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Upregulation and the clinical significance of KCNQ1OT1 and HAGLROS lncRNAs in papillary thyroid cancer

An observational study

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Abstract

Long noncoding RNAs (lncRNAs) play an important role in regulating gene expression. Changes in their expression have been associated with many types of cancer, including thyroid cancer. This study aimed to investigate how changes in the expression of potassium voltage-gated channel subfamily Q member 1 opposite strand/antisense transcript 1 (*KCNQ1OT1*) and HAGLR opposite strand lncRNA (*HAGLROS)* lncRNAs correlate with the development and clinicopathological characteristics of papillary thyroid cancer (PTC). Reverse transcription-quantitative polymerase chain reaction was used to investigate the expression of lncRNAs in both tumor and adjacent normal thyroid tissue samples of the patients. Expressions of *KCNQ1OT1* and *HAGLROS* were upregulated in the patients tumor samples compared to the adjacent normal thyroid samples. *KCNQ1OT1* expression was linked to microcarcinoma and gender, while *HAGLROS* expression was linked to microcarcinoma and tumor size. When only microcarcinoma samples were evaluated, *KCNQ1OT1* expression was higher in tumor tissues compared to normal tissues; however, no significant difference was observed in *HAGLROS* expression. Our data suggests that high expressions of *KCNQ1OT1* and *HAGLROS* might contribute to the development of PTC and disease progression, and both lncRNAs may be potential therapeutic targets in PTC patients.

Abbreviations: ceRNA = competing endogenous RNA, *HAGLROS* = HAGLR opposite strand lncRNA, HCC = hepatocellular carcinoma, *KCNQ1OT1* = potassium voltage-gated channel subfamily Q member 1 opposite strand/antisense transcript 1, lncRNA = long noncoding RNA, NSCLC = non-small cell lung cancer, PTC = papillary thyroid cancer.

Keywords: gene expression, *HAGLROS*, *KCNQ1OT1*, long noncoding RNA, microcarcinoma, papillary thyroid cancer

1. Introduction

Thyroid cancer is the most common endocrine malignancy. Its incidence is on the rise worldwide.[1,2] According to GLOBOCAN data, the number of new thyroid cancer cases diagnosed in 2020 was 586,000 – ranking at 11th out of all 36 cancer types.[3] Differentiated thyroid cancers are more common among thyroid malignancies. Cases with papillary thyroid cancer (PTC) account for more than 85% of all patients.[4] Today, PTC is a generally curable; however, it can be aggressive and even fatal in some cases. Moreover, the recurrence rate of the disease is approximately thirty percent.[5] Therefore, further studies need to be done on molecular biomarkers associated with PTC development and progression so that early diagnosis can be established for the disease and treatment targets are determined.

Long noncoding RNAs (lncRNA) are an important member of noncoding RNA class. They are larger than 200 nucleotides and not translated into a protein.[6,7] LncRNAs can regulate gene expression at different stages by interacting with mRNA, miRNA, DNA, and proteins. Thus, abnormalities in the expression of lncRNAs have been associated with various forms of cancer, including thyroid.[8] Changes in the expression of some lncRNAs–namely BRAF-activated nonprotein coding RNA, Papillary thyroid carcinoma susceptibility candidate 3, Homeobox transcript antisense intergenic RNA,

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metastasis associated lung adenocarcinoma transcript 1, Long noncoding RNA H19, Nuclear Enriched Abundant Transcript 1, Maternally expressed gene 3, Growth arrest-specific transcript 5, and Plasmacytoma variant translocation 1–have been associated with thyroid cancer's development and progression.[9]

The Potassium Voltage-Gated Channel Subfamily Q Member 1 opposite strand/antisense transcript 1 (*KCNQ1OT1*) gene is located in the region 11p15.5. The product of this gene is a 91 kb unspliced lncRNA. *KCNQ1OT1* is responsible for transcriptionally silencing a gene cluster, including important tumor suppressor genes and *KCNQ1*, via genomic imprinting.[7] It interacts with epigenetic regulators – for example polycomb repressive complex 2, histone methyltransferase G9a, and DNA methyl transferase 1 in order to silence those genes. The overexpression of *KCNQ1OT1* can cause Beckwith-Wiedemann syndrome. In some of children who suffer from this disease, embryonal tumors also point to the role of *KCNQ1OT1* in cancer development.[10] As a matter of fact, recent studies have identified increased *KCNQ1OT1* expression in retinoblastoma, acute promyelocytic leukemia,[10] bladder,[11] ovarian,[12] and non-small cell lung cancer (NSCLC).[13] However, no study has investigated the expression of *KCNQ1OT1* in thyroid cancer.

Similarly, the HAGLR opposite strand lncRNA (*HAGLROS*) is located in the region 2q31.1. It has only one transcript: a 699 nucleotide *HAGLROS* lncRNA.[14] Other recent studies have found that *HAGLROS* expression increases in various cancers and this lncRNA has oncogenic properties. One study in particular concluded that increased *HAGLROS* expression contributes to the development of gastric cancer and poor prognosis.[15] Likewise, Zheng et al[16], reported that *HAGLROS* expression significantly increased in triple negative breast cancer and this increase was associated with poor overall survival. In addition, some studies have reported increased *HAGLROS* expression in hepatocellular carcinoma (HCC),[17] esophageal squamous cell carcinoma,[18] ovarian cancer,[19] NSCLC,[20] and osteosarcoma.[21] One study based on TCGA dataset reported that *HAGLROS* was among the 10 top genes that exhibited increased expression in papillary thyroid cancer.[22] However, no other studies on this subject currently exist.

Therefore, this study focused on examining the correlations between the development and clinicopathological features of papillary thyroid cancer and the expression profiles of *KCNQ1OT1* and *HAGLROS*.

2. Methods

2.1. Patients and tissue specimens

Giresun University's Clinical Research Ethics Committee approved this study (Approval: 05/12/2019/25). Informed consent was obtained from all individual participants included in the study. We used power analysis to estimate the required sample size and found as 54 to achieve 90% power for medium effect size. In our study, this number was exceeded with a sample size of 128. PTC patients to be included in the study were selected from those who had not received any cancer treatment before surgery (such as radiotherapy, chemotherapy or other treatments). A total of 137 PTC patients who had undergone at thyroidectomy at Giresun University's Faculty of Medicine between 2015 and 2021 were included in the study. Tumor and noncancerous thyroid tissue samples of the each patient included in the study were examined by the pathology department. Pathologists confirmed the diagnosis of PTC and determined the tumor tissue blocks and matched noncancerous thyroid tissue blocks. Tissue samples were obtained from formalin-fixed paraffin-embedded tissue blocks that had been archived in the same pathology department. After RNA extraction, 9 patients were excluded due to poor RNA quality (RNA samples whose A260/A280 ratio was not between 1.8–2.1/ degraded RNA samples). This brought the number down to 128 – expression analysis was conducted on them. The researchers obtained the subjects clinicopathological traits (age, gender, tumor diameter, and TNM stage) from their patient records and summarized them in Table 1. The 6 patients whose lymphovascular invasion findings could not be reached are shown as unknown in table 1.

2.2. RNA isolation and reverse transcription - quantitative polymerase chain reaction (RT-qPCR)

First, 5-µm thick samples were taken from the paraffin blocks using a microtome. Next, they were treated with 1 ml xylene to remove the paraffin, and then washed with 100%, 70% and 50% ethanol. Then, total RNA extraction was carried out using a RNeasy formalin-fixed paraffin-embedded kit (Qiagen GmbH) according to the manufacturer's instructions. RNA concentration and purity were assessed using a NanoDrop 1/1C Microvolume UV–Vis Spectrophotometer (Thermo Fisher Scientific, Inc.). Next, the RNA samples were subjected to agarose gel electrophoresis to evaluate their integrity. The samples that proved to be of poor quality were excluded from the study. Afterwards, complementary DNA synthesis was conducted according to the manufacturer's instructions using a Revert Aid RT Reverse Transcription kit (Thermo Fisher Scientific, Inc.). Next, all of samples were stored at – 80 °C until expression analysis. To avoid detection bias, the samples were randomly numbered without specifying whether they were tumors or controls, so that researchers who would do laboratory analyzes did not know whether the sample was a tumor or a control sample. Expression analyses were conducted using a Light Cycler 480 SYBR-Green I Master mix (Roche Diagnostics GmbH)–final volume: 20 µL–on a Light Cycler 480 Real-Time PCR system (Roche Diagnostics GmbH) according to the manufacturer's instructions. The following cycling protocol was performed for the qRT amplification: initial denaturation at 95°C for 1 minute, followed by 45 cycles at 95°C for 10 seconds, 57°C for 30 seconds, and 72°C for 30 seconds. The *β actin* gene was used as an endogenous control to normalize the expression of lncRNAs. All of the samples were tested in triplicates. Relative gene expression levels of the target lncRNAs were examined using the $2^{-\Delta\Delta CT}$ method.[23] All of the primer sequences for the qRT PCR were as follows: 5'-GGGAGCTGTTGTCCCTTACC-3' (forward) and 5'-TTCGGAGTGGTAACTGTGCC-3' (reverse) for *KCNQ1OT1*; 5'-CTGATCCACCTGGAACACTTT-3' (forward) and 5'-CTCCTCCGCTTGCGATTT-3' (reverse) for *HAGLROS*; 5'-TCTACAATGAGCTGCGTGTG -3' (forward) and 5'-GGTCTCAAACATGATCTGGGT-3' (reverse) for *β actin*.

2.3. Statistical analyses

Statistical analysis was conducted on SPSS 15.0 (SPSS Inc., Chicago, IL). Expression levels of lncRNAs between tumor and normal tissues were compared using the paired Student *t* test. The correlation between the clinicopathological features and the expressions of lncRNAs was evaluated using the chi-square test. For analyses purposes, the patient group was divided into 2 smaller groups – low and high expression – according to their median lnc expression values. Continuous variables were expressed in mean ± standard deviation. *P* values <.05 were considered statistically significant. Figures were created using GraphPad Prism version 8.0.

3. Results

3.1. KCNQ1OT1 and HAGLROS are significantly upregulated in PTC tissues

The relative expression levels of *KCNQ1OT1* and *HAGLROS* in the tumor and normal thyroid tissues (n = 128 for each

Table 1

The relationship of KCNQ1OT1 and *HAGLROS* expressions with clinicopathological characteristics of PTC patients. Statistical analysis was performed using chi-square test.

		KCNQ1OT1 expression				*HAGLROS* expression			
Variables	**Number of patients**	**Low**	**High**	**Odds ratio (95% CI)**	***P* value**	**Low**	**High**	**Odds ratio (95% CI)**	***P* value**
Gender				3.222 (1.170–8.875)	.019*			1.620 (0.639–4.109)	.307
Female	106	58	48			70	36		
Male	22	6	16			12	10		
Age (yr)				0.796 (0.370–1.712)	.559			1.243 (0.553–2.790)	.598
<45	37	17	20			25	12		
≥45	91	47	44			57	34		
Microcarcinoma				0.362 (0.173–0.758)	.006*			0.364 (0.163–0.814)	.012*
No	79	32	47			44	35		
Yes	49	32	17			38	11		
Tumor diameter (cm)				1.772 (0.839-3.745)	.132			2.842 (1.319–6.121)	.007*
<2	86	47	39			62	24		
≥2	42	17	25			20	22		
Lymphovascular invasion				0.739 (0.305–1.788)	.501			1.456 (0.596–3.556)	
No	97	47	50			63	34		.408
Yes	25	14	11			14	11		
Unknown	6					5	1		
Primary tumor					.353				.499
T1	103	55	48	-		68	35	-	
T2	19	7	12			10	9		
T3	6	2	4			4	2		
Lymph node metastasis				0.238 (0.026–2.191)	.365			0.433 (0.047–3.997)	.654
No	123	60	63			78	45		
Yes	5	4	1			4	1		
TNM staging				1.000 (0.137–7.325)	1.000			0.585 (0.059–5.794)	1.000
I	124	62	62			79	45		
II	4	2	2			3	1		
Extrathyroidal extension				0.360 (0.107–1.215)	.089			0.450 (0.119–1.705)	.231
No	114	54	60			71	43		
Yes	14	10	4			11	3		
Multicentricity				0.664 (0.321–1.374)	.269			0.924 (0.434–1.967)	.838
No	82	38	44			52	30		
Yes	46	26	20			30	16		
Multifocality				1.296 (0.639–2.629)	.472			1.589 (0.764–3.305)	.214
No	76	40	36			52	24		
Yes	52	24	28			30	22		

HAGLROS = HAGLR opposite strand lncRNA, KCNQ1OT1 = potassium voltage-gated channel subfamily Q member 1 opposite strand/antisense transcript 1, PTC = papillary thyroid cancer,
* $P < .05$ was considered statistically significant.

group) were identified using qRT PCR. Both *KCNQ1OT1* (fold change: 2.67, $P < .001$) and *HAGLROS* expressions (fold change: 1.83, $P < .001$) were significantly higher in tumor tissues compared to adjacent normal thyroid tissues (Figs. 1A and 2A).

3.2. Associations of KCNQ1OT1 and HAGLROS expressions with clinicopathological features of the PTC patients

The patients (n = 128) were divided into 2 groups – low and high expression – to examine the relationship between the clinicopathological features and the expression levels of lncRNAs. Accordingly, the expression level of *KCNQ1OT1* was associated with the gender ($P = .019$) and microcarcinoma ($P = .006$), while *HAGLROS* expression was associated with microcarcinoma ($P = .012$) and tumor diameter ($P = .007$). However, no significant correlation was determined between the expressions of lncRNAs and other clinical parameters – namely age, lymphovascular invasion, lymph node metastasis, primary tumor, TNM stage, extra thyroidal extension, multicentricity, and multifocality (Table 1). Hence, the expression of lncRNAs was subsequently examined only in papillary microcarcinoma samples (tumor size of ≤ 1). The expression of *KCNQ1OT1* was higher in papillary microcarcinoma tumor samples than it was in the normal thyroid tissues ($P = .048$); however, no significant difference was found in *HAGLROS* expression ($P = .272$), (Figs. 1B and 2B). On the other hand, upon examining the papillary carcinoma samples only, both *KCNQ1OT1* and *HAGLROS* expressions were also significantly higher in tumor tissues than they were in the normal ones.

4. Discussion

Recent studies have revealed that lncRNAs can regulate the expression of genes involved in various cellular processes at different levels, thus playing a key role in the regulation of biological processes. Indeed, this data supports the notion that lncRNAs are key to tumorigenesis and disease progression.[24] In the literature, changes in the expression of lncRNAs have been associated with the development and progression of many types of cancer.[25] On the other hand, *KCNQ1OT1* has been associated with the development and prognosis of colorectal cancer, sarcoma, osteosarcoma, tongue squamous cell carcinoma, and breast cancer.[7] However, to the best of our knowledge, no one has yet studied the relationship between these lncRNAs and PTC development (including its clinical features)–beyond one

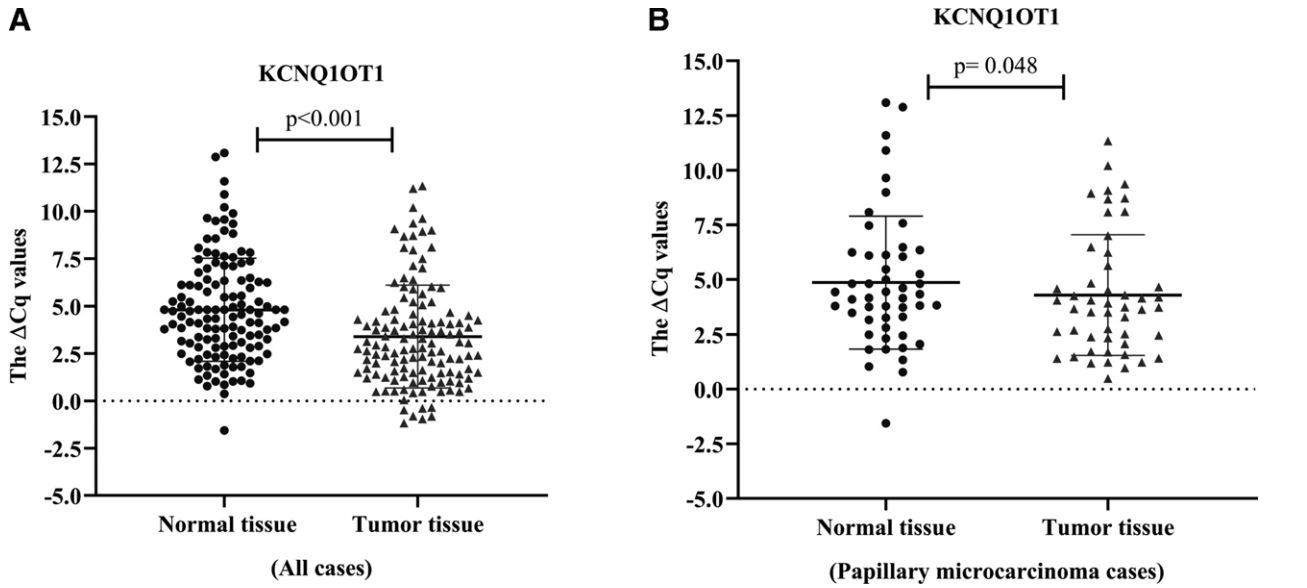

Figure 1. (A) Relative expression of KCNQ1OT1 in tumor and normal tissues of all cases (n = 128) b Relative expression of KCNQ1OT1 in tumor and normal tissues of papillary microcarcinoma cases (n = 48). All of the data are presented as the mean ± standard deviation. Paired Student *t* test was used for statistical analysis. *P* < .05 was statistically significant.

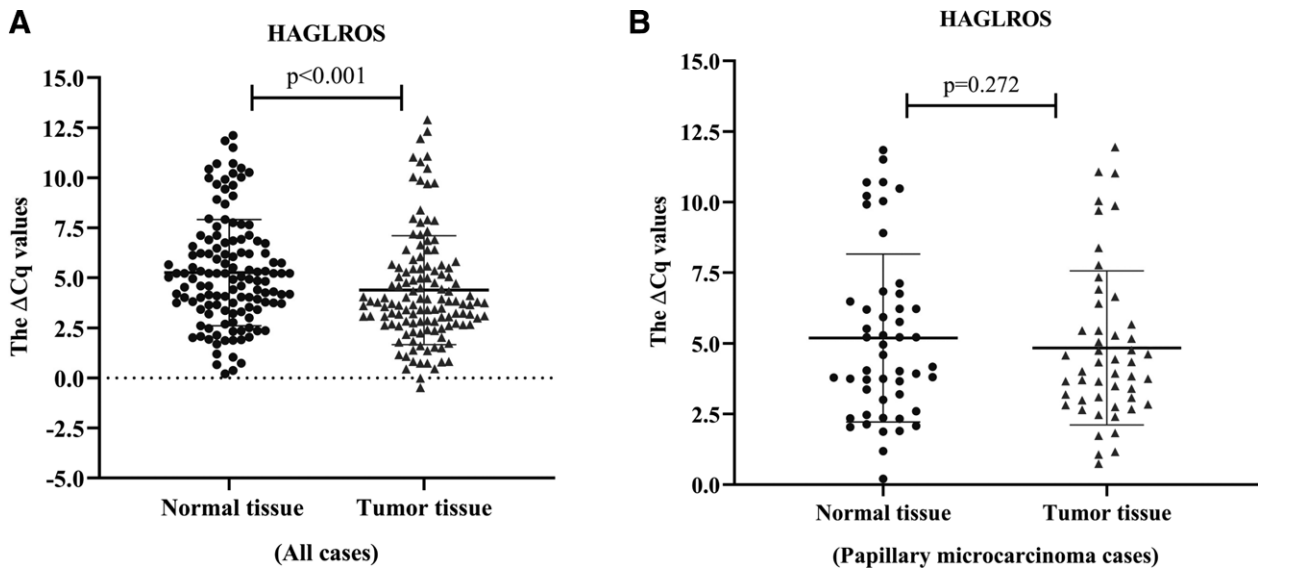

Figure 2. (A) Relative expression of *HAGLROS* in tumor and normal tissues of all cases (n = 128) b Relative expression of *HAGLROS* in tumor and normal tissues of papillary microcarcinoma cases (n = 48). All of the data are presented as the mean ± standard deviation. Paired Student *t* test was used for statistical analysis. *P* < .05 was statistically significant.

study investigating the relationship between *HAGLROS* and PTC.[22]

One study reported that the expression of *KCNQ1OT1* was upregulated in tumor samples of NSCLC patients and NSCLC cell lines. The findings of the present study revealed that *KCNQ1OT1* regulated *JAG1* expression by sponge *miR-129-5p*, and thereby increased proliferation, migration and invasion in NSCLC cells. Therefore, it seems as though *KCNQ1OT1* might be an important therapeutic target for NSCLC.[13] Another study reported that *KCNQ1OT1* upregulated *CAPN10* expression through sponging *miR-142-5p*, thereby promoting proliferation and migration of ovarian cancer cells.[12] Gong et al[26], found that expression of *KCNQ1OT1* was upregulated in tumor samples of glioma patients and glioma cell lines. They have also showed that *KCNQ1OT1* enhances *Cyclin E2* expression by acting as *miR-370* sponge, and thus contributes to glioma tumorigenesis. Zhang et al[27], argued that increased expression of *KCNQ1OT1* contributed to the development of tongue squamous cell carcinoma, and is associated with poor prognosis. The authors also reported that *KCNQ1OT1* expression was linked to Gleason score, T stage, and lymph node status. The findings of the present study revealed that the expression of *KCNQ1OT1* was upregulated in PTC tumor samples compared to the adjacent noncancerous thyroid tissues. Moreover, its expression was associated with microcarcinoma and gender. In addition, there was also elevated *KCNQ1OT1* expression in the tumor samples of papillary microcarcinoma patient group. The results of the present study were compatible with the literature and indicated that increased *KCNQ1OT1* expression might contribute to the development of PTC. Furthermore, this increased expression

of *KCNQ1OT1* in the papillary microcarcinoma tumor samples suggested that this lncRNA might play a role in the early stages of PTC tumorigenesis. Therefore, future studies ought to evaluate its usability as an early diagnosis marker with larger numbers of samples. The incidence of PTC is 3 times greater in women than it is in men.[4] Likewise, it was found in the present study that the ratio of female patients to male patients was approximately 5:1 and 16 of the 22 male patients fell in the high expression group (Table 1). In other words, the increase in *KCNQ1OT1* expression in male PTC patients might be more significant and is more likely to cause disease. However, since there is no other study in the literature that found a relationship between *KCNQ1OT1* expression and gender, these data should be confirmed by other studies with more PTC patients.

Various studies on different cancer types have revealed that *KCNQ1OT1* contains a binding site for various miRNAs and contributes to tumorigenesis with competing endogenous RNA (ceRNA) function.[7] Of these, miRNAs, *miR-296-5p, miR-211-5p, miR-124-3p, miR-204, miR-145-5p, miR-506, 129-5p, miR-153, miR-15a* and *miR-9-5p* also act as tumor suppressor miRNAs in PTC.[7,28] Although the interaction between *KCNQ1OT1* and these miRNAs in PTC needs to be confirmed by functional studies, it nevertheless suggests that *KCNQ1OT1* may contribute to PTC tumorigenesis, thereby supporting the data of the current study.

A study by Tang et al[29], reported that *HAGLROS* was overexpressed in tumor samples from HCC patients and HCC cell lines. They moreover suggested that *HAGLROS* upregulated the expression of *karyopherin α2* by sponging for *miR-26b-5p* and inactivated the p53 signaling pathway, thus contributing to malignant progression of HCC. A study in head and neck squamous cell carcinoma reported that *HAGLROS* was 1 of 13 optimal diagnostic biomarkers.[30] Another study suggested that the expression of *HAGLROS* increased in triple negative breast cancer and high *HAGLROS* expression in particular was associated with poor overall survival.[16] Shu et al[31], also reported that high *HAGLROS* expression contributed to the development and poor prognosis of diffuse large B-cell lymphoma through interaction with miR-100. Guo et al[22],–in their study on papillary thyroid cancer TCGA data – demonstrated that *HAGLROS* was among the top 10 aberrantly expressed lncRNAs. In the present study, it was determined that *HAGLROS* expression was significantly higher in PTC tumor samples compared to the adjacent normal thyroid tissues. Moreover, *HAGLROS* expression was associated with microcarcinoma and tumor size. On the other hand, *HAGLROS* expression did not change significantly in the papillary microcarcinoma samples alone. The data of the present study are similar to that of Guo et al, as well as studies conducted on different cancer type and pointing out that *HAGLROS* plays a role in the development and progression of PTC. On the other hand, the absence of any significant change in *HAGLROS* expression in the papillary microcarcinoma patient group suggests that the possible role of *HAGLROS* in PTC tumorigenesis begins to become evident after the disease reaches a certain stage.

The contribution of *HAGLROS* to PTC tumorigenesis may be possible by playing the role of ceRNA. Studies in different cancers have reported that *HAGLROS* harbors a binding site for *miR-206, miR-152* and *miR-26b-5p* and functions as ceRNA.[18,21,29,32] These miRNAs were also tumor suppressor miRNAs whose expression was downregulated in PTC.[28,33–35] Hence, *HAGLROS* might contribute to PTC tumorigenesis via these miRNAs.

The present study has two limitations: The lack of functional studies to the support expression data, and; The partially small number of patients. Nevertheless, we have managed to demonstrate that *KCNQ1OT1* and *HAGLROS* lncRNAs are highly expressed in PTC tissues, *KCNQ1OT1*expression is high in microcarcinoma samples, and *HAGLROS* expression is associated with tumor size. The results of the present study indicated that *KCNQ1OT1* and *HAGLROS* may contribute to PTC development and disease progression and they have the potential to be used as therapeutic targets for PTC. Large-scale studies involving patients from different populations would be beneficial for the generalizability of our results.

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