

## Original Article

# The expression of SIRT7 was down-regulated and correlated with tumor size in thyroid carcinoma

Zhouxun Chen<sup>1\*</sup>, Xiaoxi Chen<sup>1\*</sup>, Wei Han<sup>2\*</sup>, Yifan Zhou<sup>3</sup>, Zuoqian Yu<sup>1</sup>, Peichen Zhang<sup>1</sup>, Wenyi Wu<sup>1</sup>, Guanbao Zhu<sup>1</sup>, Guoyu Huang<sup>1</sup>

<sup>1</sup>Department of Gastrointestinal Surgery, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou 325000, China; <sup>2</sup>Institute of Basic Medical Science, Zhejiang Medical College, Hangzhou 310053, China; <sup>3</sup>Wenzhou Medical University, Wenzhou 325000, China. \*Equal contributors.

Received December 20, 2015; Accepted March 30, 2016; Epub May 15, 2016; Published May 30, 2016

**Abstract:** Background: Several members of the SIRT family (i.e., SIRT1-7), which are a highly conserved family of NAD<sup>+</sup> dependent enzymes, play an important role in tumor formation. Recently, several studies have suggested that SIRT7 was abnormally expressed in several tumor types. However, current understanding of SIRT7 expression and its association with the clinico-pathological features of thyroid cancer remains poor. Methods: We evaluated SIRT7 protein expression levels in thyroid carcinoma and corresponding normal thyroid tissue by immunohistochemical staining on a tissue microarray that included 43 thyroid carcinoma specimens. We also determined the association between SIRT7 expression levels and selected clinicopathological parameters in thyroid carcinoma. Results: We found that the expression level of SIRT7 in thyroid carcinoma was significantly lower than corresponding normal tissue levels ( $P=0.0001$ ). Moreover, lower SIRT7 levels were observed in big tumor size ( $P=0.030$ ). Conclusions: Our results suggest that SIRT7 may be involved in the development of thyroid cancer and is a promising target for both the diagnosis and potential therapy of thyroid cancer.

**Keywords:** SIRT7, carcinoma, thyroid papillary carcinoma

## Introduction

Thyroid cancer is the most common malignant tumor of the endocrine gland and its global incidence over the past few decades has seen rapid growth [1-3]. There are four types of thyroid cancer, including papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer. In particular, papillary thyroid cancer accounts for more than 80% of thyroid malignancies [4].

The causes and pathological changes of thyroid cancer are complex, which includes the contributory effects of diet, the environment, and genetic and/or epigenetic factors. In recent years, we have made great progress in understanding the molecular pathological changes seen in thyroid cancer [4]. Many genes and signaling pathways have been found to play a key role in the development of thyroid cancer. These include the BRAFV600E mutation, PIK3-

CA, CTNNB1, TP53, EGFR, the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway, the FOXO pathway, and the MAPK and PI3K-AKT pathways [5]. In addition to these advances, we need to further study the molecular mechanism of thyroid cancer development and the corresponding genetic changes in an attempt to gain improved understanding of the molecular pathology of thyroid cancer, and to discover novel biomarkers and therapeutic targets for the diagnosis and potential prognosis of this condition.

The SIRT family (SIRT1-7) is a group of NAD<sup>+</sup>-dependent acetylases, deacetylases and ADP-ribosyltransferases, which play an important role in energy metabolism, genome stability, aging and stress resistance [6]. Until now, almost all of the SIRT family members were considered to be involved in the formation and development of tumors [7]. For example, SIRT1, which is the most studied SIRT to date, acetylates histone proteins and a series of non-his-

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**Table 1.** Correlation between the clinicopathologic variables and SIRT7 expression in thyroid carcinoma

Clinicopathologic parameters	SIRT7 expression			X <sup>2</sup>	P-value <sup>a</sup>
	All cases	Low	High		
Age (years)				1.640	0.257
≤45	16	11	5		
>45	27	23	4		
Gender				0.307	0.701
Male	17	13	4		
Female	26	21	5		
Tumor size (cm)				5.208	<b>0.030</b>
≤2	19	12	7		
>2	24	22	2		
Stage (T)				4.861	0.156
T1	24	17	7		
T2	16	15	1		
T3	2	1	1		
T4	1	1	0		
Stage (N)				0.374	0.711
N0	20	15	5		
N1	23	19	4		
Stage (M)				1.004	0.587
M0	43	34	9		
M1	0	0	0		
UICC stage				2.586	0.119
I	22	15	7		
II	4	4	0		
III	2	2	0		
IV	15	13	2		

Bold values are statistically significant ( $P < 0.05$ ). <sup>a</sup>Chi-square test.

tone substrates, and by doing so, affects the formation of tumors. These processes include effects on the DNA mismatch repair protein Ku70, the tumor suppressor gene p53, and the apoptotic protein FOXO [8, 9].

SIRT7 is mainly expressed in the nucleus, which interacts with polymerase I RNA and regulates transcription of the ribosomal gene (rDNA) [10]. SIRT7 is also believed to play an important role in the transcription of RNA Pol I [11]. Studies have found that SIRT7 can inhibit tumor growth in a mouse model and in murine cell-lines [12]. However, other studies have shown that SIRT7 can promote tumor growth by inhibiting tumor suppressor gene transcription [13]. Current research shows that SIRT7 is up-regulated in

cancers of the breast, liver, colon and gastric system [14-18]; however, the expression of SIRT7 in pancreatic cancer is down-regulated and higher SIRT7 expression is associated with improved prognosis of pancreatic cancer [19]. In thyroid cancer, there are contradictory results. For example, De *et al.* [20] found that SIRT7 was upregulated in thyroid cancer cells and tissues, and yet Aljada *et al.* [21] found that the mRNA expression of SIRT7 in thyroid cancer was lower than that found in normal thyroid tissues. The tissue samples of both the above studies of SIRT7 in thyroid cancer were very small; in addition, so far no studies have previously reported the relationship between SIRT7 expression and the clinico-pathological parameters of thyroid cancer. Thus, our present understanding of the correlation of SIRT7 and thyroid cancer is insufficient.

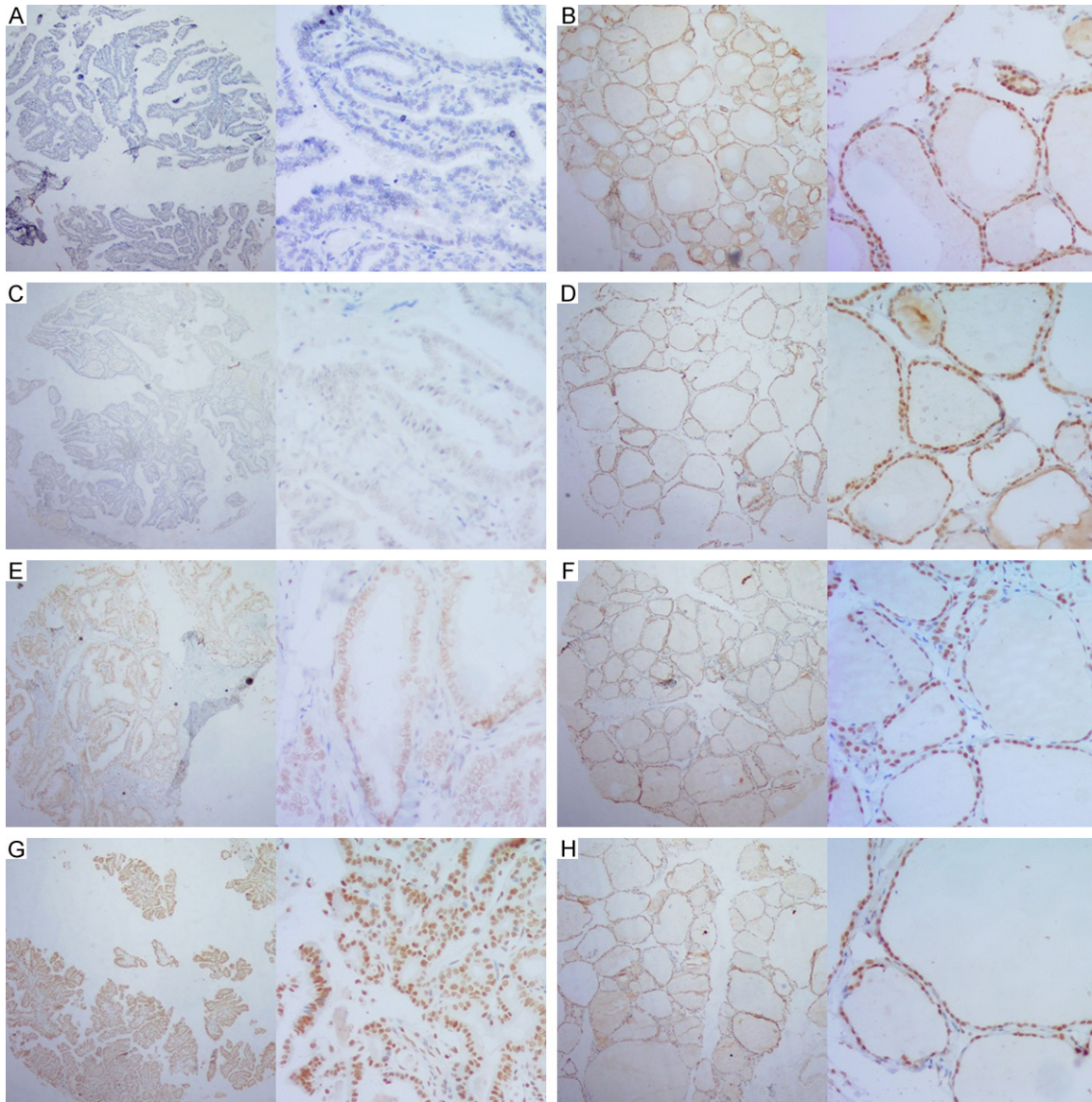
In the current study, we have analyzed the relationship between SIRT7 expression levels and thyroid carcinoma in 43 cases of human thyroid carcinoma and normal thyroid tissues adjacent to normal thyroid tissues by using immunohistochemical methods. We found that SIRT7 expression was down-regulated in human thyroid carcinoma tissues and that SIRT7 expression was identified in patients presenting with thyroid cancer that were prone to a greater tumor size. Our results suggest that SIRT7 might be involved in the development of thyroid cancer and thus represents a promising new target in the diagnosis and treatment of thyroid cancer.

### Materials and methods

#### Tissue microarray

Tissue chips obtained from a commercial chip company (Superchip Inc., Shanghai, China). There were 43 patients, and a total of 86 points, on one chip. Each sample consisted of papillary thyroid carcinoma and normal thyroid tissue. The diameter of the chip was 1.5 mm, which was covered by paraffin. Among the 43 patients, there were 17 males and 26 females that were aged from 14 to 91 years, with an average age of  $47.8 \pm 14.6$  years. The clinicopathological parameters included: age, gender, tumor size, pathological differentiation, and depth of tumor invasion, number of lymph node metastases, distant metastases, and American Cancer Tissue (UICC) Staging criteria. The major

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**Figure 1.** Representative immunohistochemical staining of SIRT7 in human thyroid carcinoma tissues. SIRT7 was expressed in the nuclei, and was significantly lower in tumor tissues as compared with adjacent normal thyroid tissue. The micrographs showed negative (A), weak (C), medium (E) and strong (G) staining of SIRT7 in the thyroid carcinoma tissues. The relevant expression of SIRT7 in corresponding adjacent normal thyroid tissues in cases showing (A, C, E and G) were shown in (B, D, F and H), respectively. (Magnification: left panel  $\times 50$ , right panel  $\times 200$ ).

pathological parameters are summarized in **Table 1**.

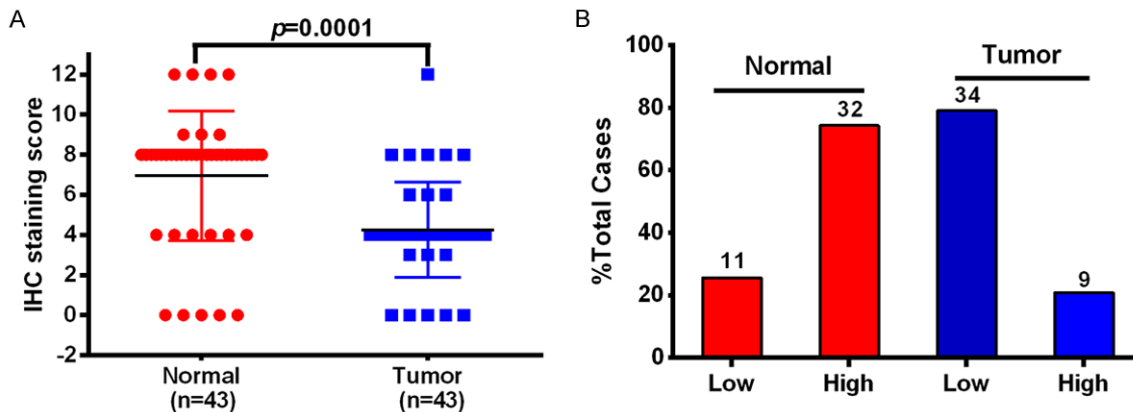
### *Immunohistochemistry*

After baking in a  $60^{\circ}\text{C}$  oven for about two hours, the tissue array was sequentially treated by xylene dewaxing, ethanol hydration and an EDTA antigen retrieval solution (pH 9.0) for 5 minutes to permit antigen retrieval. Next, endogenous peroxidase was quenched by 15

minute treatment in 3% hydrogen peroxide solution. Rabbit anti-human SIRT7 polyclonal antibody (1:1000, Abgent, Suzhou, China) was incubated overnight at  $4^{\circ}\text{C}$ . Secondary antibody was applied using the GTVision Kit (Gene Tech Inc., Shanghai, China). The chip was then stained with diaminobenzidine (DAB), and then counterstained with hematoxylin. The chip was then dehydrated and sealed with coverslips according to standard procedures. Tissue treated with antibody dilution solution was used as



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**Figure 2.** SIRT7 protein levels in 43 thyroid carcinoma tissues and paired adjacent normal thyroid tissue as measured by tissue microarray. A. SIRT7 protein levels were significantly lower than adjacent normal thyroid tissue. B. In thyroid carcinoma, SIRT7 is more likely to be low expressed as compared the high expression of SIRT7 that was found in normal tissues.

a negative control. Slides were examined by light microscopy by two independent pathologists that were blinded to patient information. Every tissue point was evaluated by both staining intensity (i.e., according to the following scale: 0, no staining; 1, weak staining; 2, medium staining; and 3, strong staining) and staining area (i.e., according to the following scale: 0, <5%; 1, 5%-25%; 2, 25%-50%; 3, 50%-75%; 4, >75%). The final staining score was obtained by multiplying the staining intensity score by the staining area score as previously described [22]. The tissue points were divided into two groups based on the final staining score, thus: low, 0-4; and high, 6-12. If the evaluation of the staining was inconsistent, it was reevaluated by the same two pathologists using a multi-headed microscope until both pathologists arrived at a consistent or consensus conclusion.

### Statistical analysis

Statistical analysis was performed using the 20<sup>th</sup> edition of the statistical software program SPSS. Paired Student's t-test analysis was used to measure immunohistochemical data significance in cancer and cancer adjacent tissues. An analysis of the relationship between SIRT7 expression and the clinic-pathological parameters such as age, gender, tumor size, pathological differentiation, TNM classification, UICC staging was done by Chi square and Fisher's exact tests. An alpha value of  $P < 0.05$  (by two tailed analysis) were considered statistically significant differences.

### Results

#### *Expression level of SIRT7 protein was significantly decreased in thyroid carcinoma*

By immunohistochemical staining of human thyroid carcinoma and normal tissues that were adjacent to the carcinoma, we found that SIRT7 expression was mainly expressed in the nuclei (Figure 1). The expression of SIRT7 in thyroid cancer was significantly lower than that found in normal tissues according to the statistical analysis of the staining scores, and the difference was statistically significant (Figure 2A). We further divided the sample into SIRT7 low expression and high expression in both groups according to the respective score. We found that in normal thyroid tissues, high SIRT7 expression was 74.4% (32/43), and low SIRT7 expression was 25.6% (11/43). In addition, these values were 20.9% (9/43) and 79.1% (34/43) in thyroid carcinoma tissues (Figure 2B), respectively.

#### *SIRT7 expression and clinical pathological data of thyroid*

To clarify the clinical significance of SIRT7 expression in patients with thyroid carcinoma, we analyzed the relationship between SIRT7 expression and clinical pathological parameters. We found that the expression of SIRT7 was significantly associated with tumor size ( $P = 0.030$ ). Patients with low SIRT7 expression were found to be prone to a greater tumor size.

We did not find that SIRT7 expression was associated with other pathological parameters including age, sex, pathological differentiation, depth of tumor invasion, lymph node positive number (N), distant metastasis (M) or UICC staging ( $P > 0.05$ ). The relationship between SIRT7 expression and clinical pathological data of human thyroid cancer is summarized in **Table 1**.

### Discussion

In this experiment, we analyzed the expression of SIRT7 and its relationship with the clinicopathological parameters by tissue microarray containing 43 cases of human thyroid carcinoma and normal tissues that were adjacent to the tumor. Our results showed that SIRT7 was mainly expressed in the nucleus, and its expression in human thyroid carcinoma tissues was significantly lower than that of normal thyroid tissues. In thyroid carcinoma, SIRT7 high was 74.4%, and SIRT7 low was 25.6%. By contrast, in normal thyroid tissues that were adjacent to cancer, SIRT7 high was 20.9%, and SIRT7 low was 79.1%. In addition, the expression levels of SIRT7 in thyroid cancer were significantly correlated with tumor size. Patients with lower SIRT7 expression are prone to a greater tumor size. Our results suggested that SIRT7 might be involved in the development of thyroid cancer.

According to the current study, multiple SIRT family members play different roles in different tumors, which might depend on the specific tissue and tumor types [23]. Take SIRT1 for example, which was up-regulated in gastric cancer [24], colorectal cancer [25], prostate cancer [26] and skin cancer [27], which suggests that it should play a key role in tumor formation. However, other studies have found that SIRT1 expression is decreased in breast cancer [28], and it can inhibit the formation of intestinal tumors in a murine APC<sup>min/+</sup> model [29]. Similarly, SIRT2 was down-regulated in breast cancer [30], glioma [31] and skin cancer [32]; however, SIRT2 expression was enhanced in acute myeloid leukemia [33] and prostate cancer [34]. Thus, we cannot easily extrapolate the observations made for one tumor type and the conclusions drawn from them, to the study of another tumor type.

It was found that the expression of SIRT7 was up-regulated in most tumors. For example,

Jeong *et al.* [15] found SIRT7 was up-regulated in human HCC tissues and that knocked down SIRT7 inhibited the growth of HCC cells both *in vitro* and *in vivo* by affecting the cell cycle and autophagy-related proteins. Yu *et al.* [14] found that the expression of SIRT7 in colon cancer was up-regulated, and that SIRT7 affected the proliferation and migration of colon cancer cells by regulating the MAPK signaling pathway and EMT. Ashraf *et al.* [16] found that the expression of SIRT7 was up-regulated in breast cancer, while Geng *et al.* [17] found that the expression of SIRT7 was associated with poor prognosis in breast cancer. In addition, SIRT7 expression was augmented in gastric and ovarian cancer cells [18, 35]. However, McGlynn *et al.* [19] found that the expression of SIRT7 in pancreatic cancer was decreased and that pancreatic cancer patients showing high SIRT7 expression had a longer survival time. These results suggest that SIRT7 may also function as both a tumor oncogene and a tumor suppressor gene.

There is no consistent conclusion on the research observations made for SIRT7 in thyroid cancer. De *et al.* [20] found that the expression of SIRT7 in thyroid cancer cells and thyroid cancer tissues was upregulated, but Ahmad *et al.* [21] conducted a qPCR Cancer Survey cDNA array, which contained multiple tumor samples including cancers of the breast, colon, liver, and thyroid, and found that the mRNA expression levels of SIRT7 were significantly down-regulated in thyroid cancer ( $P < 0.05$ ).

In our current studies, by using a tissue microarray, which contained a larger sample size, we found that the expression of SIRT7 in human thyroid cancer tissues was lower, and that lower SIRT7 expression in patients with thyroid cancer was prone to a greater tumor size. Our results also suggested that SIRT7 expression might play a role in tumor suppression in thyroid cancer. Since tumor size is an important prognostic factor for thyroid cancer, our results also suggest that SIRT7 is likely to be a very promising prognostic marker for thyroid cancer.

To the best of our knowledge, our study is the first to explore the relationship between SIRT7 expression levels and the clinic-pathological parameters in human thyroid carcinoma specimens. However, we chose the type of thyroid papillary carcinoma, and the next logical step in

our studies will be to use a larger sample and to study a wider variety of tumor types to verify the results reported herein. We will also further analyze the relationship between SIRT7 expression and the prognosis of thyroid cancer patients, and reveal the effect of SIRT7 on the biological behavior of thyroid cancer cells.

In summary, our study shows that the expression of SIRT7 in thyroid carcinoma was significantly lower than that found in normal paracarcinoma tissues. Our results suggest that SIRT7 may play an important role in the development of thyroid cancer and might represent a promising target for the diagnosis and treatment of thyroid cancer.

### Acknowledgements

This study was funded by: the Nutriology of the Medical Support Discipline of Zhejiang Province.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Guanbao Zhu and Guoyu Huang, Department of Gastrointestinal Surgery, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou 325000, China. Fax: +86 57755579441; E-mail: zhuguanbao1958@gmail.com (GBZ); huangguoyu.greg@gmail.com (GYH)

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