OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Underexpression of INPPL1 is associated with aggressive clinicopathologic characteristics in papillary thyroid carcinoma

This article was published in the following Dove Press journal:
OncoTargets and Therapy

Yi-Li Zhou[1,*]
Chen Zheng[1,*]
Yi-Tong Chen[2]
Xue-Min Chen[1]

[1]Department of Thyroid and Breast Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China; [2]Department of Clinical Medicine, Tai Zhou University Medical School, Taizhou, Zhejiang, China

*These authors contributed equally to this work

Purpose: To study the relationship between *INPPL1* gene and clinicopathologic characteristics of papillary thyroid carcinoma (PTC).

Patients and methods: INPPL1 expression in PTCs was tested by quantitative real-time reverse transcription PCR. The Cancer Genome Atlas (TCGA) RNA-seq data and our mRNA data were used to analyze and reveal the relationship between INPPL1 and aggressive clinicopathologic characteristics of PTC.

Results: When compared to normal thyroid tissues, INPPL1 was significantly downregulated in PTC tissues, as revealed by our data and TCGA data. INPPL1 underexpression was remarkably related to aggressive clinicopathologic characteristics such as lymph node metastasis (LNM), histological type, tumor size, mulitifocality, and disease stage in TCGA data. Meanwhile, LNM was confirmed to be associated with underexpression of INPPL1 in our data. In addition, logistic analysis clearly showed that underexpression of INPPL1 was an independent factor for LNM in PTC.

Conclusion: INPPL1 may be a novel tumor suppressor gene in PTC, which was significantly correlated with aggressive clinicopathologic characteristics, especially LNM.

Keywords: papillary thyroid carcinoma, INPPL1 expression, lymph node metastasis, The Cancer Genome Atlas

Introduction

Thyroid cancer is the most common malignant tumor in the endocrine system and among the neck tumors, whose incidence is increasing globally in recent years. In the USA, ~56,870 new cases were estimated in 2017.[1] The prognosis of most thyroid cancer patients is good,[2] especially in those with papillary thyroid carcinoma (PTC) which is the most common type of thyroid cancer and accounts for ~80% of all thyroid cancer cases.[3] However, PTC is highly metastatic and recurrent after routine treatment, and some patients of PTC have poor prognosis such as disease recurrence and even death.[4] Certain clinical and pathological characteristics such as advanced disease stages, extrathyroidal extension, and lymph node metastasis (LNM) have been associated with a poor prognosis of this disease.[5] LNM is a major factor for recurrence and mortality,[6–8] whose incidence ranges from 20% to 50%[9,10] and which leads to recurrence and secondary surgery.[11–13] The occurrence and development of thyroid carcinoma are mainly affected by genomic variation, including activation of oncogene and silencing of tumor suppressor gene. It has been proved that *BRAF* mutation promotes the occurrence and development of thyroid carcinoma by abnormal activation of MAPK pathway,[14] and that the mutation of TERT promoter[15] and PIK 3CA gene[16] also

Correspondence: Xue-Min Chen
Department of Thyroid and Breast Surgery, The First Affiliated Hospital of Wenzhou Medical University, Nan Bai Xiang Street, Ouhai District, Wenzhou City, Zhejiang Province 325000, China
Tel +86 577 5557 9463
Fax +86 577 5557 9463
Email tgtx2018@163.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OTT.S185803

plays an important role. Although great progress has been made in gene research, the pathogenesis and many features of thyroid cancer are still unknown. Therefore, searching for new potential molecular markers and elucidating their molecular mechanisms in the development of thyroid cancer become necessary.

Inositol phosphatase 1 (INPPL1), which is located on chromosome 11, encodes an SH2-containing 5′-inositol phosphatase (SHIP2), a member of the inositol 5-phosphatase family, which is involved in the regulation of insulin function. SHIP2 also plays a role in the regulation of EGFR turnover and actin remodeling.[17,18] SHIP2 dephosphorylates 5-phosphate of phosphatidylinositol-3,4,5-trisphosphate and plays important roles in regulating the PI3K/Akt pathway in physiology and disease. SHIP2 is widely expressed in human type II diabetes mellitus and multiple dysplasia, but its role in human cancer remains unclear. In recent years, it has been reported that SHIP2 has both tumor-promoting and antitumor functions in human tumors, which largely depend on the cell model.[19] In the glioblastoma cell line 1321 N1, which does not express PTEN, downregulation of SHIP2 expression promotes cell proliferation by reducing the expression of key regulatory proteins (such as p27) in cell cycle and is involved in the migration by controlling phosphatidylinositol 4,5-bisphosphate in the cell membrane.[19,20] SHIP2 is frequently downregulated in gastric cancer, and its underexpression promotes the development and proliferation of gastric cancer by activating PI3K/AKT signal.[21] However, high expression of SHIP2 was found in breast cancer, hepatocellular carcinoma, non-small cell lung cancer, and colorectal cancer, which was associated with poor survival.[22–26] It can be seen that *INPPL1* gene plays different roles in different tumors. The expression and role of *INPPL1* gene in thyroid carcinoma have not been reported. It is important to study the expression and biological function of human *INPPL1* gene in thyroid carcinoma to understand the occurrence and development of thyroid carcinoma.

As next generation sequence has developed, our previous study performed whole transcriptome sequencing of 19 pairs of primary thyroid cancer samples with matched adjacent normal thyroid tissues.[27] The present study found by application of bioinformatics that human INPPL1 expression is significantly downregulated in PTC tumors. Thus, we confirm this finding using quantitative real-time reverse transcription PCR (qRT-PCR) in 49 PTC samples. Also, we investigate the relationship between INPPL1 expression and the clinicopathologic characteristics in PTC using The Cancer Genome Atlas (TCGA) data and our data. Furthermore, the relationship between INPPL1 expression and LNM in PTC was assessed using logistic regression analysis. The role of *INPPL1* gene in PTC has been discussed in this study.

Patients and methods

Patients and samples

Fresh paired samples including PTC tissues and noncancerous tissues from 49 PTC patients were collected. The samples after resection were immediately snap-frozen in liquid nitrogen and subsequently stored at −80°C before RNA extraction. Final histological diagnosis of all the samples was confirmed as PTC by two pathologists. The study was conducted with the approval of Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University and the written informed consent was received from the patients.

RNA extraction and qRT-PCR

Total RNA was extracted from 49 paired samples using TRIzol reagent according to the manufacturer's protocol (Thermo Fisher Scientific), and the ReverTra Ace qPCR RT Kit (Toyobo) was used for cDNA. qRT-PCR was conducted by Thunderbird SYBR qPCR Mix (Toyobo) on the Roche 480 System (Hoffman-La Roche Ltd). Each sample was in triplicate. GAPDH was used as an internal control. The primer sequences for INPPL1 were as follows: INPPL1, 5′-AGCTGCCCACGCTCAAACCAA-3′ (forward) and 5′-AGGTCAGGAACTGTTGGGCCGT-3′ (reverse).

TCGA data

Thyroid cancer RNA-seq data and corresponding clinical information were downloaded from the TCGA database. INPPL1 expression data were available for 502 PTC cancer samples compared with 59 normal thyroid samples.

Statistical analysis

The normally distributed data were expressed as mean±SD and were evaluated by Student's *t*-test. Categorical variables were expressed as percentage and evaluated by chi-squared test. Logistic regression analysis was conducted to estimate the ORs of certain factors. Variables with $P<0.05$ in the univariate analysis were used in a multivariate analysis. All *P*-values were two sided, and *P*-value <0.05 was considered statistically significant with SPSS. GraphPad Prism Version 6.0 was used for the graphs.

Results

INPPL1 was underexpressed in PTC

Completing the whole transcriptome sequencing of 19 pairs of tumor and paracancerous normal tissues, we found that the expression of INPPL1 in PTC tumor tissues was significantly

Table 1 The expression of *INPPL1* gene in 19 cases of thyroid papillary carcinoma was lower than that in normal tissue by whole transcriptome sequencing

Symbol	RN-expression	RT expression	RN-RPKM	RT-RPKM	Log 2 ratio (RT/RN)	RT/RN
INPPL1	9,498	6,579	26.45727493	17.26643462	−0.615694265	Down
INPPL1	9,083	6,947	24.18663979	18.31254483	−0.401378061	Down
INPPL1	8,497	5,304	24.11030944	14.9136903	−0.693012879	Down
INPPL1	8,569	7,289	23.73650279	20.58616639	−0.205432199	Down
INPPL1	9,071	7,708	25.21148231	22.24832513	−0.180384211	Down
INPPL1	8,736	8,875	23.48319905	23.3467461	−0.008407464	Down
INPPL1	7,079	6,931	23.26834024	22.65707737	−0.038406531	Down
INPPL1	8,540	6,845	24.93012891	20.3880479	−0.290166695	Down
INPPL1	6,862	6,835	19.2547644	18.12412532	−0.087304099	Down
INPPL1	9,074	6,918	25.45064311	18.34956031	−0.471956619	Down
INPPL1	7,478	6,751	23.9880202	19.29510062	−0.314079525	Down
INPPL1	7,166	6,814	20.07660032	19.02243492	−0.077813064	Down
INPPL1	8,238	6,335	22.03098223	17.69479112	−0.316209086	Down
INPPL1	8,637	7,134	24.01109214	18.90534645	−0.344906738	Down
INPPL1	7,942	7,367	21.97389029	19.46403282	−0.174979651	Down
INPPL1	6,950	5,236	21.08686125	13.68272636	−0.623988643	Down
INPPL1	7,258	5,661	19.9869818	15.20636245	−0.394385545	Down
INPPL1	8,932	5,158	24.09809707	13.90536501	−0.793277611	Down
INPPL1	6,305	4,834	17.92797644	13.42953472	−0.416803336	Down

Abbreviations: RN, RNA normal tissues; RT, RNA tumor tissues; RPKM, Reads Per Kilobase Million.

lower than that in paracancerous normal tissues (Table 1). In order to validate the data of whole transcriptome resequencing, we began to assess INPPL1 mRNA expression in 49 samples of PTC tissues and noncancerous samples by qRT-PCR. As shown in Figure 1, INPPL1 mRNA expression was remarkably downregulated in tumors against that in the adjacent noncancerous tissues ($P<0.001$). The same trend was further validated in the TCGA cohort, which included 502 PTC samples and 59 normal thyroid tissues. Accordingly, INPPL1 mRNA expression was significantly lower in PTC tissues than that in normal tissues ($P<0.001$; Figure 2). These results revealed that *INPPL1* gene may be a potential tumor suppressor gene in PTC patients.

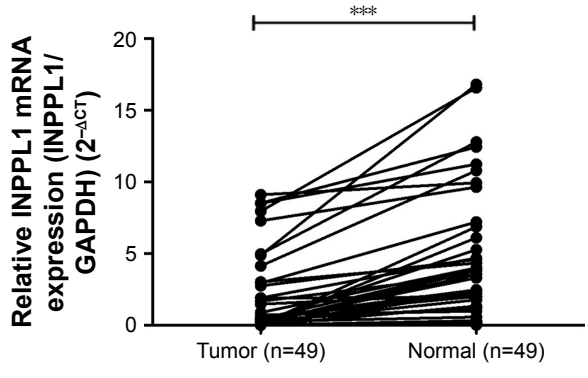

Figure 1 The mRNA expression of INPPL1 in our local cohort (n=49).
Note: INPPL1 expression was found to be significantly downregulated in PTC tissues compared with the adjacent noncancerous thyroid tissues on qRT-PCR analysis (***$P<0.001$).
Abbreviations: CT, cycle threshold; PTC, papillary thyroid carcinoma; qRT-PCR, quantitative real-time reverse transcriptase PCR.

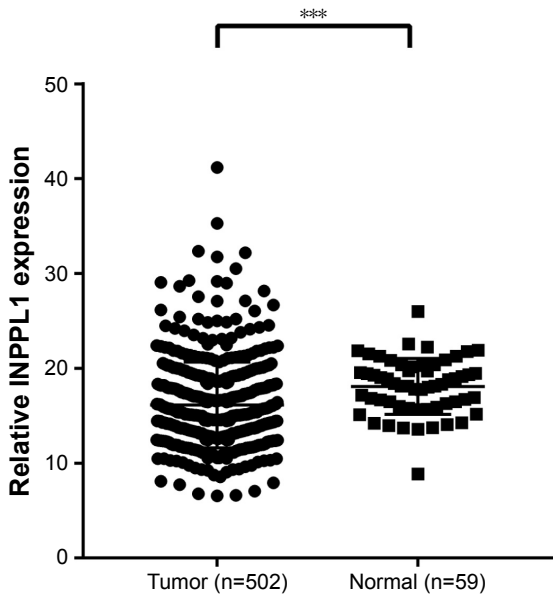

Figure 2 The mRNA expression of INPPL1 in TCGA cohort, including 502 PTC samples and 59 noncancerous thyroid samples.
Note: INPPL1 expression was significantly downregulated in PTC in the TCGA cohort (***$P<0.001$).
Abbreviations: PTC, papillary carcinoma; TCGA, The Cancer Genome Atlas.

Relationship between INPPL1 expression and clinicopathologic characteristics in PTC

In order to explore whether low INPPL1 expression was associated with tumorigenesis and progression of PTC, we studied the relationship of INPPL1 with clinicopathologic characteristics. We divided the 502 PTC patients into low INPPL1 expression group (n=252) and high INPPL1 expression (n=250) group on the basis of the median value according to the INPPL1 expression level in the TCGA cohort. Results showed that INPPL1 underexpression was related to histological type (P=0.001), tumor size (P=0.046), clinical stage (P=0.007), LNM (P=0.001), and multifocality (P=0.019), as shown in Table 2. However, age, gender, and distant metastasis were not found to have significant associations with INPPL1 expression ($P \geq 0.05$). At the same time, the results of our validation cohort were consistent with the TCGA finding that low INPPL1 expression corresponded to more LNM (P=0.038; Table 3). These findings supported *INPPL1* gene as a tumor suppressor gene associated with PTC.

Table 2 The relationship between INPPL1 expression and clinicopathologic features in the TCGA cohort

Clinicopathologic features	Low expression (n=252)	High expression (n=250)	*P*-value
Age (years)			
Mean±SD	47.49±15.35	47.19±16.33	0.210
<45	112	114	0.795
≥45	140	136	
Gender			0.245
Male	62	73	
Female	190	177	
Tumor size (mm)			0.046*
≥20	190	167	
<20	62	81	
Disease stage			0.007*
I–II	153	180	
III–IV	98	69	
Node metastasis			0.001*
Yes	145	78	
No	91	138	
Multifocality			0.019*
Yes	126	100	
No	120	146	
Distant metastasis			0.195
Yes	10	5	
No	242	245	
Histological type			0.001*
Classical	196	160	
Other types	56	90	

Note: *P<0.05.
Abbreviation: TCGA, The Cancer Genome Atlas.

Table 3 The relationship between INPPL1 expression and clinicopathologic features in our cohort

Clinicopathologic features	Low expression (n=24)	High expression (n=25)	*P*-value
Age (years)			
Mean±SD	47.6±9.0	46.6±10.7	0.730
<45	8	10	0.628
≥45	16	15	
Gender			0.084
Male	5	11	
Female	19	14	
Tumor size (mm)			0.560
≥20	5	7	
<20	19	18	
Disease stage			0.321
I–II	11	15	
III–IV	13	10	
Node metastasis			0.038*
Yes	20	14	
No	4	11	
Multifocality			0.162
Yes	6	11	
No	18	14	

Note: *P<0.05.

INPPL1 underexpression was an independent indicator for LNM in PTC

Further study was conducted to find the relationship of INPPL1 expression with LNM. Univariate logistic regression analysis in TCGA data revealed that the relative variables for LNM were histological type (OR=2.383, 95% CI=1.544–3.680, P<0.001), age (OR=0.62, 95% CI=0.427–0.899, P=0.012), gender (OR=1.551, 95% CI=1.022–2.353, P=0.039), tumor size (OR=2.525, 95% CI=1.652–3.858, P<0.001), and INPPL1 expression (OR=0.335, 95% CI=0.242–0.520, P<0.001), as shown in Table 4. Multivariate logistic regression analysis in TCGA data also revealed that histological subtype (OR=2.281, 95% CI=1.440–3.613, P<0.001), age (OR=0.577, 95% CI=0.385–0.865, P=0.008), gender (OR=1.549, 95% CI=1.010–2.509, P=0.045), tumor size (OR=2.44, 95% CI=1.555–3.830, P<0.001), and INPPL1 expression (OR=0.360, 95% CI=0.241–0.540, P<0.001) were independent indicators for LNM (Table 5). Meanwhile, multivariate logistic regression analysis from our

Table 4 Univariate logistic regression analysis for the risk of lymph node metastasis in TCGA cohort

Factors	OR	95% CI	*P*-value
INPPL1 expression (high vs low)	0.335	0.242–0.520	<0.001
Histological type	2.383	1.544–3.680	<0.001
Age, years (≤45 vs >45)	0.62	0.427–0.899	0.012
Gender (male vs female)	1.551	1.022–2.353	0.039
Tumor size (mm)	2.525	1.652–3.858	<0.001
Multifocality	1.446	0.994–2.103	0.054

Abbreviation: TCGA, The Cancer Genome Atlas.

validation cohort also suggested that low INPPL1 expression aggravated the LNM risk of PTC patients (OR=0.156, 95% CI=0.033–0.742, *P*=0.020; Table 6), which was consistent with the TCGA findings. In general, INPPL1 underexpression can indicate the high risk of LNM independently in PTC.

Discussion

PTC is the most common endocrine malignant tumor, and its incidence is increasing year by year.[1] Although the prognosis of most thyroid cancer patients is favorable,[2] some PTCs are characterized by capsular invasion and lymph node (the incidence being 20%–50%[9,10]) and distant metastasis, which lead to the possibility of disease recurrence and secondary surgery.[11–13] PTCs show different biological behaviors during tumorigenesis due to genomic variations. It is insufficient to make individualized treatment strategies and assess the risk of each PTC patient based only on the current clinical and pathological parameters. Finding new molecular biomarkers to predict the clinical progress and metastasis of PTCs is urgent. So far, indicators to assess the status of LNM are still lacking.

High-throughput sequencing of variable gene variations has been widely used in the study of molecular mechanism of cancer. In our study, transcriptome sequencing was performed in 19 pairs of PTC tumors and adjacent normal tissues, and the results showed that the expression of INPPL1 in PTC tumor tissues was lower than that in adjacent normal thyroid tissues. This finding might suggest its possible role as a tumor suppressor in thyroid cancer.

Table 5 Multivariate logistic regression analysis for the risk of lymph node metastasis in TCGA cohort

Factors	OR	95% CI	*P*-value
INPPL1 expression (high vs low)	0.360	0.241–0.540	<0.001
Histological type	2.281	1.440–3.613	<0.001
Age, years (≤45 vs >45)	0.577	0.385–0.865	0.008
Gender (male vs female)	1.549	1.010–2.509	0.045
Tumor size (mm)	2.44	1.555–3.830	<0.001

Abbreviation: TCGA, The Cancer Genome Atlas.

Table 6 Multivariate logistic regression analysis for the risk of lymph node metastasis in our cohort

Factors	OR	95% CI	*P*-value
INPPL1 expression (high vs low)	0.156	0.033–0.742	0.020
Age, years (≤45 vs >45)	1.323	0.320–5.478	0.699
Gender (male vs female)	1.573	0.341–7.246	0.561
Tumor size (mm)	1.184	0.215–6.525	0.846
Multifocality	4.351	0.790–23.967	0.091

INPPL1 encodes SHIP2, which is involved in the regulation of insulin function, EGFR turnover, and actin remodeling.[17,18] INPPL1 may be a promising therapeutic target for not only type 2 diabetes, but also cancer, neurodegenerative diseases, and atherosclerosis.[28] Among cancers, high expression of INPPL1 was found in breast cancer, hepatocellular carcinoma, non-small cell lung cancer, and colorectal cancer, where it is associated with poor survival.[22-26] INPPL1 supports the metastatic growth in breast cancer and it is a valuable biomarker for breast cancer. By interacting with c-CBL, INPPL1 can prevent the conversion of EGFR and enhance the Akt activation induced by EGF, thus promoting the proliferation and metastasis of breast cancer cells.[22,29] In ER-negative breast cancer stem cells, INPPL1 activates Akt and JNK and upregulates epithelial mesenchymal transition markers and vimentin.[30] INPPL1 expression contributes to the malignant potential of colorectal cancer by enhancing chemoresistance, cell migration, and cell invasion.[31] However, overexpression of INPPL1 in glioblastoma cells inhibits Akt activation and leads to cell cycle arrest and migration.[19,20] INPPL1 is often downregulated in gastric cancer, and the decreased INPPL1 expression promotes the development and proliferation of gastric cancer by activating PI3K/AKT signal.[21] It can be seen that INPPL1 plays different roles in different tumors.

In this study, we first reported the underexpression of INPPL1 in PTC and it was associated with aggressive clinicopathologic characteristics, especially LNM. INPPL1 mRNA expression detected by qRT-PCR was remarkably downregulated in PTC tissues against that in noncancerous tissues. This result was consistent with our finding of whole transcriptome sequencing. TCGA cohort analysis also confirmed this finding, which is similar to the expression of INPPL1 in gastric cancer.[21] Clinicopathologic feature analysis in TCGA cohort showed that underexpression of NINPPL1 was remarkably related to aggressive clinicopathologic characteristics,

including tumor size, multifocality, advanced disease stage, and LNM. In our cohort, LNM was confirmed to be associated with the underexpression of INPPL1, which was consistent with TCGA data. Other features have not shown statistical correlation, which may be due to the limited number of cases. Moreover, logistic regression analysis indicated that the underexpression of INPPL1 was an independent factor for LNM in PTCs. This seems to suggest that the *INPPL1* gene may inhibit the migration of thyroid cancer, as it does in glioblastoma.[20] All these findings support INPPL1 as a tumor suppressor gene associated with PTC and further study must to be conducted.

Our study still contains certain limitations. First, the cellular molecular mechanisms of INPPL1 in the progression of PTC need to be further investigated. Furthermore, the relationship between INPPL1 and prognosis of PTC in large samples needs to be studied.

Conclusion

INPPL1 was generally underexpressed in PTC. Low INPPL1 expression indicates high risk of LNM in PTC. INPPL1 may be a potential tumor suppressor gene in PTC, and it is worth studying further.

Acknowledgment

The Major Science and Technology Projects of Zhejiang Province (2015C03052) supported this work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7–30.
2. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab*. 2005;90(10):5723–5729.
3. Morris LG, Tuttle RM, Davies L. Changing trends in the incidence of thyroid cancer in the United States. *JAMA Otolaryngol Head Neck Surg*. 2016;142(7):709–711.
4. Burns WR, Zeiger MA. Differentiated thyroid cancer. *Semin Oncol*. 2010;37(6):557–566.
5. Ito Y, Miyauchi A. Prognostic factors and therapeutic strategies for differentiated carcinomas of the thyroid. *Endocr J*. 2009;56(2):177–192.
6. Kim SK, Kwon AY, Back K, et al. Predictive factors of lymph node metastasis in follicular variant of papillary thyroid carcinoma. *Ann Surg Oncol*. 2017;24(9):2617–2623.
7. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case–control study. *Cancer*. 2006;106(3):524–531.
8. Zidan J, Karen D, Stein M, et al. Pure versus follicular variant of papillary thyroid carcinoma: clinical features, prognostic factors, treatment, and survival. *Cancer*. 2003;97(5):1181–1185.
9. Mustafa M, Kuwert T, Weber K, et al. Regional lymph node involvement in T1 papillary thyroid carcinoma: a bicentric prospective SPECT/CT study. *Eur J Nucl Med Mol Imaging*. 2010;37(8):1462–1466.
10. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. *CA Cancer J Clin*. 2013;63(6):373–394.
11. Lee YC, Na SY, Park GC, et al. Occult lymph node metastasis and risk of regional recurrence in papillary thyroid cancer after bilateral prophylactic central neck dissection: a multi-institutional study. *Surgery*. 2017;161(2):465–471.
12. Lee YM, Sung TY, Kim WB, et al. Risk factors for recurrence in patients with papillary thyroid carcinoma undergoing modified radical neck dissection. *Br J Surg*. 2016;103(8):1020–1025.
13. Liu FH, Kuo SF, Hsueh C, Chao TC, Lin JD. Postoperative recurrence of papillary thyroid carcinoma with lymph node metastasis. *J Surg Oncol*. 2015;112(2):149–154.
14. Xing M. BRAF mutation in thyroid cancer. *Endocr Relat Cancer*. 2005;12(2):245–262.
15. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol*. 2014;32(25):2718–2726.
16. Hou P, Liu D, Shan Y, Liu Z, et al. Genetic alterations and their relationship in the phosphatidylinositol 3-kinase/Akt pathway in thyroid cancer. *Clin Cancer Res*. 2007;13(4):1161–1170.
17. Backers K, Blero D, Paternotte N, Zhang J, Erneux C. The termination of PI3K signalling by SHIP1 and SHIP2 inositol 5-phosphatases. *Adv Enzyme Regul*. 2003;43:15–28.
18. Raaijmakers JH, Deneubourg L, Rehmann H, et al. The PI3K effector Arap3 interacts with the PI(3,4,5)P3 phosphatase SHIP2 in a SAM domain-dependent manner. *Cell Signal*. 2007;19(6):1249–1257.
19. Elong Edimo W, Schurmans S, Roger PP, Erneux C. SHIP2 signaling in normal and pathological situations: its impact on cell proliferation. *Adv Biol Regul*. 2014;54:142–151.
20. Elong Edimo W, Ghosh S, Derua R, et al. SHIP2 controls plasma membrane PI(4,5)P2 thereby participating in the control of cell migration in 1321 N1 glioblastoma cells. *J Cell Sci*. 2016;129(6):1101–1114.
21. Ye Y, Ge YM, Xiao MM, et al. Suppression of SHIP2 contributes to tumorigenesis and proliferation of gastric cancer cells via activation of Akt. *J Gastroenterol*. 2016;51(3):230–240.
22. Prasad NK, Tandon M, Badve S, Snyder PW, Nakshatri H. Phosphoinositol phosphatase SHIP2 promotes cancer development and metastasis coupled with alterations in EGF receptor turnover. *Carcinogenesis*. 2008;29(1):25–34.
23. Fu M, Fan W, Pu X, et al. Elevated expression of SHIP2 correlates with poor prognosis in non-small cell lung cancer. *Int J Clin Exp Pathol*. 2013;6(10):2185–2191.
24. Fu M, Gu X, Ni H, et al. High expression of inositol polyphosphate phosphatase-like 1 associates with unfavorable survival in hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2013;6(11):2515–2522.
25. Prasad NK, Tandon M, Handa A, et al. High expression of obesity-linked phosphatase SHIP2 in invasive breast cancer correlates with reduced disease-free survival. *Tumour Biol*. 2008;29(5):330–341.
26. Yang J, Fu M, Ding Y, et al. High SHIP2 expression indicates poor survival in colorectal cancer. *Dis Markers*. 2014;2014:218968–7.
27. Wang QX, Chen ED, Cai YF, et al. A panel of four genes accurately differentiates benign from malignant thyroid nodules. *J Exp Clin Cancer Res*. 2016;35(1):169.
28. Suwa A, Kurama T, Shimokawa T. SHIP2 and its involvement in various diseases. *Expert Opin Ther Targets*. 2010;14(7):727–737.
29. Prasad NK. SHIP2 phosphoinositol phosphatase positively regulates EGFR-Akt pathway, CXCR4 expression, and cell migration in MDA-MB-231 breast cancer cells. *Int J Oncol*. 2009;34(1):97–105.
30. Fu CH, Lin RJ, Yu J, et al. A novel oncogenic role of inositol phosphatase SHIP2 in ER-negative breast cancer stem cells: involvement of JNK/vimentin activation. *Stem Cells*. 2014;32(8):2048–2060.
31. Hoekstra E, das AM, Willemsen M, et al. Lipid phosphatase SHIP2 functions as oncogene in colorectal cancer by regulating PKB activation. *Oncotarget*. 2016;7(45):73525–73540.