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The Differential Expression of Wnt10a in PTC and HT with PTC*

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ABSTRACT Objective: To investigate the expression and clinical significance of Wnt10a in papillary thyroid carcinoma (PTC) and Hashimoto's thyroiditis associated with papillary thyroid carcinoma (HT-PTC). **Methods:** The relative expression of Wnt10a mRNA was determined by real time-polymerase chain reaction (RT-PCR) in 41 fresh thyroid tissues (18 PTC tissues, 12 HT with PTC tissues and 11 nodular goiter tissues). The relative expression of Wnt10a protein was determined by immunohistochemical SP method in 50 paraffin-embedded thyroid tissues (20 PTC tissues, 20 HT with PTC tissues and 10 nodular goiter tissues). **Results:** ① Statistical analysis showed that the expression of Wnt10a was significantly higher in PTC and HT with PCR tissues than in nodular goiter tissues ($P<0.05$) and the expression was significantly higher in PTC tissues than in HT with PTC tissues ($P<0.05$). ② The Wnt10a protein expression had significant difference between thyroid cancer and nodular goiter ($P<0.05$), but the expression did not have significant difference between PTC and HT with PTC ($P>0.05$). ③ The expression of Wnt10a mRNA and protein had no significant relation with age, gender and lymph node metastasis in thyroid cancers ($P>0.05$) and only have relationship with pathological type. **Conclusions:** We identified that Wnt10a was differentially and highly expressed in PTC tissues and HT with PTC tissues. The study provided an effective early detection biomarker of PTC and hoping to contribute to the early diagnosis and pathological type determination of thyroid cancer.

Key words: PTC; HT with PTC; Wnt10a; RT-qPCR; Immunohistochemistry

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Introduction

Thyroid carcinoma is one of the most common endocrine malignancies, of which PTC (papillary thyroid carcinoma) accounts for 60%~70% and the incidence of PTC is increasing in recent years[1].

HT (Hashimoto's thyroiditis), also named as Hashimoto's disease or CLT (chroniclymphocytic thyroiditis), is an autoimmune disease. In recent years, an increasing number of reports indicated that the incidence of HT with PTC (Hashimoto's thyroiditis associated with papillary thyroid carcinoma) is rising [2,3]. Clinicians and experts at home and abroad paid much attention to HT with PTC nowadays. Larso [4] found that HT patients may have a higher risk of suffering from thyroid carcinoma than ordinary people. Thus researching the pathogenesis of HT with PCT actively and searching for an iconic gene to detecting the occurrence and prognosis of HT with PTC is significant for early diagnosis and clinical treatment.

Wnt signaling pathway is a critical path of cell development and growth regulation [5,6].The Wnt proteins coded by Wnt genes combine with relevant membrane receptors and cause the transporting from cytoplasm to nucleus of β -catenin. The β -catenin in nucleus activates the transcription of related genes and plays an important role in tissue formation, function exerting and embryonic development [7-9]. Precursor mRNA transcripted by gene Wnt10a in nucleus synthesizes corresponding protein through editing and translation, and thus exerts the biological functions of Wnt10a [10]. A variety of tumors occurred when the pathway was abnormal. It has been reported that Wnt10a is highly expressed in many malignant tumors such as esophageal cancer, gastric cancer, colorectal cancer, renal cell cancer and endometrial cancer [11-16], but the relationship between Wnt10a mRNA and thyroid cancer has not been reported.

In this study, we compared the Wnt10a mRNA and protein expression among PTC, HT with PTC and nodular goiter using qPCR (Real-time Quantitative PCR Detecting System) and immunohistochemistry, further we explored the associations between Wnt10a expression and clinicopathological characteristics of PTC (Pathological type, degree of differentiation, TNM stage, lymph node metastasis) to provide a new reference for PTC diagnosis, treatment and prognostic.

1 Materials and methods

1.1 Materials

The current study was conducted on 96 patients of Asian descent who had undergone thyroid surgery in Affiliated hospital of Qingdao University between January, 2014 and June, 2014, in which 41 tissues were fresh thyroid tissues and 50 were paraffin-embedded tissues. This study complies with the Declaration of Helsinki and was approved by the Local Ethics Committee. Informed consent was obtained from each subject or his/her guardian.

There were 18 PTC tissues, 12 HT with PTC tissues and 11

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nodular goiter tissues in fresh thyroid tissues and 20 PTC tissues, 20 HT with PTC tissues and 10 nodular goiter tissues in paraffin-embedded tissues. The average age of all patients is 47.80 ± 13.02 in fresh tissues. There were no significant differences in the age and sex ratios and the PTC patients did not get any preoperative radiotherapy, chemotherapy or other cancer treatment. The tissues were diagnosed by intraoperative quick frozen section and postoperative pathologic examination. The fresh tissues were collected from surgical operation and kept in ultra-low temperature freezer.

1.2 Methods

1.2.1 RNA extraction Genomic RNA was extracted from frozen specimens by standard techniques. RNA was extracted using a TRIpure LS Reagent (Bioteke, Beijing, China) according to the manufacturer's instructions. The RNA quality was assessed using nuc leic acid-protein analyzers (Thermo, USA). cDNA was synthesized from 5 ng total RNA that extracted from 41 fresh tissues, using the Thermo RT Kit cDNA Regent (Bioteke, Beijing, China).

1.2.2 Determining of Wnt10a mRNA The expression levels of Wnt10a were quantified using the Power 2 × SYBR Real-time PCR Premixture (Bioteke, Beijing, China). According to the manufacturer's instructions, qPCR was performed on the Roche Light Cycler® 96. The expression of mRNA was defined based on the threshold of amplification cycle number (Ct), and the quantity of each mRNA was normalized to the expression of U6 nuclear RNA using the equation of $2^{-\triangle Ct}$ ($\triangle Ct$=Ct Wnt10a-CtU6).The upstream primer sequence of Wnt10a was CCCATCTTCAGCAGAGGTTTCC (5'~ 3') and the downstream primer sequence was CAGCCACAGGCCTTCAGTTT (5'~ 3'). The upstream primer sequence of U6 was GCTTCGGCAGCACATATACTA (5'~ 3') and the downstream primer sequence was AACGCTTCACGAATTTGCGT (5'~ 3'). PCR primers were synthesized by Hanyu Bio (Shanghai, China).

1.2.3 Immunohistochemistry Wnt10a rabbit anti-human monoclonal antibody was synthesized by Abcam Company. All tissues were fixed in 10% neutral formalin, embedded in paraffin, sliced routinely. Each wax block and immunohistochemical stain were taken from 4 μm thick sections according to the kit instructions. PBS was used as negative control instead of primary antibody and a known breast cancer positive sheet was used as positive control. The immunohistochemical results were blind diagnosed by two pathologists with 5% - 10% difference. The expression of Wnt10a protein was determined by the sum of the scores of intracellular cytoplasmic staining intensity and percentage of positive cells [17]. 5 high-power field (200 ×) were selected randomly to judge the result: ① No staining counted 0 point, pale yellow counted 1 point, brown counted 2 points, tawny counted 3 points. ② Cells positive rate <5% counted 0 point, 5%-25% counted 1 point, 25%-50% counted 2 points,>50% counted 3 points. The results were judged by the sum of the two scores above: 0 point was negative, l-2 point was weak positive (+) , 3-4 point was medium positive (++) , 5-6 point was strong positive (+++).

1.3 Statistical analysis

The Wnt10a expression data were analyzed using SPSS version 17.0. The data was signified by median (interquartile range) if the data was non-normal distributed or heterogeneity of variance. The data was signified by mean ± standard deviation if the data was normal distributed and homogeneity of variance. The Mann-Whitney U test of two independent samples was used to compare the expression of Wnt10a in PTC tissues, HT with PTC tissues and nodular goiter tissues combined with different pathological parameters. The x^2 test and Fisher exact test were used to analyze the data of immunohistochemistry. P<0.05 was considered statistically difference.

2 Results

According to statistics, there was no significant difference between the three groups in age, gender and thyroid function (TSH, FT3, FT4). (P>0.05)

2.1 Expression of Wnt10a mRNA in thyroid tissues

The melting curves of Wnt10a and U6 showed that the primers were characteristic for the amplification. Confirmed by agarose gel electrophoresis, the length of amplification products of qPCR was consistent with the target gene fragment. The relative expression level of mRNA was $2^{-\triangle Ct}$, $\triangle Ct=Ct_{Wnt10a}-Ct_{U6}$. The relative expression of Wnt10a mRNA was 2.49×10^{-5} (0.68×10^{-5}, 15.28×10^{-5}), 1.26×10^{-5} (0.97×10^{-5}, 13.73×10^{-5}), 0.37×10^{-5} (0.26×10^{-5}, 0.94×10^{-5}) in PTC, HT with PTC and nodular goiter tissues respectively. Statistical analysis showed that the expression of Wnt10a was significantly higher in PTC and HT with PCR tissues than in nodular goiter tissues (P<0.05) and the expression was significantly higher in PTC tissues than in HT with PTC tissues (P<0.05). The results showed that the expression of Wnt10a had relationship with the thyroid tissue differentiation and histological type.

2.2 Expression of Wnt10a protein in thyroid tissues

Wnt10a protein granule mainly expressed in the cytoplasm of tumor cells, did not express in nucleus and occasional expressed in intercellular substance. (Figure1- ABCDEFGHIJKL).

According to statistics, the Wnt10a protein expression had significant difference not only between PTC and nodular goiter (P<0.05), but also between HT with PTC and nodular goiter

Table 1 Expression of Wnt10a protein in thyroid tissues

Type	n	-	+	++	+++	Positive rate	P value
PTC	20	1	3	9	7	95 %	P1=0.152
HT with PTC	20	2	7	7	4	90 %	
Nodular goiter	10	6	2	2	0	40 %	P2=0.001

Note: P1 showed the comparison of PTC and HT with PTC. P>0.05, the difference did not have statistical significance. P2 showed the comparison of PTC and nodular goiter, HT with PTC and nodular goiter. P<0.05, the difference had statistical significance.

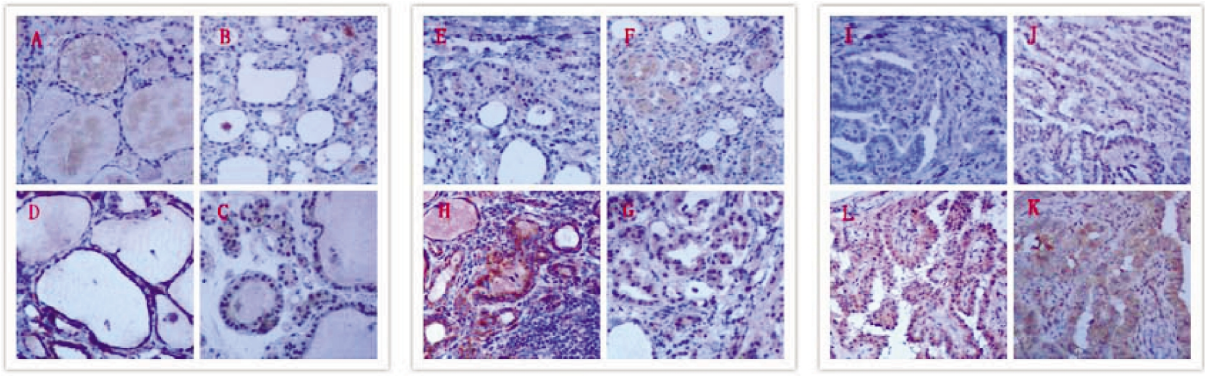

Fig. 1 The expression of wnt10a protein showed a significant difference in the three kinds of thyroid tissues (× 200)
Note: A-D: the expression of wnt10a protein in nodular goiter: A -, B -, C +, D ++
E-H: the expression of wnt10a protein in HT with PTC: E-, F+, G ++, H +++
I-L: the expression of wnt10a protein in PTC: I -, J +, K ++, L +++

(P<0.05). By contrast, the expression did not have significant difference between PTC and HT with PTC (P>0.05). (Table 1)

2.3 Correlation between Wnt10a mRNA expression and thyroid cancer clinical factors

According to statistics, the expression of Wnt10a mRNA had no significant relation with age, gender and lymph node metastasis both in PTC and HT with PTC (P>0.05). Among the comparison in different TNM staging, the expression of Wnt10a mRNA only had significant difference between Ⅰ/Ⅱ and Ⅲ/Ⅳ staging (P<0.05), the pairwise comparisons of other stages had no statistical significance (Table 2). Moreover, we detected the BRAF genes in thyroid tissues and found that the Wnt10a mRNA expression had no significant difference in BRAF positive and negative groups (P>0.05).

2.4 Correlation between Wnt10a protein expression and thyroid cancer clinical factors

According to statistics, the expression of Wnt10a protein had no significant relation with all of the clinical factors as age, gender, differentiation, lymph node metastasis and TNM staging (P>0.05). The conclusion was consistent with the studies in endometrial carcinoma. The results indicated that the Wnt10a ex-

Table 2 Correlation between Wnt10a mRNA expression and thyroid cancer clinical factors

Parameter	PTC			X^2	P	HT PTC			X^2	P
	n	Expression				n	Expression			
		-	+++				-	+++		
Age										
<45	12	1	11	0.702	0.402	10	1	9		1
≥ 45	8	0	8			10	1	9		
Gender										
Male	8	0	8	0.702	0.402	2	0	2	0.237	0.619
Female	12	1	11			18	2	16		
Lymphatic Matastasis										
Yes	3	0	3	0.186	0.666	2	1	1	3.851	0.195
No	17	1	16			18	1	17		
TNM staging										
Ⅰ/Ⅱ	15	1	14	0.351	0.554	18	1	17	3.851	0.195
Ⅲ/Ⅳ	5	0	5			2	1	1		

Table 3 Correlation between Wnt10a protein expression and thyroid cancer clinical factors

Parameter	PTC			X^2	P	HT PTC			X^2	P
	n	Expression				n	Expression			
		-	+++				-	+++		
Age										
<45	12	1	11	0.702	0.402	10	1	9	-	1
≥ 45	8	0	8			10	1	9		
Gender										
Male	8	0	8	0.702	0.402	2	0	2	0.237	0.619
Female	12	1	11			18	2	16		
Lymphatic Matastasis										
Yes	3	0	3	0.186	0.666	2	1	1	3.851	0.195
No	17	1	16			18	1	17		
TNM Staging										
Ⅰ/Ⅱ	15	1	14	0.351	0.554	18	1	17	3.851	0.195
Ⅲ/Ⅳ	5	0	5			2	1	1		

pression is unrelated with clinical factors.

3 Discussion

Thyroid cancer is one of the most common malignancies in clinic. In recent years, an increasing incidence of HT with PTC indicated that HT with PTC had become to the fastest growing solid malignancy. The occurrence and progression of HT with PTC is caused by the cooperation of a variety of pathogenic factors and regulatory mechanisms. We carried out the study to explore an efficient molecular marker of clinical diagnosis and prognosis of thyroid cancer.

Wnt protein is an extracellular ligand presenting in many living bodies. Wnt protein, acting as morphogen, controls embryonic morphological development through stimulating concentration-dependent reaction intracellular away from the signaling area [18]. Wnt pathways, regulating various important links to control growth process of animals, can be divided into classical pathways that determine cell fate and non-classical pathways that control cell movement and tissue polarity. The classic Wnt signal pathway is a β -catenin protein accumulative cascade process caused by Wnt protein combining with LRP5/ LRP6 coreceptor and specific receptor of FZD (Frizzled) family, and leading to trigger intracellular signaling transduction [19, 20]. The non-classic signal pathway is transducted by OR2/ RYK coreceptor and FZD family [21-23]. Katoh M found that genetic factors, inflammatory factors and senescence were the risk factors for human tumor [21]. The expression levels of Wnt 1, Wnt 3 and Wnt 10b gene were up-regulted when the activation of classic Wnt pathways happened in tissue regeneration combining with chronic persistent inflammation and breast canceration caused by MMTV (mouse mammary tumor virus). Moreover, the expression of inhibitory factors of Wnt signal transduction pathway reduced, leading to the overexpression of Wnt protein and tumorigenesis [21-25].

Our study showed that the expression of Wnt10a was significantly higher in PTC and HT with PCR tissues than in nodular goiter tissues, and the expression was significantly higher in PTC tissues than in HT with PTC tissues. The results showed that the expression of Wnt10a had relationship with the thyroid tissue differentiation and histological type. The conclusion was consistent with the studies in Wnt10a in the past [10-16]. The result suggested that upregulation of Wnt10a mRNA played an important role in the process of thyroid cancer incidence. The Immunohistochemistry result of our study found that the expression of Wnt10a mainly located in the cytoplasm of follicular cells of the PTC, and the expression was more obviously in the specimens that had classical papillary and follicular structures. Wnt10a protein mainly expressed in atypical proliferated follicular epithelium and little expressed in normal glands follicular epithelium. The result was consistent with the argument that HT canceration was the early event that caused papillary carcinoma [4, 26,27]. In the transition region of epithelial cells between HT and papillary, epithelial over proliferated, atypical proliferate and finally conversed to papillary nests, and that was the direct morphological basis of HT canceration [28,29]. The Immunohistochemistry result showed that the expression difference of Wnt10a in PTC and HT with PTC was obviously. We speculated that the expression of Wnt10a protein was not only regulated by Wnt10a, but also by a variety of related genes. Therefore, Wnt10a signal pathway required more in-depth study.

Although our current study provided significant results, there are still some limitations. First, the number of our samples was limited. In the future, large scale research may provide more reliable information. Second, the Wnt10a signaling pathway was not the only factor that promoted the development of thyroid cancer.

In summary, we initially identified that Wnt10a mRNA was highly expressed in PTC and HT with PTC. What's more, the expression was different between PTC and HT with PTC. It was hoped to detect the tumor progression by detecting common genetic variation existing in both HT and PTC through molecular pathology technology because of that most of the HT with PTC patients had no obvious clinical manifestation and test result [30, 31]. The study provided an effective early detection biomarker of PTC. Our group will focus on the function and mechanism of Wnt10a and regulate the relative signal pathways in PTC, aiming to provide a strong theoretical basis for clinical treatment.

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Wnt10a 在甲乳癌及桥本合并甲乳癌中的差异表达 *

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摘要 目的：探讨无翅型 MMTV 整合位点家族成员 10a（Wnt10a）在甲状腺乳头状癌(papillary thyroid carcinoma，PTC)和桥本合并甲状腺乳头癌（Hashimoto's thyroiditis associated with papillary thyroid carcinoma ）中的表达及其临床意义。**方法：**采用 qRT-PCR 方法检测 Wnt10a mRNA 在 41 例新鲜甲状腺组织（PTC 组织 18 例，HT 合并 PTC 组织 12 例，结节性甲状腺肿组织 11 例）中的表达；用免疫组化 SP 法检测 Wnt10a 蛋白在 50 例甲状腺石蜡标本（PTC 组织 20 例，HT 合并 PTC 组织 20 例，结节性甲状腺肿组织 10 例）中的表达。**结果：**① RT-PCR Wnt10a mRNA 在甲状腺癌组织中的表达明显高于其在良性甲状腺肿瘤组织中的表达($P < 0.01$)，差异有显著性；Wnt10a mRNA 在 PTC、HT 合并 PTC 组织中的阳性表达强度分别为 2.49×10^{-5}（0.68×10^{-5}，15.28×10^{-5}），1.26×10^{-5}（0.97×10^{-5}，13.73×10^{-5}）；$P<0.05$，差异具有显著性。Wnt10a mRNA 在 PTC、HT 合并 PTC 组织中的表达分别是结节性甲状腺肿组织的 9.98、2.69 倍。② SP 法：Wnt10a 在甲状腺癌组织中的表达明显高于其在良性甲状腺肿瘤组织中的表达。Wnt10a mRNA 和蛋白在甲状腺癌组织中的表达与肿瘤大小、临床分期、淋巴结转移等临床因素无明显关系($P>0.05$)，只与甲状腺癌组织的病理分型相关，($P<0.05$)。**结论：**Wnt10a 在甲状腺乳头状癌和桥本合并甲状腺乳头癌中呈现高表达，且有差异性，有望作为甲状腺癌的病理分型的参考指标，有助于甲状腺癌的早期诊断及病理分型的判定，使患者得到及时有效治疗。

关键词：Wnt10a；甲状腺乳头状癌；桥本氏甲状腺炎合并甲状腺乳头癌；RT-qPCR；免疫组化
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