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Thymosin beta 10 correlates with lymph node metastases of papillary thyroid carcinoma

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ABSTRACT

Background: Thymosin beta 10 (TMSB10) has recently been recognized as being an important player in the metastatic cascade including tumor angiogenesis, invasion, and metastasis. However, a role for this protein in papillary thyroid carcinoma (PTC) has not yet been established.

Methods: Real-time polymerase chain reaction was used to examine the expression of TMSB10 messenger RNA in 36 cases of thyroid tissue samples: normal thyroid, PTC without lymph node metastases (LNM) and PTC with LNM ($n = 12$ cases in each subgroup). For immunohistochemistry, 130 patients with PTC were selected during the period of 2004–2005, 91 with and 39 without LNM. Statistical analysis was applied to evaluate the correlation between TMSB10 expression and LNM of PTC.

Results: By real-time polymerase chain reaction analysis, the expression of TMSB10 messenger RNA in normal thyroid tissue, PTC without LNM, and PTC with LNM tissue were significantly different ($P < 0.0001$). On immunohistochemistry analysis of 130 patients with PTC, in which 91 cases had cervical LNM and 69 cases had central neck LNM, high expression levels for TMSB10 were more common in patients with cervical LNM compared with patients without (81% *versus* 33%, $P < 0.001$). Similarly, high expression levels of TMSB10 were more common in patients with central neck LNM compared with those without (87.0% *versus* 44.3%, $P < 0.001$).

Conclusions: High expression levels of TMSB10 correlated with LNM in PTC, especially in the central neck region. Patients with PTC with low levels of TMSB10 expression may be unlikely to have central neck LNM and could therefore avoid prophylactic central neck dissection.

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1. Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for 80%–90% of all thyroid cancers [1–3]. Unlike the majority of malignant carcinomas, PTC displays peculiar characteristic. For example, although the prevalence of microcarcinoma in an autopsy series has been reported up to 36% among the general population, clinical prevalence of PTC is at most 0.1%. Although the overall survival rate of PTC exceeds 90%, cervical lymph node metastases (LNM) are found in 30%–80% of patients when diagnosed, including occult metastases [4]. Ito *et al.* [5] found a high rate (64%) of occult LNM in 1321 patients with PTC, whereas Wada *et al.* [6] reported a rate of 39.5% in the lateral compartment of patients with micro-PTC. Cervical LNM in PTC has been found to be one of the most significant factors for locoregional recurrence, and it also has been regarded as the first sign of a potentially lethal outcome [7–10]. It is well established that in patients with local recurrence, surgery is still the first option for treatment but it is associated with a higher risk of complications. Therefore, studying the molecular mechanism of cervical LNM of PTC has great significance for providing a biological basis for clinical treatment.

To date, the molecular mechanisms of PTC cervical LNM are unclear despite the intensive efforts that have been made in this field, such as studies investigating P27, cyclin-D1, BRAF, CCR7, and STAT3 among others.

As an important member of the β-thymosin family, thymosin beta 10 (TMSB10) has biological activities as an actin-sequestering protein involved in cell motility. Aberrant cell migration contributes to tumor pathology, such as the metastatic cascade, including tumor angiogenesis, invasion, and metastasis [11]. Hence, we hypothesize that high expression of TMSB10 may be correlated with aggressiveness and metastatic behaviors of PTC, which to date has not been studied.

In this study, we aim to investigate the expression of TMSB10 in a cohort of PTC to determine the clinical significance of TMSB10 overexpression in cervical LNM of PTC.

2. Materials and methods

2.1. Patients, clinical sample and tissue specimens

A total of 130 consecutive patients with PTC were selected from Sun Yat-sen University Cancer Center during the period of 2004–2005. In all cases, patients underwent thyroidectomy (total or lobectomy and isthmusectomy) together with central neck dissection or therapeutic lateral neck dissection. All patients underwent ipsilateral central neck dissection. Seventy-one cases received therapeutic lateral neck dissection. Prophylactic lateral neck dissection was not performed on any patients. Only those patients who were found to have lateral neck LNM clinically and had positive biopsy results underwent therapeutic lateral neck dissection. Indications for total thyroidectomy are mainly based on conventional high-risk factors, including age <15 or >45 y, radiation history, known distant metastases, cervical LNM, gross extrathyroidal extension, tumors >4 cm in diameter or bilateral nodularity. Patients without the previously mentioned high-risk factors received lobectomy and isthmusectomy. Histopathology revealed the true node-negative cases, which complemented our clinical assessment via ultrasound. The pathologic assessments confirmed the diagnosis of PTC including aggressive subvariants, such as tall cell, columnar cell, and diffuse sclerosing variants. The classification of thyroid carcinoma was based on the TNM Staging for Thyroid Cancer (seventh edition, 2010). Two pathologists separately assessed the specimens to document primary tissue diagnosis and the presence of LNM in nodes sectioned. Specimens were used after receiving patients' written consent, and ethical approval was granted from the Institutional Research Ethics Committee of the Sun Yat-sen University Cancer Center.

For reverse transcriptase polymerase chain reaction (RT-PCR), 36 cases of PTC tissue and normal thyroid tissue samples were obtained from thyroidectomy specimens of patients diagnosed with PTC immediately after surgery and stored at −80°C, which were divided into three subgroups: normal thyroid, PTC without LNM and PTC with LNM, 12 cases in each subgroup. The tumor purity of these tissues was established by histopathologic analysis of adjacent sections before RNA analysis. Regarding immunohistochemistry, PTC samples were obtained from paraffin-embedded PTC tissue samples from 130 cases; of which, 91 cases had LNM and 39 were without LNM. For comparison, 18 benign thyroid tissue specimens confirmed by a pathologist, including 10 nodular goiter tissues and eight normal thyroid tissues, were also selected. The clinical information of this patient cohort is summarized in Table 1.

2.2. RNA extraction, RT-PCR, and real-time quantitative PCR analysis

Total RNAs from fresh tissues were purified from tissues using TRIzol Reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions, and 2-μg RNA of each sample was reverse transcribed using SuperScript RT kit (Invitrogen Life Technologies, Carlsbad, CA). Full-length open reading frame of TMSB10 was amplified by PCR from complementary DNA samples of normal thyroid tissues and thyroid carcinoma tissues. RT-PCR was carried out using a CFX96 Real-Time System (Bio-Rad, Palo Alto, CA) (PREMIER Biosoft International, Palo Alto, CA). Sequences of the primers were as follows:

TMSB10-real-sense: 5′-TGGCAGACAAACCAGACATGG-3'
TMSB10-real-antisense: 5′-CGAAGAGGACGGGGGTAGG-3'
GAPDH-real-sense: 5′-GACTCATGACCACAGTCCATGC-3'
GAPDH-real-antisense: 5′-AGAGGCAGGGATGATGTTCTG-3'

We used the SYBR Green kit (Invitrogen Life Technologies) to execute the amplification of the complementary DNA. The RT-PCR cycling parameters were performed as follows: denaturation at 95°C for 15 s, annealing at 55°C for 30 s, and extension at 72°C for 30 s. The expression data were normalized to the geometric mean of housekeeping gene GAPDH to control the difference in expression levels and analyzed using the 2-Delta Delta C (T) method described by the previous report [12]. All experiments were performed in triplicate.

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