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ORIGINAL ARTICLE

Correlations of HOTAIR expression with pathological stage, CT characteristics and prognosis of patients with papillary thyroid carcinoma

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Summary

Purpose: *To detect the expression level of HOTAIR in patients with papillary thyroid carcinoma (PTC) and further investigate its associations with the pathological stage, computed tomography (CT) characteristics and prognosis of these patients.*

Methods: *The expression level of HOTAIR was assessed in normal tissues and thyroid cancer tissues of PTC patients and nodular goiter tissues of patients with nodular goiter via reverse transcription-polymerase chain reaction (RT-PCR). Additionally, the relations of HOTAIR expression level with the clinicopathological features, CT characteristics and prognosis of PTC patients were analyzed. Finally, Western blotting was employed to detect the protein expression level of vascular endothelial growth factor (VEGF) in the normal tissues, thyroid cancer tissues and nodular goiter tissues.*

Results: *The expression level of HOTAIR was notably higher in the thyroid cancer tissues than in the normal tissues and nodular goiter tissues ($p<0.05$). The high expression of HOTAIR was significantly correlated with tumor size, depth of invasion, lymph node metastasis, TNM stage and distant metastasis ($p<0.05$). Univariate and multivariate analyses revealed that factors such as tumor size, TNM stage, lymph node metastasis and distant metastasis had statistical significance. CT imaging showed that the high expression of HOTAIR had obvious associations with tumor density, shape, strengthening residual circle and calcification ($p<0.05$). Kaplan-Meier analysis revealed that the 7-year survival of PTC patients with a low expression of HOTAIR was clearly better than that of those with a high HOTAIR expression. Lastly, it was found that the protein expression of VEGF was higher in the thyroid cancer tissues than that in the normal tissues and nodular goiter tissues ($p<0.05$). Besides, the expression of VEGF in the thyroid cancer tissues was remarkably higher in PTC patients with a high expression of HOTAIR than in those with a low HOTAIR expression ($p<0.05$).*

Conclusions: *The expression level of HOTAIR is distinctly increased in PTC tissues, and has a positive correlation with the pathological stage and poor prognosis of patients. HOTAIR can serve as a diagnostic or prognostic marker for patients with papillary thyroid carcinoma.*

Key words: *HOTAIR, papillary thyroid carcinoma, VEGF, pathological stage, prognosis*

Introduction

Papillary thyroid carcinoma (PTC) shows an increasing incidence rate in recent years, with younger average age at onset, and has become the most common malignant tumor of endocrine organs [1]. PTC is a low-grade malignant tumor, so most PTC patients have a good prognosis. However, lymph node metastasis is still detected in some patients in the early stage of disease, which becomes one of the key factors affecting the quality of life of patients [2,3]. For this reason, further clarifying the

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pathogenesis and discovering the molecular markers for thyroid cancer are of great significance for the early diagnosis and prognostic evaluation of this disease.

Human transcriptome includes many protein-coding messenger ribonucleic acids (mRNAs) and massive non-protein-coding transcripts like long non-coding RNAs (lncRNAs) and microRNAs (miRs) [4,5]. In recent years, attention has been gradually paid to the role of lncRNAs in human diseases. Increasing evidence denotes that lncRNAs, "star molecules" that are able to interact with RNAs, DNAs or proteins, and promote or inhibit the expression of protein-coding genes, can regulate many important activities, such as mammalian cell proliferation, differentiation, apoptosis, development and metabolism [6]. Besides, the diagnostic value of lncRNAs in tumors is also increasingly favored. For instance, lncRNA SPRY4-IT has a close correlation with the poor prognosis of patients with thyroid cancer, and can affect the development and progression of thyroid cancer [7]. However, there is no report on the role of lncRNA-Homeobox transcript antisense intergenic RNA (HOTAIR) in PTC.

In this study, the expression of HOTAIR was first detected in normal tissues and thyroid cancer tissues of PTC patients and nodular goiter tissues of patients with nodular goiter, and the correlations of the expression level of HOTAIR with the clinicopathological characteristics, imaging characteristics and prognosis of PTC patients were further analyzed. Finally, the pathogenic mechanism of HOTAIR in PTC was explored.

Methods

Tissue specimens

A total of 100 pairs of thyroid cancer tissue and normal tissue specimens surgically removed were collected, followed by removal of bloodiness with normal saline. Next, the specimens were cut into pieces, put into Eppendorf (EP) tubes and stored in a refrigerator at -80°C, or otherwise, the specimens were not cut off but fixed with 10% neutral formalin. Besides, 35 cases of nodular goiter tissues were collected during the same period. The postoperative pathological results of tissues from PTC patients and patients with nodular goiter were confirmed by pathologists of our hospital, and these patients had no primary tumors in other parts of the body. Normal tissues were sampled at about 2 cm from the edge of the tumor, without cancer cell infiltration pathologically confirmed after operation. In addition, the gender, age, pathological stage and tumor metastasis status of PTC patients were collected. This study was approved by the Ethics Committee of Zhongda Hospital. Signed written informed consents were obtained from all participants before the study entry.

Computed tomography (CT) scan

Scan was carried out using a GE light-speed 64-slice spiral CT scanner as follows: patients were in supine position with cervical hyper extension. Then, CT plain scan (slice thickness: 5-10 mm, and parameters: 50 mA, 130 V) was performed first. After that, enhancement scan was conducted on the location of lesions with the same body position, with Omnipaque (100 mL, injection rate: 3 mL per second) as the contrast agent. The imaging data of each patient were collated, based on which imaging analysis of key indicators such as location, morphology, density and calcification status of lesions was completed by radiologists of the CT room without knowing the clinical information of patients.

Detection of expression level of HOTAIR via reverse transcription-polymerase chain reaction (RT-PCR)

Firstly, the total RNAs were extracted from the thyroid cancer tissues and normal tissues of PTC patients and nodular goiter tissues of patients with nodular goiter by TRIzol method (Invitrogen, Carlsbad, CA, USA). Next, the concentration and purity of the RNAs extracted were measured by an ultraviolet spectrophotometer, with A_{260}/A_{280}=1.8-2.0, so as to implement the following procedures: the RNAs were reversely transcribed into complementary DNAs (cDNAs) that were then stored in the refrigerator at -80°C. Subsequently, RT-PCR was carried out using the system consisting of 2.5 μL of 10× Buffer, 1 μL of cDNAs, 0.5 μL of forward primers (20 μmol/L), 0.5 μL of reverse primers (20 μmol/L), 10 μL of LightCycler® 480 SYBR Green I Master (2×), and 5.5 μL of ddH_2O. Note: The amplification system of RT-PCR was the same. Primer sequences used in the study are shown in Table 1.

Measurement of vascular endothelial growth factor (VEGF) expression through Western blotting

Freshly frozen thyroid tissues in the refrigerator at -80°C in each group were firstly taken out, preliminarily cut into pieces using scissors, and ground thoroughly with a grinder. Then, the tissues were subjected to ultrasonic lysis, and the resulting lysate was centrifuged. Thereafter, the supernatant was aspirated and sub-packaged into Eppendorf (EP) tubes. Later, the protein concentration was determined through bicinchoninic acid (BCA) method (Pierce, Rockford, IL, USA) and ultraviolet spectrophotometric assay, and all the sample proteins were maintained at a constant volume and equal concentration. Next, the proteins were subpackaged and preserved in the refrigerator at -80°C.

Table 1. Primer sequences of indicators in RT-PCR

Target gene		*Primer sequence*
GAPDH	Forward	5' -ACGAAAGCTAGTGTGTGACCA- 3'
	Reverse	5' -ACGTAGCTAGTGTAGTCGTAGT- 3'
HOTAIR	Forward	5' -CCGTGATAGTCGATCGTAGTGC- 3'
	Reverse	5' -ACGTAGTCGTAGTCCCACACCC- 3'

Total proteins extracted were subjected to sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). After that, the proteins in the gel were transferred onto a cellulose acetate/polyvinylidene fluoride (PVDF) membrane (Millipore, Billerica, MA, USA) and incubated with VEGF primary antibodies (diluted in PBS at 1:400) at 4°C overnight. Following the incubation with goat anti-rabbit secondary antibodies in the dark for 1 h, the protein bands were scanned and quantified using an Odyssey membrane scanner (Seattle, WA, USA).

Follow-up

The 100 PTC patients were given endocrine therapy with levothyroxine sodium tablets after operation. All patients were followed up via outpatient B-ultrasound, CT and TSH examinations and telephone calls. The longest follow-up time was 7 years. Kaplan-Meier survival curves were plotted at the same time.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was utilized for analysis of all data. Measurement data were expressed as mean ± standard deviation. T-test was employed for data comparison between groups. Categorical data were analyzed using x^2 test or Fisher's exact test. The Cox proportional hazards model was adopted for multivariate survival analysis. P<0.05 suggested that the difference was statistically significant.

Results

Expression of HOTAIR in thyroid cancer tissues and normal tissues of PTC patients

RT-PCR results (Figure 1) showed that the expression level of HOTAIR was markedly higher in the thyroid cancer tissues than that in the normal tissues (p<0.05).

Expression of HOTAIR in PTC patients and patients with nodular goiter

According to Figure 2, the expression level of HOTAIR was prominently higher in the thyroid cancer tissues than in the nodular goiter tissues (p<0.05).

Correlations of HOTAIR expression level with clinical features of PTC patients

Subsequently, the associations of HOTAIR expression with clinicopathological parameters of 100 PTC patients were analyzed, and the significance of the expression for their clinicopathological characteristics and prognosis were investigated. As shown in Table 2, there were no statistically significant differences in the gender and age between PTC patients with a high expression of HOTAIR and those with a low HOTAIR expression (p>0.05). However, the tumor size, depth of invasion, lymph node metastasis, TNM stage and distant metastasis displayed statistically significant differences between the two groups of patients (p<0.05). Specifically, PTC patients with a high expression of HOTAIR had larger tumors, deeper invasion, more metastatic lymph nodes, higher TNM staging, and more distantly metastatic tumors. These results imply that PTC patients with a high HOTAIR expression have more significant clinical characteristics than those with a low expression of HOTAIR.

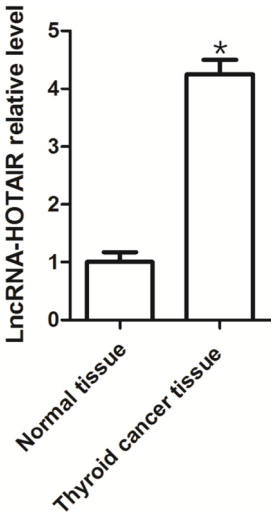

Figure 1. Expression of HOTAIR in thyroid cancer tissues and normal tissues of PTC patients. Normal tissue: adjacent tissues, and Thyroid cancer tissue: thyroid carcinoma tissues. *p<0.05: a statistical difference of Cancer tissue *vs.* Normal tissue.

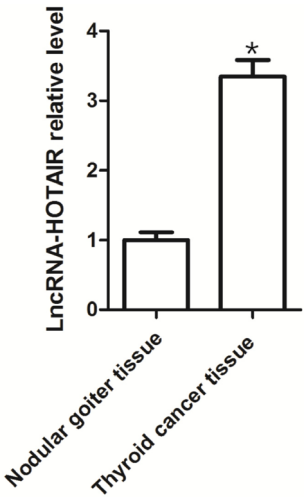

Figure 2. Expression of HOTAIR in PTC patients and patients with nodular goiter. Nodular goiter tissue: nodular tissues of patients with nodular goiter, and Thyroid cancer tissue: thyroid carcinoma tissues. *p<0.05: high HOTAIR vs. Nodular goiter tissues.

Table 2. Correlations of HOTAIR expression level with clinicopathological features of PTC patients (n=100)

Clinicopathological data	*Number of patients*	*HOTAIR expression level*		x^2	*p*
		High expression n (%)	*Low expression n (%)*		
Gender				3.229	0.782
Male	62	34 (54.8)	28 (45.2)		
Female	38	16 (42.1)	22 (57.9)		
Age, years				0.331	0.349
≤45	26	18 (69.2)	8 (30.8)		
>45	74	38 (51.4)	36 (48.6)		
Tumor size, cm				5.192	0.031
≤1	70	32 (45.7)	38 (54.3)		
>1	30	22 (73.3)	8 (26.7)		
Depth of invasion				22.129	<0.001
T1	15	3 (20)	12 (80)		
T2	18	5 (27.8)	13 (72.2)		
T3	40	33 (82.5)	7 (17.5)		
T4	27	18 (66.7)	9 (33.3)		
Lymph node metastasis				18.293	<0.001
N0	14	2 (14.3)	12 (85.7)		
N1	30	11 (36.7)	19 (63.3)		
N2	34	30 (88.2)	4 (11.8)		
N3	22	20 (90.9)	2 (9.1)		
TNM stage				24.932	<0.001
I	11	3 (27.3)	8 (72.7)		
II	20	6 (30)	14 (60)		
III+IV	69	50 (72.4)	19 (27.5)		
Distant metastasis				12.902	0.001
M0	88	41 (46.6)	47 (53.4)		
M1	12	1 (8.3)	11 (91.7)		

Table 3. Univariate and multivariate analyses of HOTAIR and overall survival of PTC patients

	Univariate analysis			*Multivariate analysis*		
	HR	*p*	*95% CI*	*HR*	*p*	*95% CI*
LncRNA-HOTAIR expression	0.421	<0.001	0.301-0.662	0.470	<0.0018	0.322-0.871
High *vs.* Low						
Age (years)	2.228	0.081	0.522-0.892	0.917	0.562	0.619-1.286
≤45 *vs.* >45						
Tumor size	0.415	0.003	0.283-0.781	0.488	0.206	0.569-2.863
≤1 cm *vs.* >1 cm						
Depth of invasion	0.772	0.416	0.116-0.629	0.637	0.622	0.412-1.821
T1/2 *vs.* T3/4						
TNM stage	7.883	<0.001	5.839-9.302	8.291	<0.001	4.990-11.283
I/II *vs.* III/IV						
Lymph node metastasis	1.992	<0.001	1.672-2.198	3.271	<0.001	2.873-4.002
N0-1 *vs.* N2-3						
Distant metastasis	6.892	<0.001	2.199-14.212	2.119	0.681	0.263-1.226

Table 4. Correlations of HOTAIR expression level with CT characteristics of PTC patients (n=100)

Clinicopathological data	*Number of patients*	*HOTAIR expression level*		x^2	*p*
		Low expression n (%)	*High expression n (%)*		
Density				6.123	0.031*
Uniform	55	44 (80)	11 (20)		
Uneven	45	6 (13.3)	39 (86.7)		
Shape				5.203	0.003*
Regular	30	25 (83.3)	5 (16.7)		
Irregular	70	25 (35.7)	45 (64.3)		
Strengthening residual circle				3.228	0.001
(-)	36	30 (83.3)	6 (16.7)		
(+)	66	20 (30.3)	44 (69.7)		
Calcification				4.029	0.021
(-)	46	36 (78.3)	10 (21.7)		
(+)	54	14 (25.9)	40 (74.1)		

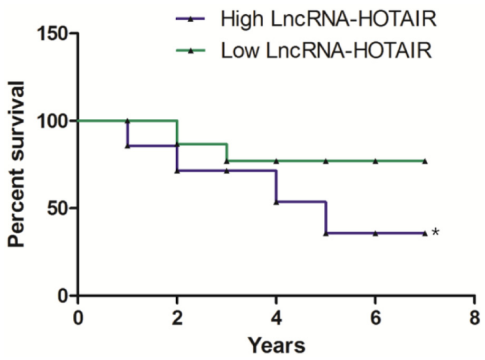

Figure 3. Comparison of 7-year survival rate between PTC patients with a high HOTAIR expression and those with a low expression of HOTAIR. High HOTAIR: PTC patients with a high HOTAIR expression, and Low HOTAIR: PTC patients with a low expression of HOTAIR. *p<0.05: High vs. Low HOTAIR.

Effect of HOTAIR expression on prognosis of PTC patients

The effect of HOTAIR expression on the prognosis of PTC patients was further determined via univariate and multivariate analyses. Univariate analysis showed that the poor prognosis of PTC patients was closely correlated with the high expression of HOTAIR (HR=0.421, 95% CI=0.301-0.662, p<0.001), tumor size (HR=0.415, 95% CI=0.283-0.781, p=0.003), TNM stage (HR=7.883, 95% CI=5.839-9.302, p<0.001), lymph node metastasis (HR=1.992, 95 % CI=1.672-2.198, p<0.001) and distant metastasis (HR=6.892, 95% CI=2.199-14.212, p<0.001) (Table 3). The results of multivariate analysis uncovered that the high expression of HOTAIR (HR =0.470, 95% CI=0.322-0.871, p<0.0018) and lymph node metastasis (HR=3.271, 95% CI =2.873-4.002, p<0.001) were independent risk factors for PTC patients with a poor prognosis (Table 3).

Correlations of HOTAIR expression with CT characteristics of PTC patients

The CT reports of PTC patients were further analyzed, and it was discovered that in comparison with PTC patients with a low HOTAIR expression, those with a high HOTAIR expression exhibited higher proportions of uneven density (p<0.05), irregular shape (p<0.05), strengthening residual circle (p<0.05), and calcification (p<0.05) (Table 4).

Comparison of 7-year survival rate between PTC patients with a high HOTAIR expression and those with a low expression of HOTAIR

The 100 PTC patients were followed up for 7 years. The results showed that the 7-year overall survival rate of PTC patients with a low expression of HOTAIR was significantly higher than that of those with a high HOTAIR expression (p<0.05) (Figure 3).

Relations of HOTAIR expression with VEGF expression in PTC patients

The results of Western blotting (Figure 4) showed that the protein expression of VEGF was dramatically higher in the thyroid cancer tissues than that in the normal tissues and nodular goiter tissues (p<0.05), and it was visibly higher in PTC patients with highly expressed HOTAIR than that in those with lowly expressed HOTAIR (p<0.05).

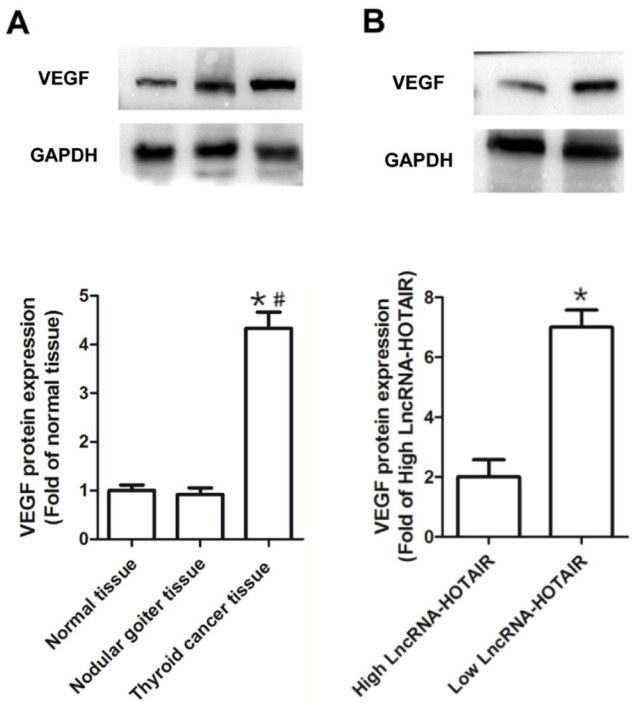

Figure 4. Relations of HOTAIR expression with VEGF expression in PTC patients. **A:** Normal tissue: adjacent tissues, Nodular goiter tissue: nodular tissues in patients with thyroid goiter, and Thyroid cancer tissue: thyroid cancer tissues. *p<0.05 vs. Normal tissues, and #p<0.05: a statistical difference vs. Nodular goiter tissues. **B:** High HOTAIR: PTC patients with High and Low HOTAIR expression. *p<0.05 of High vs. Low HOTAIR.

Discussion

Thyroid cancer, the most common thyroid malignancy, accounts for 1% of all malignant tumors. It can be classified into 4 types: papillary carcinoma, follicular carcinoma, medullary carcinoma, and anaplastic carcinoma, among which anaplastic thyroid carcinoma displays the worst prognosis [8]. Thyroid cancer is caused by various factors, such as long-term iodine deficiency, long-term radiation to the thyroid, abnormal hormone levels and genetic mutations [9]. Additionally, studies have manifested that thyroid cancer is also induced by hyperthyroidism, thyroid hyperplasia, and chronic lymphatic thyroiditis [10]. Thyroid cancer has no typical characteristics in the early stage, but symptoms such as dysphagia, dyspnea and hoarseness may occur in the advanced stage. Thyroid cancer cells further metastasize and spread to distant organs and lymph nodes with the progression of disease [11]. As a result, patients usually have cancer cells already spread at diagnosis, so they are prone to missing the best opportunity for treatment. Further discovering diagnostic and prognostic markers for thyroid cancer is of great significance for the early diagnosis and prognostic assessment of thyroid cancer patients.

LncRNAs, a kind of non-coding RNAs with over 200 bp in length, are considered as "transcription noise" at first, but have been proven in subsequent studies to participate in various important bioactivities, including epigenetic control, gene expression regulation, RNA maturation (including splicing and editing), and maintenance of chromatin structure [12,13]. Besides, the role of lncRNAs in tumors has gradually been revealed. For example, lncRNA-NEAT1 can act as a prognostic biological marker for clear cell renal cell carcinoma, and affects the progression of the carcinoma by regulating epithelial-mesenchymal transition (EMT) [14]. LncRNA-PROX1-AS1 has an obviously high expression level in thyroid cancer cells than in normal thyroid epithelial cells, and its silencing may modulate the expression of EMT to suppress the invasion and migration of thyroid cancer cells [15]. HOTAIR, a member of the lncRNA family, plays a crucial regulatory role in the development, progression and prognosis of many tumors. A previous study reported that down-regulating HOTAIR is able to repress the proliferation, invasion and migration of colon cancer cells by mediating cell cycle-related protein p21, suggesting that HOTAIR serves as an important oncogene [16]. In the case of lung cancer, the expression of HOTAIR significantly rises and has an association with metastasis and poor prognosis of lung cancer, and is also capable of promoting the proliferation, survival, invasion, metastasis and drug resistance of lung cancer cells [17]. Moreover, the up-regulation of HOTAIR expression is positively correlated with tumor progression and down-regulation of miR-217 in the case of renal cell carcinoma, further indicating that HOTAIR can facilitate the growth of renal cancer cells by regulating the miR-217/HIF-1α/AXL axis [18]. In this study, it was found that the expression level of HOTAIR was clearly raised in the thyroid cancer tissues, and its high expression was prominently associated with the more significant pathological characteristics and poor prognosis of patients, suggesting that HOTAIR plays an oncogenic role in the development and progression of PTC.

Neovascularization is a basic process during the growth, metastasis and spread of tumors, in which VEGF pathway is the key regulator. A previous study revealed that during tumorigenesis, the VEGF signaling pathway is evidently activated, and its expression level has a distinctly positive correlation with the malignancy of tu-

mors. HOTAIR is able to promote tumor invasion by up-regulating VEGF, MMP-9 and EMT-related genes [19]. The results of this study uncovered that the expression level of VEGF was significantly higher in the thyroid cancer tissues than in the normal tissues and nodular goiter tissues, and it was positively correlated with the expression of HOTAIR. Therefore, it is speculated that HOTAIR may facilitate the enhancement of malignant phenotype of thyroid cancer cells by up-regulating VEGF.

Conclusions

HOTAIR displayed a distinctly increased expression level in thyroid cancer tissues, and its expression was positively correlated with poor prognosis of patients. HOTAIR is expected to become a novel diagnostic marker for patients with thyroid cancer.

Conflict of interests

The authors declare no conflict of interests.

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