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■ ORIGINAL ARTICLE ■

$P2X_7$ Receptor Expression in Coexistence of Papillary Thyroid Carcinoma with Hashimoto's Thyroiditis

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Background: This study was aimed at investigating the relation of $P2X_7$ receptor ($P2X_7R$) expression with the clinicopathological features of papillary thyroid carcinoma (PTC) coexisting with Hashimoto's thyroiditis (HT). **Methods:** We examined 170 patients (84, PTC with HT; 86, PTC without HT). $P2X_7R$ expression was examined by immunohistochemical methods. The staining intensity and patterns were evaluated and scored using a semi-quantitative method. **Results:** The PTC with HT group was more likely to contain women and had less extrathyroid extension, lymph node (LN) metastasis, lymphovascular invasion, and recurrence than the PTC without HT group. Patients positive for $P2X_7R$ had significantly higher frequencies of lymphovascular invasion, extrathyroid extension, LN metastasis, and absence of HT. As shown by multivariate analysis, the expression of $P2X_7R$ was significantly higher if HT was absent and extrathyroid extension was present. In the PTC with HT group, the expression of $P2X_7R$ was significantly higher in patients with tumor multifocality, lymphovascular invasion, and extrathyroid extension. In the PTC without HT group, the expression of $P2X_7R$ was significantly higher in women and those having tumor multifocality. **Conclusions:** Coexistence of PTC with HT is associated with good prognostic factors, and $P2X_7R$ expression in PTC was correlated with poor prognostic factors and the absence of HT.

Key Words: Hashimoto Disease; Thyroid cancer, papillary; Receptors, purinergic $P2X_7$

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer and represents the first most prevalent malignancy in Korea, especially in Korean women.[1] PTC often occurs in conjunction with Hashimoto's thyroiditis (HT), which is a common form of chronic autoimmune thyroid disease and clinically characterized by circulating autoantibodies to primary thyroid antigens including thyroglobulin and thyroid peroxidase.[2] HT is pathologically characterized by the presence of diffuse plasma and lymphocytic cell infiltration, oxyphilic cells, the formation of lymphoid follicles and reactive germinal centers, and parenchymal atrophy.[3] The pathogenesis of PTC coexisting with HT is uncertain. The prognostic impact of the coexistence of HT with PTC has also been controversial. Some investigators have reported that PTC coexisting with HT is associated with good prognosis, lower recurrence rate, and a less aggressive disease at presentation.[4] However, others have reported that the coexistence of HT has no such protective effect on PTC patient outcome.[5,6] Moreover, the significance of this coexistence with respect to lymph node metastasis continues to be debated.[7]

$P2X_7$ receptor ($P2X_7R$) is plasma membrane receptor, functionally expressed in human T cells, and plays a critical role in

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cell survival and growth. Because the natural ligand of $P2X_7Rs$ is an extracellular adenosine triphosphate (ATP), ATP directly activates the receptors. Activation of $P2X_7R$ by ATP may lead to the release of several kinds of pro-inflammatory cytokines, as well as increasing cell membrane permeability and potentially resulting in apoptosis. A high ATP concentration affects T cell apoptosis by up-regulating and engaging the $P2X_4R$ and $P2X_7R$ subtypes.[8] Recently, $P2X_7R$ expression has been documented in several malignant tumors. In prostate, $P2X_7R$ overexpression has been suggested for the early detection of prostate cancer.[9,10] In contrast, $P2X_7R$ expression was decreased in endometrial and uterine epithelial cancers.[11,12] $P2X_7R$ expression was found to be strongly up-regulated in PTC and thyroid cancer cell lines, while it is barely expressed in normal human primary thyrocytes,[13] suggesting its possible involvement with tumorigenesis. Nevertheless, there have been only a few reports evaluating the $P2X_7R$ expression in PTC.[13,14] The clinical or pathological significance of $P2X_7R$ expression has not been investigated in PTC coexisting with HT. In the present study, we evaluate the clinicopathological features of PTCs according to coexistence with HT, and investigate a possible prognostic correlation of $P2X_7R$ expression with PTC coexisting with HT.

MATERIALS AND METHODS

Patients and tissue samples

This study was conducted using formalin-fixed, paraffin-embedded tissue samples obtained from 170 PTC patients who underwent thyroid surgery at Kangdong Sacred Heart Hospital between January 2006 and December 2007. Among the 170 patients, 84 had available data including the preoperative serum thyroid autoantibodies and pathology reports for HT. HT was diagnosed on the basis of histological findings of diffuse lymphoplasmacytic infiltration with germinal centers, parenchymal atrophy with oncocytic change, and variable amounts of stromal fibrosis throughout the thyroid gland. Lymphovascular invasion was assessed with light microscopy and defined as tumor cells that were present within a vascular space with identification of endothelial lining.[15] After histological review, PTC cases were categorized into two groups, PTC with HT (n=84) or PTC without HT (n=86). Clinical information including age, sex, treatment modality, and survival or recurrence was adapted from medical records and radiologic findings and then analyzed. All glass slides from 170 patients with PTC were reviewed by two pathologists for diagnosis confirmation and selection of a representative section for immunohistochemical study. Diagnosis and histologic differentiation were evaluated according to the World Health Organization classification, and tumor staging was based on the American Joint Committee on Cancer updated tumor-node-metastasis cancer staging system. This study was approved by Institutional Ethics Committee of Kangdong Sacred Heart Hospital Seoul, Korea.

Tissue microarray block preparation

After a case review for diagnostic confirmation, a tissue microarray was constructed. The largest definite tumor area was selected for the tissue microarray block. A circle was drawn on the slide around the most representative area. Using the slide as a guide, core samples were obtained from each paraffin-embedded block using a tissue microarray tool (Quick-Ray, Unitma, Seoul, Korea). A punch size 3 mm in diameter was used. Nine cores were embedded in each block in 3×3 arrangements. In total, 19 tissue microarray blocks were produced from the 170 tumor samples.

Immunohistochemistry

The 4-μm thick tissue sections were deparaffinized using EZ Prep solution. CC1 standard (pH 8.4 buffer contained Tris/Borate/ethylenediaminetetraacetic acid) was used for antigen retrieval. DAB inhibitor (3% H_2O_2 endogenous peroxidase) was blocked for 4 minutes at 37°C. Slides were incubated with anti-$P2X_7R$ antibodies (1:300, goat IgG, Abcam, Cambridge, UK) for 40 minutes at 37°C, and then incubated with a secondary antibody (Universal HRP Multimer, Ventana Medical Systems, Melbourne, VIC, Australia) for 8 minutes at 37°C. After incubation, slides were stained with the DAB H_2O_2 substrate for 8 minutes, followed by hematoxylin and bluing reagent counterstaining at 37°C. A reaction buffer (pH 7.6, Tris buffer) was used as a washing solution.

Immunohistochemical evaluation

Both the intensity of immunohistochemical staining and the proportion of stained tumor cells were semi-quantitatively evaluated. The staining intensity was scored as follows: 0, negative; 1, weak; 2, moderate; and 3, strong. Staining proportion was rated according to the percentage of positive cells and scored as follows: 0, less than 10%; 1, 11% to 25%; 2, 26% to 75%; 3, more than 75%. The scores of staining intensity and proportion were multiplied to produce a weighted immunoreactive score (0-6). Cases with a score ≥3 were considered high expression and those with a score ≤2 were defined as low expression. Two pathologists blinded to the patients' clinical data interpreted all

immunostained slides, and cases with discrepant scores were re-evaluated to achieve a consensus score.

Statistical analysis

Results are expressed as mean ± standard deviation or frequencies and proportions where appropriate. Comparisons between groups were performed using the Student's t-tests for continuous data. Differences in the frequency of single variables were tested using the χ^2 test. Univariate and multivariate analyses were used to estimate the influence of $P2X_7R$ expression on clinicopathological parameters. SPSS ver. 18 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and a $p < .05$ was considered statistically significant.

RESULTS

Clinicopathological features

Patients consisted of 18 men and 152 women with an age range of 26 to 76 years (mean, 47.5 ± 11.7 years). The 170 cases consisted of 150 conventional PTC (88.2%) and 20 variants (11.8%), including follicular variants (n = 16), oncocytic variants (n = 3), and a diffuse sclerosing variant (n = 1). Extrathyroid extension and lymphovascular invasion were identified in 45.9% (78/170) and 48.8% (83/170) of cases, respectively. In addition, 64 patients (37.6%) had multifocality. Lymph node metastasis was identified in 41.8% (71/170) of cases. The clinical and pathological characteristics according to the presence of HT are summarized in Table 1. PTC patients with HT were more likely to be women ($p = .01$), with less lymphovascular invasion ($p < .001$) and extrathyroid extension ($p < .001$). Less lymph node metastasis ($p < .001$) was evident among the PTC with HT group compared to the PTC without HT group. There were no statistical differences in terms of age, histological variant, tumor size, or tumor multifocality between the PTC with HT and PTC without HT groups. Of the 84 patients with HT, only one patient (1.2%) had recurrence during a mean follow-up of 64.3 ± 11.1 months, whereas six (7%) patients without HT had recurrence during a mean follow-up of 64.8 ± 8.6 months. Lower recurrence ($p = .026$) was noted in the PTC with HT group, however, this observation is not mentioned in the table because of the low number of patients. Two patients expired during the follow-up period, but their cause of death was not clear; hence, they were excluded.

Table 1. Clinicopathological features of PTC according to presence of HT

Characteristic	PTC with HT (n = 84)	PTC without HT (n = 86)	p-value
Age at diagnosis (yr)	47.1 ± 11.6	48.8 ± 12.2	.33
< 45	30 (35.7)	22 (25.6)	
≥ 45	54 (64.3)	64 (74.4)	
Gender			.01
Male	4 (4.7)	14 (16.3)	
Female	80 (95.3)	72 (83.7)	
Histological variant			.14
Variants	13 (15.4)	7 (8.1)	
Conventional	71 (84.6)	79 (91.9)	
Tumor multifocality			.84
Yes	31 (36.9)	33 (38.4)	
No	53 (63.1)	53 (61.6)	
Tumor size (cm)			.11
< 2	76 (90.4)	70 (81.4)	
2-4	6 (7.1)	15 (17.4)	
> 4	2 (2.5)	1 (1.2)	
Lymphovascular invasion			< .001
Yes	24 (28.6)	59 (68.6)	
No	60 (71.4)	27 (31.4)	
Extrathyroid extension			< .001
Yes	23 (27.4)	55 (64)	
No	61 (72.6)	31 (36)	
Lymph node metastasis			< .001
Yes	20 (23.8)	51 (59.3)	
No	64 (76.2)	35 (40.7)	

Values are presented as mean ± standard deviation or number (%).
PTC, papillary thyroid carcinoma; HT, Hashimoto's thyroiditis.

$P2X_7R$ expression in PTC

The 170 patients consisted of 90 having high $P2X_7R$ expression and 80 having low $P2X_7R$ expression. Of the 90 patients with high $P2X_7R$ expression, 66 patients had PTC only (73.3%) and 24 patients had PTC with HT (26.7%). $P2X_7R$ was mainly expressed in the cytoplasm of PTC (Fig. 1). High $P2X_7R$ expression was significantly associated with lymphovascular invasion ($p < .001$), extrathyroid extension ($p < .001$), and lymph node metastasis ($p < .001$). However, tumor size, tumor multifocality, and histological variant were not statistically associated with $P2X_7R$ expression (Table 2). Table 3 shows results of the multivariate logistic analysis investigating factors that potentially affect $P2X_7R$ expression. No significant association between $P2X_7R$ expression and age (odds ratio [OR], 1.42; 95% confidence interval [CI], 0.63 to 3.21; $p = .40$), gender (OR, 0.75; 95% CI, 0.2 to 2.8; $p = .67$), tumor multifocality (OR, 1.15; 95% CI, 0.31 to 3.99; $p = .87$), lymphovascular invasion (OR, 1.31; 95% CI, 0.48 to 3.61; $p = .59$), or lymph node metastasis (OR, 1.81; 95% CI, 0.71 to 4.6; $p = .21$) was found. However, there was a significant association between high $P2X_7R$ expression and extrathyroid extension (OR, 3.16; 95% CI, 1.31 to 7.6; $p = .01$).

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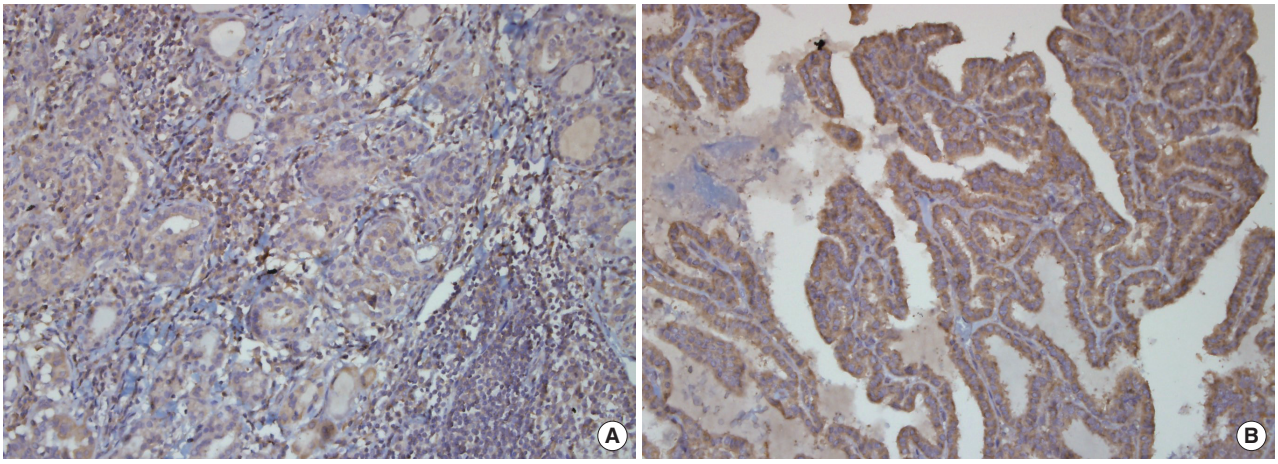

Fig. 1. Immunohistochemical expression of $P2X_7$ receptor ($P2X_7R$) in papillary thyroid carcinomas (PTCs). (A) Low expression of $P2X_7R$; PTC with Hashimoto's thyroiditis (HT). (B) High expression of $P2X_7R$; PTC without HT.

Table 2. $P2X_7R$ expression in papillary thyroid cancer

Characteristic	$P2X_7R$ low expression (n=80)	$P2X_7R$ high expression (n=90)	p-value
Age at diagnosis (yr)	47.5±12.2	48.4±11.7	.13
<45	29 (36.2)	23 (25.6)	
≥45	51 (63.8)	67 (74.4)	
Gender			.08
Male	5 (6.2)	13 (14.4)	
Female	75 (93.8)	77 (85.6)	
Histological variant			.78
Variants	10 (12.5)	10 (11.1)	
Conventional	70 (87.5)	80 (88.9)	
Tumor multifocality			.12
Yes	35 (43.8)	29 (32.2)	
No	45 (56.2)	61 (67.8)	
Tumor size (cm)			.55
<2	70 (87.5)	76 (84.4)	
2-4	8 (10)	13 (14.4)	
>4	2 (2.5)	1 (1.2)	
Lymphovascular invasion			<.001
Yes	23 (28.8)	60 (66.7)	
No	57 (71.2)	30 (33.3)	
Extrathyroid extension			<.001
Yes	20 (25)	58 (64.4)	
No	60 (75)	32 (35.6)	
Lymph node metastasis			<.001
Yes	21 (26.2)	50 (55.6)	
No	59 (73.8)	40 (44.4)	
Hashimoto's thyroiditis			<.001
Yes	60 (75)	24 (26.7)	
No	20 (25)	66 (73.3)	

$P2X_7R$, $P2X_7$ receptor.

Expression of $P2X_7R$ in PTC with or without HT

High $P2X_7R$ expression was significantly associated with an absence of HT (OR, 5.43; 95% CI, 2.45 to 12; p<.001). In the group with coexisting HT, $P2X_7R$ expression was significantly higher in patients with tumor multifocality (p=.05), lymphovascular invasion (p<.001), and extrathyroid extension (p<.001) (Table 4). For the PTC without HT group, $P2X_7R$ expression was significantly higher in women (p<.001) and the tumor multifocality group (p<.001) (Table 5).

Table 3. Multivariate analysis of factors potentially affecting the expression of $P2X_7R$

Factor	Odds ratio	95% Confidence interval	p-value
Age	1.42	0.63-3.21	.4
Gender	0.75	0.2-2.8	.67
Multifocality	1.15	0.31-3.99	.87
Lymphovascular invasion	1.31	0.48-3.61	.59
Lymph node metastasis	1.81	0.71-4.6	.21
Extrathyroid extension	3.16	1.31-7.6	.01
Hashimoto's thyroiditis	5.43	2.45-12	<.001

$P2X_7R$, $P2X_7$ receptor.

DISCUSSION

In the present study, we found that PTC with HT correlated with more favorable biological characteristics than PTC without HT. In PTC, the absence of HT was associated with high frequencies of female patients, extrathyroid extension, lymph node metastasis, lymphovascular invasion, and frequent recurrences. Similarly, the presence of autoimmune thyroiditis in thyroid cancer has been correlated with good prognosis. Recent meta-analysis demonstrated that PTCs with coexisting HT are strongly associated with female patients, tumor multifocality, the absence of extrathyroidal extension, absence of lymph node metastasis, and high recurrence-free survival rates.[16] Kim *et al*.[7] also suggested that PTC coexisting with HT may protect against

Table 4. $P2X_7R$ expression in papillary thyroid cancer with Hashimoto's thyroiditis

Characteristic	$P2X_7R$ (scores 0-2) (n=60)	$P2X_7R$ (scores 3-9) (n=24)	p-value
Age at diagnosis (yr)			.07
<45	25	5	
≥45	35	19	
Gender			.33
Male	2	2	
Female	58	22	
Histological variant			.85
Variants	9	4	
Conventional	51	20	
Tumor multifocality			.05
Yes	26	5	
No	34	19	
Tumor size (cm)			.17
<2	52	24	
2-4	6	0	
>4	2	0	
Lymphovascular invasion			<.01
Yes	12	12	
No	48	12	
Extrathyroid extension			<.01
Yes	11	12	
No	49	12	
Lymph node metastasis			.47
Yes	13	7	
No	47	17	

$P2X_7R$, $P2X_7$ receptor.

Table 5. $P2X_7R$ expression in papillary thyroid cancer without Hashimoto's thyroiditis

Characteristic	$P2X_7R$ (scores 0-2) (n=20)	$P2X_7R$ (scores 3-9) (n=66)	p-value
Age at diagnosis (yr)			<.01
<45	19	11	
≥45	1	55	
Gender			.74
Male	3	12	
Female	17	54	
Histological variant			.55
Variants	1	6	
Conventional	19	60	
Tumor multifocality			<.01
Yes	0	34	
No	20	32	
Tumor size (cm)			.84
<2	16	53	
2-4	4	12	
>4	0	1	
Lymphovascular invasion			.48
Yes	5	22	
No	15	44	
Extrathyroid extension			.13
Yes	10	21	
No	10	45	
Lymph node metastasis			.94
Yes	8	27	
No	12	39	

$P2X_7R$, $P2X_7$ receptor.

central lymph node metastasis. Huang *et al*.[17] reported that coexisting HT with either PTC or follicular thyroid carcinoma is linked with improved clinical stage and favorable prognosis. The mechanisms by which cancer cells may be destroyed by autoimmunity have been suggested. Lymphocytic infiltrates in thyroid cancer contain cytotoxic T lymphocytes, and Fas-mediated apoptosis is the major mechanism by which cytotoxic T lymphocytes cause target cell lysis.[3] In addition, interleukin-1, secreted by infiltrating lymphocytes, inhibits human thyroid carcinoma cell growth.[18]

Only three articles have been published on the possible link between thyroid cancer and $P2X_7R$ expression.[13,14,19] *In vitro* study has shown that thyroid papillary carcinoma cell lines express high levels of $P2X_7R$.[13] Gu *et al*.[14] suggested that $P2X_7R$ expression is associated with lymph node metastasis in PTCs. In their logistic regression analysis, $P2X_7R$ expression, tumor size, and capsular invasion are predictors for lymph node metastasis, suggesting that $P2X_7R$ expression may predict the aggressiveness of PTC.[14] However, these studies have not demonstrated the association between $P2X_7R$ expression and PTC with HT.

In the present study, PTC with HT correlates with good prognostic factors. PTC with high $P2X_7R$ expression showed significantly higher frequencies of lymphovascular invasion, extrathyroid extension, lymph node metastasis, and absence of HT. In the multivariate analysis, high $P2X_7R$ expression was independently associated with the absence of HT and the presence of extrathyroid extension. Our results suggested that $P2X_7R$ expression in PTC correlates with poor prognostic factors.

In the PTC with HT group, the expression of $P2X_7R$ was significantly higher in tumor multifocality, lymphovascular invasion, and extrathyroid extension. As for the PTC without HT group, the expression of $P2X_7R$ was significantly higher in females and those with tumor multifocality. These results may imply that a different mechanism of $P2X_7R$ expression may be involved according to coexistence of HT. Recently, Beynon *et al*.[20] reported that activated memory T-cells primed by interferon-β suppress the activation of monocytes by inhibiting $P2X_7R$-mediated signaling, indicating that $P2X_7R$ expression in HT may be associated with activated T lymphocytes of HT.

In conclusion, the occurrence of PTC in HT individuals may

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predict a favorable tumor behavior such as less tumor multifocality, lymphovascular invasion, and extrathyroid extension, compared to those having PTC without HT. $P2X_7R$ expression in PTC was correlated with poor prognostic factors and the absence of HT.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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