Prognostic role of TAB3 and PIM1 protein expression in Papillary Thyroid Carcinoma

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Abstract

Background: Papillary thyroid carcinoma (PTC) is one of the most prevalent endocrine malignancies, with complex pathogenesis. Transforming growth factor-β-activated kinase 1 (TAK1)-binding protein 3 (TAB3) is implicated in cell division and metastasis. The proviral integration site for Moloney murine leukemia virus 1 (PIM1) is a key player in carcinogenesis and overexpressed in cancer tissues. However, to our knowledge no previous study assessed the role of TAB3 in PTC and only few studies assessed the role of PIM1 in PTC pathogenesis.

Objectives: The current research aimed to assess the protein expression of TAB3 and PIM1 in PTC specimens compared to the adjacent non-neoplastic thyroid tissues and to assess the correlation between their expression and the clinic-pathologic features of PTC. Then, to assess the correlation between TAB3 and PIM1 expression in PTC.

Patients and methods: TAB3 and PIM1 expression were immunohistochemically examined in fifty specimens of PTC and their adjacent non-neoplastic thyroid tissues.

Results: TAB3 and PIM1 were significantly overexpressed in PTC than in adjacent non-neoplastic tissues (p value < 0.001, each). TAB3 expression was significantly higher in older age and higher clinical stage (p= 0.003 and 0.028 respectively). A significant higher PIM1 expression was detected in PTC specimens with extrathyroidal extension (p=0.047). A significant positive correlation between TAB3 and PIM1 in PTC was detected (p=0.036).

Conclusion: The current results suggested that TAB3 and PIM1 may contribute to PTC pathogenesis and progression and may be suggested to have a promising therapeutic role.

Keywords: Papillary thyroid carcinoma; TAB3; PIM1; Immunohistochemistry.
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Introduction

Papillary carcinoma of the thyroid gland is the most frequent thyroid gland malignancy, constituting about 85% of all thyroid cancer cases and its prevalence has increased worldwide due to improved screening **(Dong et al., 2023).**

Despite PTC having an overall favorable prognosis with an expected indolent behavior, lymph node metastases exist in approximately fifty to sixty percent of cases and is widely considered one of the most significant risk factors for distant metastasis and poor prognosis (**Wang et al., 2024).** Consequently, discovering new biomarkers that can predict patients' prognosis and potentially act as therapeutic targets for such carcinoma is crucial.

Transforming growth factor-β-activated kinase 1-binding protein 3 (TAB3) is a TAK1 binding partner which implicated in inflammation, signal transduction, immunological response and tumor development. Furthermore, TAB3 contributes to cellular proliferation including cancer cells (**Xu and Lei, 2021**). TAB3 has been implicated in cancer development and has been overexpressed in different carcinomas such as hepatocellular carcinoma, small intestinal cancer, and non-small cell lung cancer (**Li et al., 2020)**. However, its role in PTC has not been previously investigated.

The proviral integration site for Moloney murine leukaemia virus 1 (PIM1) is a serine/threonine kinase that is essential for cell division and mitosis (**Guo et al., 2010)**. It has a crucial role in the development of several types of cancers (**Mahata et al., 2022)**. A negative correlation was reported between PIM1 expression and the prognosis of different tumors such as non-small cell lung cancer, gallbladder cancer, leukemia, lymphoma, colorectal carcinoma, and osteosarcoma **(Lai et al., 2022).**

Positive correlation between`TAB3 and PIM1 proteins has been previously reported in colorectal cancer (**Li et al., 2020)**. However, their correlation has not been explored in PTC.

The current research aimed to assess the immunohistochemical expression (IHC) of TAB3 and PIM1 in PTC specimens compared to the adjacent non-neoplastic thyroid tissues and to assess the correlation between their expression and the clinicopathologic features of PTC. Then, to assess the correlation between TAB3 and PIM1 expression in PTC.

Patients and methods

Ethical approval for this study was obtained by the Ethical Committee of the Faculty of Medicine, South Valley University (SVU-MED-PAT005-2-21-11-277).

Tissue specimens

The present study was applied to formalin-fixed paraffin-embedded blocks of fifty specimens of PTC and their adjacent non-neoplastic thyroid tissues. The blocks were retrieved from the pathology laboratory, at Qena University Hospital, South Valley University. Cases that received preoperative chemotherapy or radiotherapy were excluded. The clinicopathological data collected from archival reports included age, sex, tumor size, and site. Tumors were re-evaluated for the following parameters: histopathological subtypes, presence and absence of extra-thyroidal extension and tumor stage according to the American Joint

Committee on Cancer, 8th Edition (**Amin et al., 2017**),

Immunohistochemical staining

Formalin-fixed paraffin embedded tissue blocks were sectioned at 4-micron thickness. Immunohistochemistry was performed using a Dako Omnis Automated slide stainer. Sections had been incubated with primary antibodies against: TAB3 (Rabbit pAb: 1:100 dilution, clone (4EB5), Woburn, Massachusetts, USA) and PIM1 (Rabbit pAb: 1:100 dilution, clone (ARC0175), Woburn, Massachusetts, USA).

Appropriate positive and negative controls were involved in the staining procedure.

Evaluation of TAB3 and PIM1 IHC staining

Cytoplasmic staining for TAB3 (**Zhao et al., 2018)**, and nuclear PIM1 staining were considered positive (**Wen et al., 2021).**

Both proteins were assessed using a semiquantitative score in which staining intensity were graded as (0= no staining; 1= Weak staining; 2= Moderate staining, and 3= Strong staining). Then, the extent of staining of tumor cells was scored as (0= negative; 1= 1–25% positive cells; 2= 26–50% positive cells; 3= 51–75% positive cells, and 4= 76–100% positive cells). The ultimate score, which varies from 0 to 12, is obtained by multiplying the staining intensity by the extent of staining (**Zhao et al., 2018 ; Wen et al., 2021)**.

Statistical Analysis

All analyses were performed using SPSS version 27. The nonparametric Kruskal–Wallis and Mann–Whitney were used as appropriate.

Spearman correlation coefficient was applied to examine the correlation between TAB3 and PIM1 expression in PTC. *p* values < 0.05 were considered statistically significant.

Results

Clinicopathological features of the studied cases:

Most of the PTC patients were females (80%) and about 66% of patients were > 45 years. Regarding tumor size, about 82% of PTCs were more than 1 cm. The adjacent non-neoplastic thyroid tissue showed Hashimoto thyroiditis in 36% of cases and colloid goiter in the remaining cases. 46 of the cases were diagnosed as classical PTC while the remaining 4 cases diagnosed as follicular subtype. The clinicopathological features of the studied cases are summarized in **(Table.1)**.

TAB3 IHC Expression

Positive cytoplasmic TAB3 expression was detected in 44 (88%) and 23 (46%) in PTC and peritumoral tissue respectively **(Fig. 1)**.

The median expression of TAB3 in PTC was 5 (6) which was significantly higher than its expression in peritumoral tissue 0 (1) (*p* value < 0.001).

PIM1 IHC expression

Positive nuclear PIM1 expression was detected in 47 (94%) and 29 (58%) in PTC and peritumoral tissue respectively **(Fig.2)**. Its median expression in PTC was 9 (10.25) which was significantly higher than its expression in peritumoral tissue 1 (6).(*p* value < 0.001).

Table 1. Clinicopathological features of papillary thyroid carcinoma patients (N=50)

Parameters		Frequency	Percentage (%)
Age	≤45 Year	33	66%
	>45Year	17	34%
Gender	Male	10	20%
	Female	40	80%
Tumor site	Right	25	50%
	Left	7	14%
	Both	4	8%
	Isthmus	6	12%
	Right+ isthmus	6	12%
	Left+ isthmus	2	4%
Tumor size (cm)	≤1	9	18%
	>1	41	82%
Locality	Unifocal	32	64%
	Multifocal	18	36%
Extrathyroidal extension	Present	8	16%
	Absent	42	84%
Lymph node metastasis	Present	18	36%
	Absent	32	64%
Clinical stage	Stage I	44	88%
	Stage II	6	12%
T-stage	T1	20	40%
	T2	15	30%
	T3	13	26%
	T4	2	4%
N-stage	N0	32	64%
	N1a	4	8%
	N1b	14	28%
Peritumoral tissue	Hashimoto thyroiditis	18	36%
	Colloid goiter	32	64%

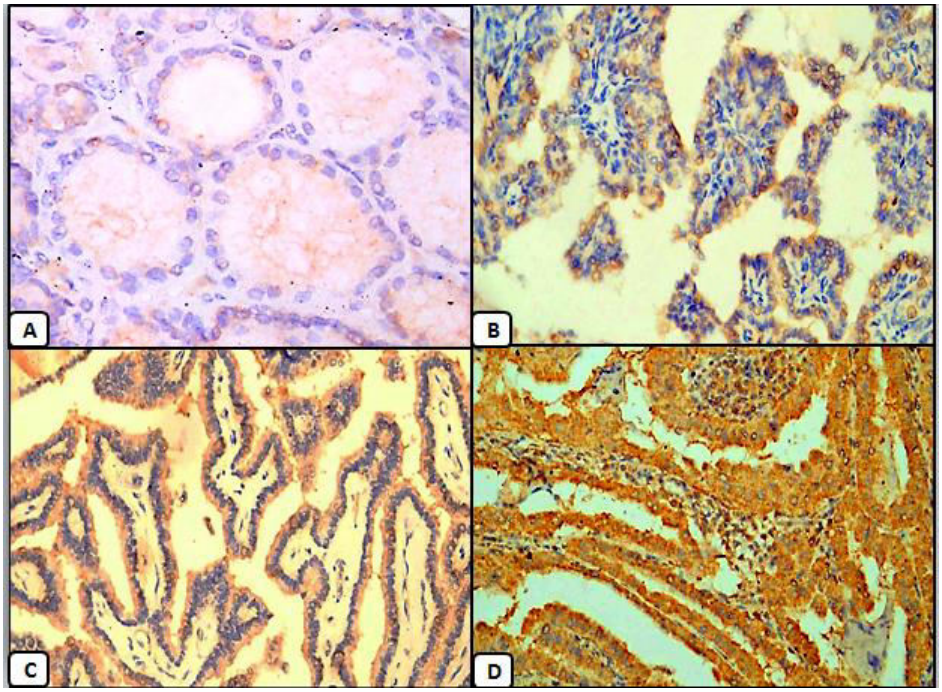

Fig.1. Immunohistochemical expression of TAB3. A) Negative TAB3 expression in non-neoplastic thyroid follicles (x400). B) Weak TAB3 expression in papillary thyroid carcinoma (x400). C) Moderate TAB3 expression in papillary thyroid carcinoma (x400). D) Strong TAB3 expression in papillary thyroid carcinoma (x400).

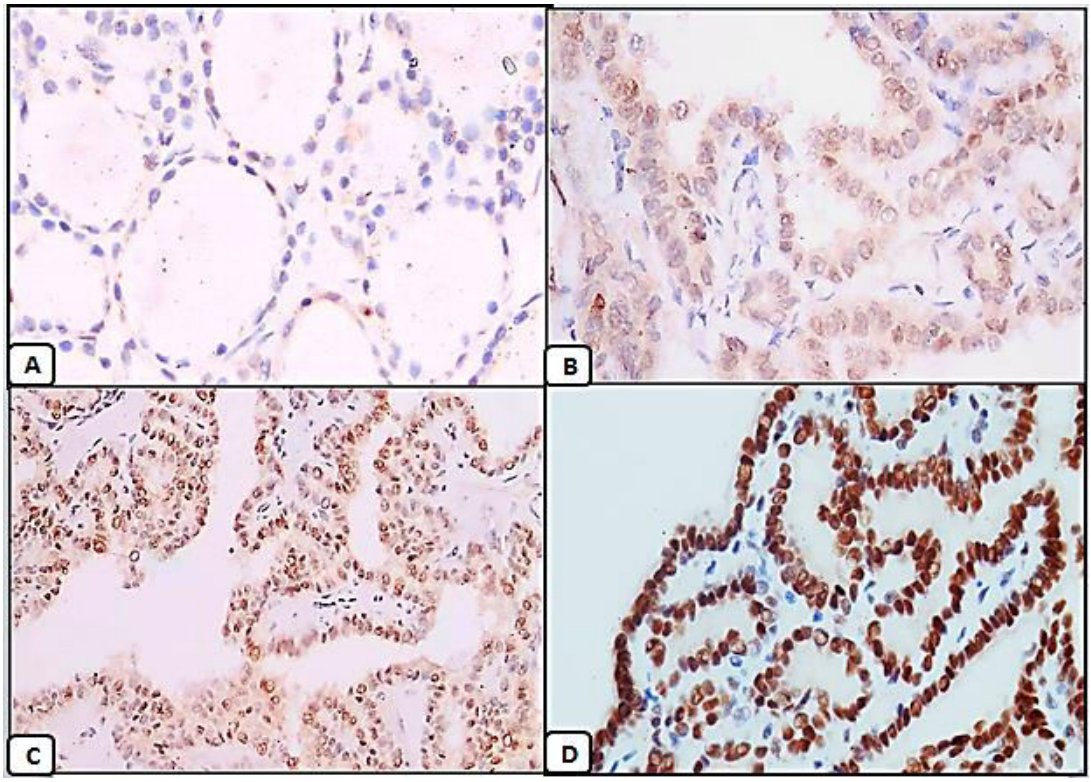

Fig.2. Immunohistochemical expression of PIM1. A) Negative PIM1 expression in non-neoplastic thyroid follicles (x400). B) Weak PIM1 expression in papillary thyroid carcinoma (x400). C) Moderate PIM1 expression in papillary thyroid carcinoma (x400). D) Strong PIM1 expression in papillary thyroid carcinoma (x400).

Relationship between TAB3 expression and the clinicopathological features of PTC

A statistically significant higher TAB3 protein expression was detected in patients more than 45 years (p=0.003) and those with higher clinical stage (p =0.028). However, insignificant difference was detected between TAB3 expression and the remaining clinicopathological features **(Table.2)**.

Table 2. Relationship between TAB3 expression and the clinicopathological features of PTC cases

Parameters		TAB3 IHC score Median (range)	*p* value
Age (years)	≤45	4 (0-12)	**0.003***
	>45	8 (0-12)	
Gender	Male	6 (0-12)	**0.156**
	Female	4 (0-12)	
Tumor site	Right	6 (0-12)	**0.100[a]**
	Left	3 (2-9)	
	Both	5 (3-6)	
	Right and isthmus	4 (0-6)	
	Left and isthmus	12 (12-12)	
	Isthmus	8 (2-8)	
Tumor size (cm)	≤1	3 (0-12)	**0.871**
	>1	6 (0-12)	
Locality	Unifocal	4 (0-12)	**0.919**
	Multifocal	6 (0-12)	
Extrathyroidal extension	Present	5 (2-8)	**0.873**
	Absent	5 (0-12)	
Lymph node metastasis	Present	6 (1-8)	**0.625**
	Absent	4 (0-12)	
Clinical stage	Stage I	4 (0-12)	**0.028***
	Stage II	8 (6-12)	
T-stage	T1 &2	6 (0-12)	**0.376**
	T3 &4	4 (0-12)	
N-stage	N 0	4 (0-12)	**0.625**
	N1a &1b	6 (1-8)	

* significant (Mann-Whitney test and [a] Kruskal-Wallis's test)($p < 0.05$).

Relationship between PIM1 expression and the clinicopathological features of papillary thyroid carcinoma

Only a statistically significant higher PIM1 expression was observed in PTC with Extra thyroidal extension (p =0.047). PIM1 expression was higher among tumors with lymph node metastasis than those without with marginal significance (p=0.054). No additional clinic-pathological features showed a significant correlation to PIM1 expression **(Table .3).**

Table3. Relationship between PIM1 score and clinic-pathological features of PTC

Parameters		PIM1 IHC score Median (range)	*p* value
Age (years)	≤45	9 (0-12)	**0.862**
	>45	9 (0-12)	
Gender	Male	9 (0-12)	**0.898**
	Female	9 (0-12)	
Tumor site	Right	9 (0-12)	**0.088[a]**
	Left	4 (0-12)	
	Both	12 (6-12)	
	Right and isthmus	12 (4-12)	
	Left and isthmus	1 (1-1)	
	Isthmus	12 (4-12)	
Tumor size (cm)	≤1	4 (0-12)	**0.068**
	>1	12 (0-12)	
Locality	Unifocal	4 (1-12)	**0.185**
	Multifocal	12 (0-12)	
Extrathyroidal extension	Present	12 (0-12)	**0.047***
	Absent	5 (0-12)	
Lymph node metastasis	Present	12 (0-12)	**0.054**
	Absent	4 (0-12)	
Clinical stage	Stage I	5 (0-12)	**0.088**
	Stage 1I	12 (9-12)	
T stage	T 1 & 2	12 (0-12)	**0.109**
	T 3 & 4	2 (0-12)	
N stage	N0	4 (0-12)	**0.054**
	N 1a, 1b	12 (0-12)	

*significant(Mann-Whitney test and [a] Kruskal-Wallis's test)(p <0.05).

Correlation of TAB3 and PIM1 IHC expression in PTC: A significant positive correlation between both proteins was found in the PTC cases (*p*=0.036) **(Fig.3).**

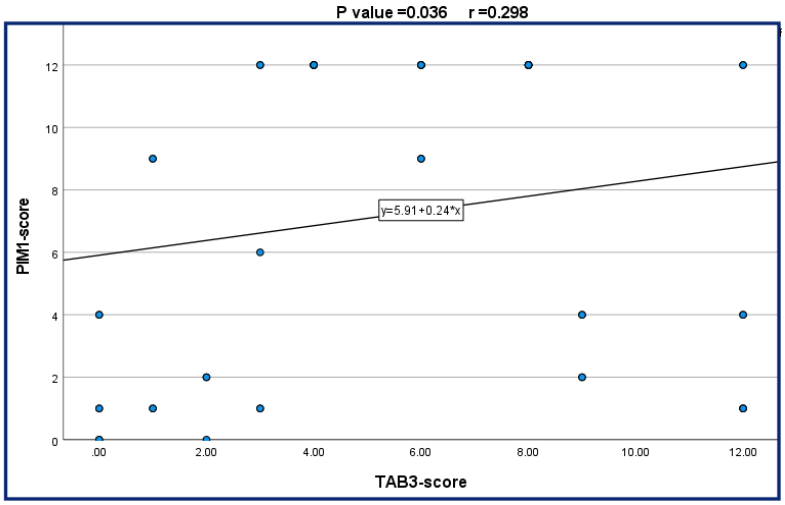

Fig.3. Spearman correlation between TAB3 and PIM1 expression.

Discussion

Approximately eighty percent of all thyroid cancer cases are papillary carcinoma of the thyroid. (**Derwich et al., 2023).** Although, PTC is well known for its favorable prognosis, it frequently presents by lymph node metastasis, posing significant treatment challenges (**Hou et al., 2020)**.

Surgery is the treatment of choice, supplemented by post operative thyroid- stimulating hormone suppression therapy and radioactive iodine. Although this regimen is effective, it does not prevent recurrence in all cases (**Li et al., 2024)**. Therefore, identifying novel markers and understanding their mechanism in PTC are crucial for improving the therapeutic approaches.

The present study included 50 specimens of papillary thyroid carcinoma (PTC) and their corresponding adjacent tissue. These specimens were investigated for the IHC expression of both PIM1 and TAB3.

Transforming growth factor b-activated kinase 1 (TAK 1) binding protein 3 (TAB3) is a member of the TAB family which is crucial in cancer development and invasion (**Zhao et al., 2018)**. To the best of our knowledge, TAB3 expression has not been previously examined in PTC.

In the present study, TAB3 was significantly overexpressed in PTC tissue compared with adjacent non-neoplastic tissue of the studied cases. This finding is consistent with the previous observation by (**Zhao et al., 2018: Chen et al., 2016)** who showed that TAB3 had been significantly overexpressed in esophageal squamous cell carcinoma tissues when compared to adjacent non-neoplastic tissues in the majority of cases and TAB3 was significantly overexpressed in (NSCLC) tissues compared with non-tumorous adjacent samples respectively.

In the current results, a statistically significant correlation between high TAB3 expression with older age and higher clinical stage of PTC was noted. This finding suggested that TAB3 may contribute to PTC progression and growth**.** Although no previous studies assessed TAB3 in PTC, it was correlated with poor prognostic factors in other cancers. **Luo et al., 2017** reported that the high TAB3 expression had been significantly related to lymph node metastases, venous invasion and advanced TNM stage, demonstrating that TAB3 overexpression is included in colorectal cancer aggressiveness and metastases.

Zhao et al., 2018 reported that the high TAB3 protein expression was significantly related to lymph node metastases and pathological grade of esophageal squamous cell carcinoma revealing that high expression of TAB3 was considerably attributed to poor prognosis.

Chen et al., 2016 reported that TAB3 overexpression in NSCLC was apparently related to lymph node metastasis and tumor size revealing that TAB3 overexpression promotes cell proliferation and is speculated to be a therapeutic target for NSCLC.

In Hepatocellular carcinoma, knockdown of TAB3 has been reported to intensify chemosensitivity of HCC cells **(Zhao et al., 2014).**

It has been demonstrated that TAB3 can activate TGF-β-activated kinase 1 which is an intracellular molecule that regulates NF-κB and mitogen-

activated protein kinase signaling pathways which play crucial roles in cell metabolism, survival, immunlogical response, and carcinogenesis **(Guo et al., 2024)**.

In addition, NF-κB and Mitogen-activated protein kinase were reported to be increased in human PTC and were associated with proliferation, invasion and metastasis in thyroid cancer cell lines (**Cormier et al., 2023).**

No previous study reported a correlation between higher TAB3 and older age. Thus we can suggest that this finding may be attributed to genetic factors that requires further investigation.

The findings of the current research showed that PIM1 had been overexpressed in PTC tissues compared to adjacent non-neoplastic tissues. To our knowledge, only one previous study assessed the immunohistochemical expression of PIM1 in PTC (**Wen et al., 2021)** which reported overexpression of PIM1 in PTC than in adjacent non neoplastic tissues which is consistent with the current study. They suggested that PIM1 played a role in the pathogenesis of PTC (**Wen et al., 2021)**.

The result of the present study found that high PIM1 expression in the studied cases was significantly correlated with extrathyroidal extension. Also, it was higher in carcinoma with lymph node metastasis suggesting its essential role in the progression of PTC.

Similar to the finding of the current research, **Wen et al., 2021** described that high PIM1 expression had been significantly related to capsular invasion and lymph node involvement. In addition, PIM1 over-expression has been demonstrated in several malignancies as prostate cancer, malignant melanoma and leukemia and has been implicated in the development and drug resistance of these cancers (**Takeuchi et al., 2023)**.

Chua et al., 2023, showed that PIM1 was overexpressed in primary HCC tissue and markedly correlated with extra-hepatic metastasis. Furthermore, PIM1 knockdown could inhibit HCC proliferation, invasion and metastasis indicating that PIM1 may be a promising target for therapy.

According to **Anwar et al** study, the initiation and progression of cancer has extended great relevance to the function of survival kinases. Expanding evidence has suggested the essential role of oncogenic kinase PIM1 in biological processes of cancer cells, such as proliferation, cell cycle progression, apoptosis and invasion.

It has been suggested that PIM1 can promote tumor progression by different ways. PIM1 can activate cell division cycle 25 A and C which promote cell cycle progression (**Li et al., 2023)**. In addition it has anti apoptotic activity by activating anti-apoptotic protein BCL-2 and suppressing the activity of the pro-apoptotic protein BAD by direct phosphorylation (**Toth and Warfel, 2021)**. Thus, it is believed that PIM1 could be a promising cancer biomarker with significant clinical implications (**Lai et al., 2022).**

In this work, significant positive correlation between PIM1 and TAB3 expression in PTC was found. Supporting this finding a study by (**Li et al., 2020)** who found a significant correlation between both proteins in colorectal

carcinoma and concluded that colorectal carcinoma proliferation is induced by PIM1which is regulated by TAB3.

It has been reported that TAB3 might regulate PIM1 through the formation of TAB3-TAK1 complex which interacts with STAT3 and regulates its phosphorylation and activation (**Li et al., 2020)**. Then Phosphorylated STAT3 translocates to the nucleus, where it stimulates the transcription of its target gene PIM1, which results in the up-regulation of PIM1 mRNA (**Mahata et al., 2022)** and in this way participates in the carcinogenesis and metastasis of numerous cancers (**Bellon and Nicot, 2023).**

Conclusion

The current results suggested that TAB3 and PIM1 may contribute to PTC pathogenesis and its progression. The positive correlation between them in PTC suggests a novel pathway by which cancer cells can promote their growth and proliferation. Further molecular studies are recommended to confirm the role of TAB3 and PIM1 in PTC and their possible role as therapeutic targets**.**

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