules and thyroid cancer has increased.[1–4] More than one-tenth of the world population is, to some degree, affected by goiter, and most of these harbor nodules.[5] Thyroid cancer is the most common type of endocrine malignancy worldwide, and papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. Although it has been reported that the factors that cause an increase in the incidence of thyroid nodules are the same as those that cause an increase in thyroid cancer, the pathogenesis of thyroid nodules and thyroid cancer is not fully understood. Exploring potential PTC biomarkers to distinguish nodular goiter (NG) is very

The authors report no conflicts of interest.

This study was supported by the high talent support program project of Jinzhou Medical University (2015RC011).

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Wu Z, Guo M, Yang J, Xiao Y, Liu W. Katanin subunits p60 and p80, potential biomarkers for papillary thyroid carcinoma to distinguish nodular goiter: STROBE. Medicine 2022;101:24(e29402).

Received: 28 July 2021 / Accepted: 18 April 2022

http://dx.doi.org/10.1097/MD.0000000000029402

important for clinical practice and therapeutic strategies for this cancer.

Microtubule severing is an important event in the regulation of microtubule dynamics, which is essential for fundamental cellular processes completed by microtubule-severing enzymes.[6,7] Katanin is a microtubule-severing enzyme that plays a key role in the regulation of microtubule dynamics.[8,9] The katanin protein is composed of 2 subunits, 60 kDa (p60) and 80 kDa (p80), which are encoded by the *KATNA1* and *KATNB1* genes, respectively. Katanin p60 is the catalytic subunit containing an *N*-terminal microtubule interacting and trafficking (MIT) domain that interacts with the *C*-terminal domain of katanin p80, and a C-terminal AAA + domain that binds and hydrolyzes ATP to break the microtubules. Conversely, katanin p80 is the regulatory subunit containing an *N*-terminal WD40 domain that is responsible for targeting katanin p60 to the centrosome, a central proline-rich region and *C*-terminal domain, which is required for heterodimerization with the katanin p60 subunit.[7,10,11] Katanin p60 is a member of the AAA (ATPase associated with diverse cellular activities) family and exerts diverse biological functions, including regulation of mitosis, meiosis to mitosis switching, and neuronal development.[9,11,12] Although katanin p80 does not have enzymatic properties such as katanin p60, it can target katanin p60 to the centrosome[11] and enhance the microtubule-severing activity of katanin p60.[13] The *N*-terminal WD40 domain of katanin p80 can also act as a negative regulator of microtubule disassembly.[13] Animal experiments have shown that the expression of katanin p60 and katanin p80 varies developmentally in neuronal and non-neuronal tissues.[14] The levels of katanin p60 change substantially during neuronal development and are correlated with axonal growth.[15] Katanin p60 plays an important role in embryonic survival and proliferation of neuronal progenitors.[16] Human mutations in the katanin p80 gene *KATNB1* cause severe microcephaly with brain malformations and seizures, whereas mutations in this gene in mice cause left-right asymmetry and heart defects.[17–20]

Elevated expression of katanin p60 has been shown during prostate cancer progression and may contribute to cancer metastasis.[21] Similarly, both katanin subunits p60 and p80 have been found to be correlated with lymph node metastasis and worse prognosis in breast cancer[22–24] and non-small cell lung cancer (NSCLC).[25,26] In particular, it has recently been reported that compared with adjacent PTC tissues, both are highly expressed in tumor tissues.[27] Interestingly, it has been reported that *LAPSER1*, a putative tumor suppressor, is involved in cytokinesis via its interaction with katanin p80. Consequently, since disruption of *LASPER1* has been shown to cause genetic instability and cancer,[28] this indicates that the dysregulation of katanin p80 may result in tumorigenesis. To the best of our knowledge, the role of katanin subunits p60 and p80 in distinguishing PTC from NG has not been reported.

In this study, we investigated the expression of katanin subunits p60 and p80 in PTC and NG to explore potential PTC biomarkers for distinguishing NG. The association of katanin subunits p60 and p80 with lymph node metastasis and the correlation of their expression in PTC was also studied.

2. Materials and methods

2.1. Participants

This study comprised 97 paraffin-embedded specimens of human PTC and NG that were operated and diagnosed at the First Affiliated Hospital of Jinzhou Medical University, Jinzhou Liaoning, China, from 2010 to 2020. These tissue samples included 87 cases of PTC, including 74 of the conventional or classical variant (CPTC, of which 39 cases presented with lymph node metastasis) and 13 cases of the follicular variant (FVPTC, of which 3 cases presented with lymph node metastasis) and 10 cases with NG-a benign thyroid disease. The average age of these patients was 47.64.

2.2. Immunohistochemistry

Immunohistochemistry (IHC) was performed according to the antibody manufacturer's recommended protocol and well-established methods[29,30] with minor modifications. After deparaffinization and dehydration, the sections (4 μm) of PTC and NG were microwaved in antigen unmasking solution (Vector Laboratories, Burlingame, CA) for 10 minutes. After endogenous peroxidase was inactivated, the sections were treated with blocking buffer for 1 hour and incubated with rabbit anti-katanin p60 and anti-katanin p80 polyclonal antibodies (1:100 and 1:1500, respectively; Abcam Inc., Cambridge, MA) overnight at 4°C. After rinsing, the sections were incubated in biotinylated goat anti-rabbit antibody (1:300, Vector Laboratories) for 1 hour at room temperature, followed by incubation with the avidin–biotin complex (VECTASTAIN, Vector Laboratories) and diaminobenzidine (DAB Peroxidase Substrate Kit, Vector Laboratories) for visualization of the reaction product. Human breast cancer tissues were used as a positive control. For negative controls, the primary antibody was omitted.

Evaluation and confirmation of immunohistochemical staining were performed by 2 pathologists. According to a well-established method,[29,30] katanin p60 and katanin p80 positive and total cells were independently counted by 2 authors. The values from 5 random fields per section obtained by the 2 authors were averaged and expressed as a percentage of the number of katanin p60 and katanin p80 positive cells/total cells, respectively.

2.3. Ethics approval

This study was approved by the Ethical Review Board of Jinzhou Medical University, Jinzhou, Liaoning, China. Written informed consent was obtained from all the patients.

2.4. Cell culture

Human thyroid papillary carcinoma KTC-1 cells were maintained in RPMI 1640 supplemented with 10% fetal bovine serum (FBS), streptomycin sulfate (100 U/mL), and penicillin (100 μg/mL) at 37°C in a humidified incubator with 5% CO_2.

2.5. Transient transfection

Cell transfections were performed using Lipofectamine 2000 (Life Technologies, Carlsbad, CA) according to the manufacturer's instructions. Briefly, 5 μl of Lipofectamine 2000 was diluted in 125ul Opti-MEM medium and 2.5 μg katanin p60 expression vector (human KATNA1 (NM-007044)-pcDNA3.1-EGFP) and empty vector (pcDNA3.1-EGFP, Fenghuishengwu, Hunan, China) were respectively diluted in 125ul Opti-MEM medium. The diluted Lipofectamine 2000 was added into the

diluted vectors, mixed gently, and incubated for 15 to 20 minutes at room temperature. The complexes were added to each well (6-well-plate) containing the cells and incubated at 37°C in a 5% CO_2 incubator. After 6 to 8 hours of incubation, the cells were replaced with growth medium containing FBS for 48 hours.

2.6. Protein isolation and Western immunoblotting

Cells were lysed in RIPA lysis buffer (Solarbio, Beijing, China). Total cell lysates were incubated on ice for 30 minutes, followed by microcentrifugation at 10,000 g for 10 minutes at 4°C. Protein concentrations in the supernatants were determined using the BCA protein assay (Beyotime, Shanghai, China). Equal amounts of protein (50 μg) were mixed with 5× SDS sample buffer, boiled for 4 minutes, separated by 10% SDS–polyacrylamide gel electrophoresis, and transferred onto nitrocellulose membranes. Non-specific binding was blocked with 5% nonfat milk for 1 hour and incubated overnight at 4°C with the following primary antibodies: Katanin p60 (1:1000, Abcam, Cambridge, UK), katanin p80 (1:1500, Abcam, Cambridge, UK), and GAPDH (1:1000, Beyotime, Shanghai). After washing, blots were incubated with the secondary antibody (anti-rabbit IgG-HRP, Santa Cruz Biotechnology Inc., Santa Cruz, CA) at a dilution of 1:10,000 and visualized using an ECL chemiluminescence detection system (Amersham, Buckinghamshire, UK). Band intensities were quantified by densitometry using Image-Lab analysis software (BioRad).

2.7. Statistical analysis

The χ^2 test was used to examine the differences in the expression of katanin p60 and katanin p80 in PTC (including CPTC and FVPTC) and NG. Unpaired paired *t tests* were performed to compare 2 groups, katanin p60 and katanin p80, between PTC without and with lymph node metastasis; CPTC and FVPTC; males and females; <55 and ≥55 years; and clinical stages I and II/III (based on the 8th edition of AJCC/UICC TNM stages). Data are expressed as mean ± standard deviation (SD) and *P* values. The correlation between katanin p60 and katanin p80 expression in PTC compared with their expression in NG was analyzed by Spearman correlation, and the data were expressed as *r* and *P* values. Paired *t tests* were performed to compare the expression of katanin p60 and p80 in KTC-1 cells, and the data were expressed as mean ± standard deviation (SD) and *P* value. *Statistical significance was set at* $P \leq .05$. Receiver-operating characteristic (ROC) analysis was also used to determine the cutoff values for katanin p60/katanin p80 IHC staining. All analyses were performed using the SPSS 26.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Expression of katanin p60 in PTC and NG

Katanin p60 expression in PTC tissues (including CPTC and FVPTC) and NG was examined by immunohistochemistry (Fig. 1A–C). We found that katanin p60 was not expressed in

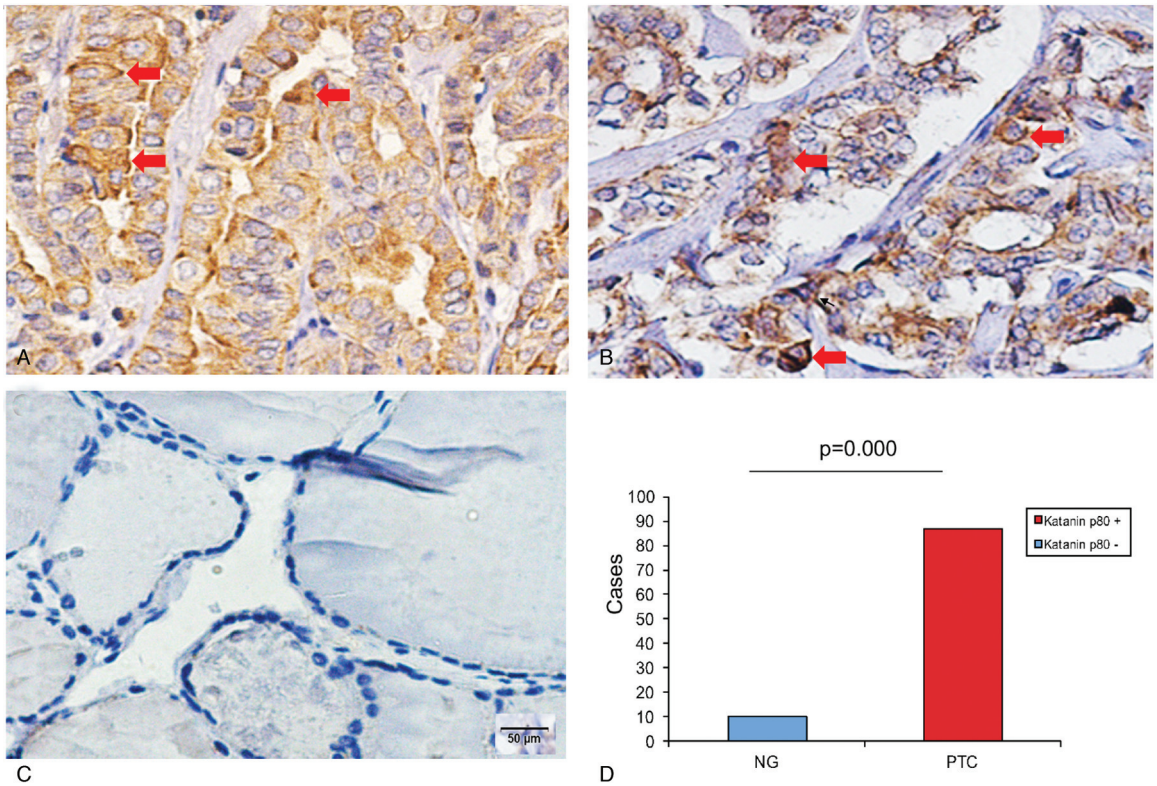


Figure 1. Expression of katanin p60 in papillary thyroid carcinoma (PTC) and nodular goiter (NG). Immunohistochemistry was performed to analyze katanin p60 expression in the tissues of PTC (including classical or conventional of papillary thyroid carcinoma [CPTC] and follicular variant of papillary thyroid carcinoma [FVPTC]) and NG (A–C, magnification 10×40). The expression of katanin p60 was examined in tissues including CPTC (A), FVPTC (B), and NG (C). Katanin p60 was not expressed in NG (0/10 cases) but was expressed in all PTC tissues (87/87 cases, $P = .000$) (D). The arrows indicate representatives of immunostaining areas. *Statistical significance was set at* $P \leq .05$.

NG (n = 10, 0/10 cases), but was expressed in all PTC tissues (n = 87, 87/87 cases, $\chi^2 = 86.49$, $P = .000$) (Fig. 1D), with an average positive value of 79.42%. The localization of katanin p60 staining was primarily cytoplasmic; however, in some cases, it was both cytoplasmic and nuclear. The cutoff value of p60 for PTC was 22.43%, with a sensitivity of 100% and specificity of 100%. To further study the differences in katanin p60 expression in PTC, a percentage of the number of katanin p60 positive cells/total cells was calculated, and we found that there was a significant increase in PTC with lymph node metastasis (n = 42, 83.18% ± 8.16%), when compared with PTC without lymph node metastasis (n = 45, 75.91 ± 13.05, $P = .002$). Furthermore, the results did not show a significant difference in katanin p60 expression between CPTC (n = 74, 79.58 ± 10.79) and FVPTC (n = 13, 78.53 ± 15.47, $P = .818$).

3.2. Expression of katanin p80 in PTC and NG

To further verify the function of katanin in PTC, the expression of the katanin regulatory subunit p80 in PTC and NG was also investigated by immunohistochemistry (Fig. 2A–C). Katanin p80 expression was not detected in NG (n = 10, 0/10 cases), but was detected in all PTC tissues, including CPTC and FVPTC (n = 87, 87/87 cases, $\chi^2 = 86.49$, $P = .000$) (Fig. 2D), with an average positive value of 61.63%. The localization of katanin p80 was primarily cytoplasmic; however, similar to p60, some cases showed immunostaining in both the cytoplasm and the nucleus. The cutoff value of p80 for PTC was 0.83%, with a sensitivity of 100% and specificity of 100%. We did not find a significant change in katanin p80 expression in PTC with lymph node metastasis (n = 42, 66.48% ± 23.72%) when compared with PTC without lymph node metastasis (n = 45, 57.10% ± 24.60%, $P = .074$). However, katanin p80 was significantly higher in CPTC (n = 74, 65.67% ± 22.18%) than in FVPTC (n = 13, 38.61% ± 25.16%, $P = .000$).

3.3. Correlation of katanin p60 and p80 in PTC

In the present study, we examined the expression of katanin p60 and p80 in the same PTC tissues and found that the level of katanin p60 was positively correlated with the level of katanin p80 in PTC (Fig. 3, $r = 0.364$, $P = .001$).

To further verify this, we overexpressed katanin p60 in human papillary thyroid carcinoma KTC-1 cells by transient transfection and found that overexpression of katanin p60 significantly increased katanin p80 expression (Fig. 4).

3.4. Association of katanin p60 and p80 with sex and clinical stage

In the present study, the association of katanin p60 and p80 expression with sex, age, and clinical stage were analyzed

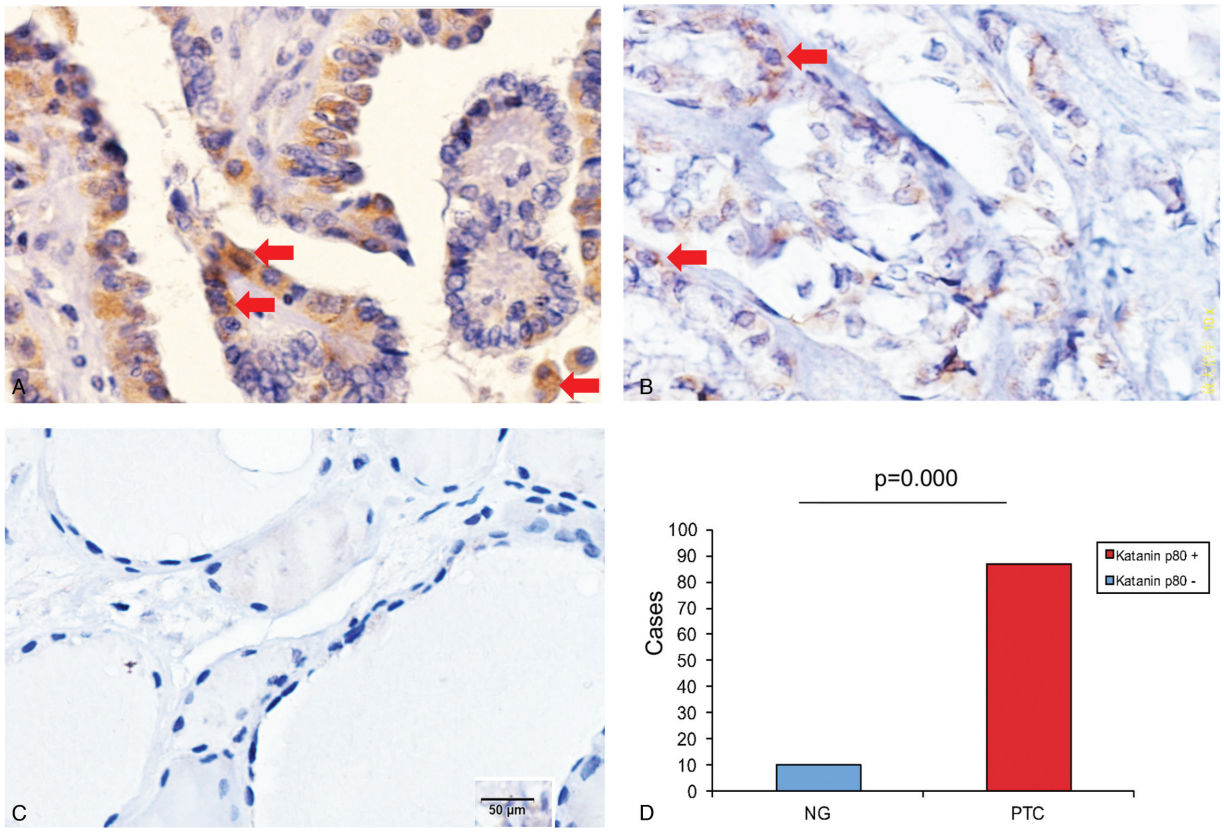


Figure 2. Expression of katanin p80 in papillary thyroid carcinoma (PTC) and in nodular goiter (NG). Using immunohistochemistry, we analyzed katanin p80 expression in the tissues of PTC (including classical or conventional of papillary thyroid carcinoma [CPTC] and follicular variant of papillary thyroid carcinoma [FVPTC]) and NG (A–C, magnification 10×40). Katanin p80 was examined in tissues including CPTC (A), FVPTC (B), and NG (C). Katanin p80 was not detected in NG (0/10 cases) but was observed in all PTC tissues (87/87 cases, $P = .000$ (D). The arrows indicate representatives of immunostaining areas. *Statistical significance was set at* $P \leq .05$.

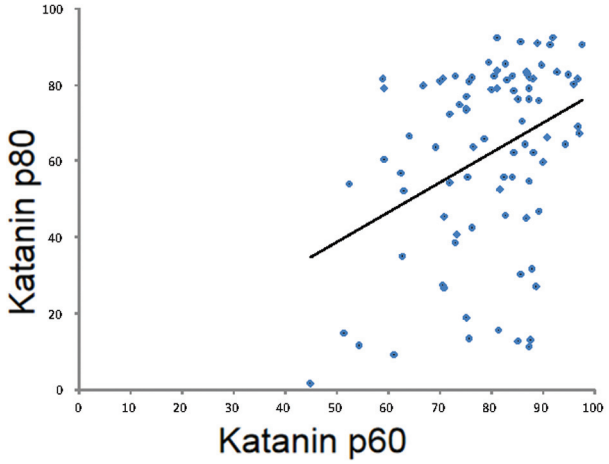


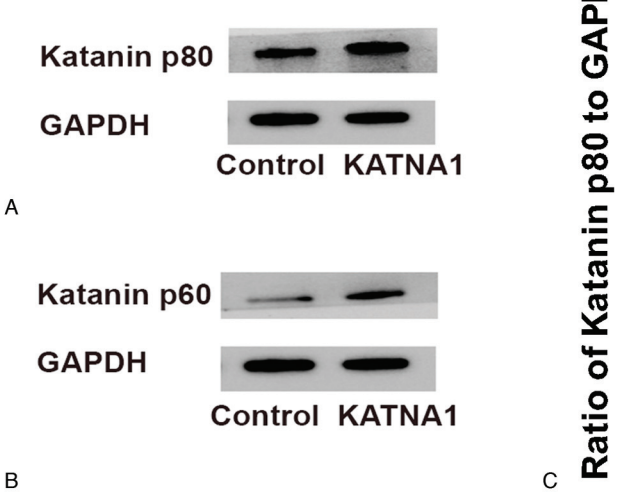
Figure 3. Correlation of increased Katanin p60 expression with increased katanin p80 expression in papillary thyroid carcinoma (PTC). Our results showed the expression of katanin subunits p60 and katanin p80 in PTC, but not in nodular goiter. There was a statistically significant correlation between katanin p60 expression and katanin p80 expression ($r=0.364$, $P=.001$, tested by Spearman correlation).

(Table 1). We did not find significant association of katanin p60 and p80 expression with gender (katanin p60: males: 81.14% ± 10.90%; females: 78.47% ± 11.81%, $P=.302$; katanin p80: male: 61.78% ± 25.64%; female: 61.54% ± 24.08%, $P=.966$). There was no significant association of katanin p60 and katanin p80 with age (katanin p60: <55: 78.63% ± 11.90%; ≥55: 81.17% ± 10.57%, $P=.344$; katanin p80: <55: 60.62% ± 25.87%; ≥55: 63.86% ± 21.43%, $P=.572$). Similarly, we also did not find a significant association of katanin p60 and p80 with clinical stages (katanin p60: I: 79.02% ± 11.75%; II/III: 81.66% ± 10.08%, $P=.449$; katanin p80: I: 60.87% ± 24.62%; II/III: 65.91% ± 24.32%, $P=.497$).

4. Discussion

The microtubule cytoskeleton is an essential cellular component that plays an important role in various biological processes such as cell division, polarity, and migration, all of which are altered in cancer. Microtubule targeting agents (MTAs) have shown significant promise as anti-cancer strategies.[31,32] The purine-type compound 5a, an MTA, demonstrated potency against NSCLC via direct targeting of katanin p60 and p80 to induce microtubule fragmentation, leading to G2/M cell cycle arrest and intrinsic apoptosis.[33] These results encouraged us to explore the role of katanin p60 and p80 in PTC development, progression, metastasis, and prognosis.

In this study, we first discovered the expression of katanin p60 and p80 in PTC tissues (including CPTC and FVPTC), but not in NG-a benign thyroid disease, suggesting that katanin p60 and p80 can be potential PTC biomarkers to distinguish NG. Our results are consistent with those of a few previous studies on other types of cancers. For instance, katanin p60 was aberrantly expressed during prostate cancer progression to bone, and overexpression of katanin p60 in prostate cells enhanced cell migration.[21] Furthermore, katanin p60 was expressed at low levels in the tissues of healthy breast tissue, increased in primary breast cancer, and further increased in bone metastatic breast cancer. Overexpression of katanin p60 has been shown to enhance breast cancer cell migration, whereas downregulation of katanin p60 reduced breast cancer cell migration.[24] Both katanin p60 and p80 expression were also significantly correlated with higher lymph node metastasis and shorter overall survival in patients with breast cancer.[22,23] Recently, similar roles of katanin p60 and p80 have also been reported in NSCLC.[25,26] These results clearly show that katanin subunits p60 and p80 are not only highly expressed in



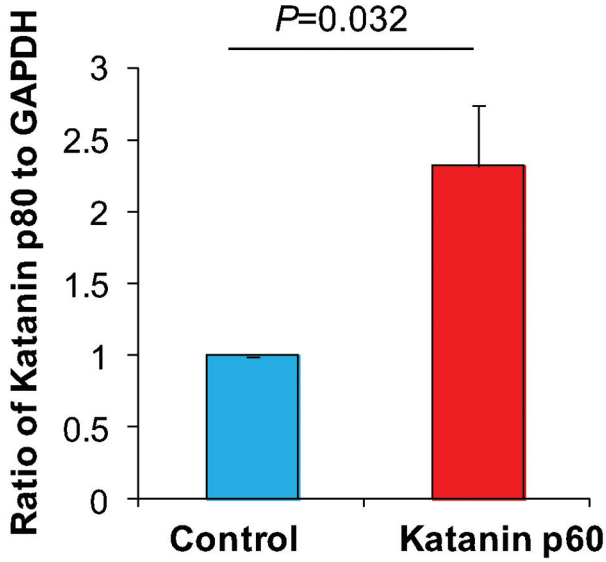


Figure 4. The effect of overexpression of katanin p60 on katanin p80 expression in KTC-1 cells. KTC-1 cells were transfected with katanin p60 (KATNA1) and empty vector (control) and examined by Western blotting with anti-katanin p60 and GAPDH antibodies, respectively. (B) also with an anti-katanin p80 antibody. Note that in A and B, the same membrane was cut into three parts according to the molecular weights of katanin p80, p60, and GAPDH, and then incubated with the corresponding antibodies. (Therefore, GAPDH in A and B were identical). (C) Statistical analysis showed that the overexpression of katanin p60 enhanced katanin p80 expression. Data were analyzed from 3 independent transfection experiments. *Statistical significance was set at* $P \leq .05$.

Table 1

Association between the clinicopathological characteristics and expression of katanin p60 and p80 in PTC.

	N	Katanin p60 (%)*	P	Katanin p80 (%)*	P
Sex			.302		.966
Male	31	81.14 ± 10.90		61.78 ± 25.64	
Female	56	78.47 ± 11.81		61.54 ± 24.08	
Age, y			.344		.572
<55	60	78.63 ± 11.90		60.62 ± 25.87	
≥55	27	81.17 ± 10.57		63.86 ± 21.43	
Clinical Stage			.449		.497
I	74	79.02 ± 11.75		60.87 ± 24.62	
II/III†	13	81.66 ± 10.08		65.91 ± 24.32	

PTC = papillary thyroid carcinoma.

* Data were expressed as mean ± SD, analyzed by unpaired *t* test.

† Twelve cases in clinical stage II and 1 case in clinical stage III.

cancer tissues, but also play a role in the proliferation, migration, and metastasis of cancer cells, and are related to the prognosis of cancer patients. Importantly, it has recently been reported that compared with adjacent PTC tissues, katanin p60 and 80 are highly expressed in tumor tissues and both were associated with lymph node metastasis.[27] However, in our study, although the expression of katanin p60 and p80 was found in PTC, not in NG, we only found a significant association between katanin p60 expression and lymph node metastasis in PTC, and this may be due in part to the benign nature of PTC relative to cancers of the prostate, breast, and NSCLC, or a fairly limited number of patients with PTC or 2 subtypes of PTC in our study.

In addition, we found that katanin subunit p60 was highly expressed in both variants of PTC, whereas katanin subunit p80 was highly expressed in CPTC and moderately expressed in FVPTC, which warrants further investigation.

Several studies have shown increased katanin p60 or p80 expression in breast, prostate, and NSCLC tissues separately,[21–26] but the relationship between katanin p60 and p80 expression in these cancers has not been reported. In this study, we also found that katanin p60 levels were positively correlated with katanin p80 levels in PTC, including CPTC and FVPTC, which is consistent with a recently reported study.[27] To further confirm this, we overexpressed katanin p60 in human papillary thyroid carcinoma KTC-1 cells and found that overexpression of katanin p60 significantly increased katanin p80 expression. As a regulatory subunit, katanin p80 positively regulates the activity of katanin p60. This indicates that there may be a positive feedback loop between katanin p60 and p80, which is intriguing and requires further study. This finding is partially consistent with a previous report that katanin p80 enhances katanin p60 severing activity.[13] Future work will aim to prove whether katanin p60 can increase katanin p80 expression or activity.

Cancer usually occurs in older populations, but our study suggests that the expression of katanin p60 and p80 is independent of age. Thyroid cancer is more common in women than in men; therefore, we analyzed whether sex affects the expression of katanin p60 and p80 in PTC. However, the results of the present study did not show a sex-specific difference in the expression of katanin p60 and p80, consistent with a recent report in PTC.[27] Furthermore, we did not find that katanin p60 and p80 expression was associated with clinical stages in patients with PTC, although a slight increase in expression was found in clinical stage II/III compared with clinical stage I. A large number of patients are needed for further study in the future.

Using ROC analysis, we found that the cutoff values of katanin p60 and p80 were 22.43% and 0.83%, respectively, for PTC, with a sensitivity of 100% and specificity of 100%. These findings further support the use of katanin p60 and p80 as potential biomarkers for PTC to distinguish NG.

In conclusion, our findings indicated that katanin subunits p60 and p80 were expressed in PTC (including CPTC and FVPTC), but not in NG. High expression of katanin p60 was significantly associated with lymph node metastasis. Compared with FVPTC, the level of katanin p80 rather than p60 was increased in CPTC, although they were both expressed in these two variants of PTC. The level of katanin p60 was significantly correlated with the level of katanin p80 in PTC. These results suggest that katanin subunits p60 and p80 can be used as potential PTC biomarkers to distinguish NG and may be novel therapeutic targets for PTC.

Acknowledgments

The authors thank Dr. Fengjie Qi for confirmation of the pathological diagnosis of the patients.

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Funding acquisition: Wei Liu.
Investigation: Miao Guo, Zhangming Wu.
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Software: Yanjie Xiao, Miao Guo.
Supervision: Wei Liu.
Validation: Jing Yang, Miao Guo, Yanjie Xiao, Zhangming Wu.
Visualization: Miao Guo, Zhangming Wu.
Writing – original draft: Zhangming Wu.
Writing – review & editing: Miao Guo, Wei Liu, Zhangming Wu.

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