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Original Article

Clinicopathologic significance and survival of TIP30 expression in laryngeal squamous cell carcinoma

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Abstract: Background: The expression and clinical significance of TIP30 and p53 in laryngeal squamous cell carcinoma (LSCC) have not been investigated. Method: We determined immunohistochemically the expression of TIP30 and p53 in surgical specimens from 105 patients with LSCC. Survivals were estimated using the Kaplan-Meier method. Results: TIP30 protein expression in LSCC patients was significantly less in tumor tissues than that of adjacent normal tissues (46.7% vs. 79.0%), while p53 protein expression was significantly increased in LSCC (15.2% vs. 63.8%) compared with adjacent normal tissues. The TIP30 expression levels were also significantly correlated with tumor stage, differentiation, and the presence of lymph nodes. The expression of TIP30 was significantly negatively correlated with that of p53 (r = -0.249, P = 0.010). LSCC patients with lower expression level of TIP30 had a significantly higher recurrence and worse overall survival than those with elevated TIP30 expression (P = 0.014 and P = 0.040, respectively). Furthermore, multivariable analysis found that patients with high expression of TIP30 had a greater than approximately 2.2-fold increased risk for death overall or recurrence than those with low expression of TIP30, supporting that down-regulation of TIP30 expression in tumors may involve in development and progression and predict poor prognosis of patients with LSCC. Conclusion: Our results may suggest that down-expression of TIP30 is closely related to carcinogenesis, progression, biological behavior, and prognosis of LSCC.

Keywords: Laryngeal squamous carcinoma, TIP30, p53, survival

Introduction

TIP30, also called CC3 or HTIP2, is a metastasis suppressor that was initially identified by differential display analysis of mRNA from the highly metastatic human small cell lung carcinoma (v-SCLC) versus less metastatic SCLC cell lines [1]. The mechanism by which TIP30 inhibited metastasis might be ascribed to its ability to promote apoptosis and inhibit angiogenesis [1-3]. The anti-tumor activity of TIP30 was further confirmed by the finding that intravenous delivery of the TIP30 gene to melanoma-bearing mice via a cationic liposome-DNA complex significantly reduced pulmonary and extrapulmonary metastases [4]. Recent advances have shown that TIP30 expression is down-regulated in melanoma, malignancy glioma, hepatocellular carcinoma (HCC), lung cancer, breast cancer, colorectal cancer, and prostate cancer, however, it expression is detected in many human normal tissues [5-8]. Unfortunately, the expression profile of TIP30, correlation between clinical parameters and p53 as well as influence on prognosis of laryngeal squamous cell carcinoma (LSCC) have remained largely unknown.

It is well known that p53 is a key regulator for cell homeostasis and is frequently mutated in various human cancers [9]. The overexpression of mutant p53 protein has been proven to be one of the most common genes altered in human malignancies. The mutant p53 may play an important role in tumorigenesis [10], development and metastasis [10-12]. It can appear

in different stages of LSCC and is an important factor in the tumorigenesis and development of LSCC [13]. The aim of the study was to investigate the expression of TIP30 in LSCC and to analyze its relationship with p53 protein as well as other clinicopathologic characters, including prognosis in patients with LSCC.

Material and methods

Patients and tumor samples

All 105 tumor samples were obtained from patients who had undergone surgery and were diagnosed with primary LSCC at General Hospital of Jinan Military Region from January 2003 to May 2007. The adjacent nontumor tissues were about 1 cm from *in situ* carcinoma. All patients gave written informed consent, and the Ethics Committee of General Hospital of Jinan Military Region approved the protocol of this study. Histopathological diagnoses were made according to the pathological classification system of the World Health Organization [14], and the tumor was staged following the tumor-node-metastasis classification of the International Union Against Cancer (UICC 2002). The clinicopathological information of patients was available including gender, age, clinic type, tumor stage, histological grade, determination of metastasis of lymph nodes and cancer-specific survival time. All patients didn't receive any radiotherapy, chemotherapy and immunotherapy and didn't have any distant metastasis before the surgery.

Immunohistochemical staining for TIP30 and p53

Immunohistochemical staining was performed on thin sections (4 μm) of paraffin-embedded archival tissues. The samples were dewaxed in 100% xylene and re-hydrated in descending ethanol series and water according to standard protocols. Heat-induced antigen retrieval was performed in 0.001 mol/L EDTA buffer for two minute at 100°C. The slides were fixed and the endogenous peroxidase activity was quenched by incubation in methanol with 3% hydrogen peroxide for 20 minutes. The slides were then washed with phosphate-buffered saline (PBS). Nonspecific binding was blocked by incubation with 2% bovine serum in Tris-buffered saline (TBS) for 30 minutes. The primary mouse-anti-human antibody against TIP30 (The polyclonal antibody against TIP30/CC3, kindly provided by Dr Hua Xiao (University of Nebraska Medical Center, Omaha, NE) was diluted to 1:200. The primary monoclonal mouse-anti-human antibody against p53 (Zhongshan, Godbridge, China) could reacts with both wild-type and mutant p53 protein. Incubation with primary antibody was carried out overnight at 4°C, and the slides were then washed 3 times in PBS containing 3%, 2%, and 1% of normal human serum. The antibody binding was visualized with 3, 3-diaminobenzidine tetrahydrochloride (DAB) before brief counterstaining with Mayer's hematoxylin. For monoclonal antibodies of mouse origin, negative controls were obtained using isotypic mouse immunoglobulin in the same dilution as the primary antibody of concern. All control experiments gave negative results.

Evaluation of TIP30 and p53 protein staining was independently performed by 2 experienced pathologists. The immunohistochemical score was recorded using a semi-quantitative and subjective grading system that considered both the intensity of staining and the proportion of tumor cells that had an unequivocal positive reaction [15]. A proportion score was assigned, which represented the estimated proportion of positively stained tumor cells (0, none; 1, < 10%; 2, ≥ 10% to < 50%; 3, ≥ 50% to < 80%; 4, ≥ 80% to < 100%). An intensity score was assigned that represented the average intensity of the positive tumor cells (0, none; 1, weak; 2, intermediate; 3, strong). Multiplication of the intensity and the proportion scores gave rise to the ultimate immunohistochemical scores: a total score greater than 3 was taken to indicate a high expression and a sum score below 3 indicated a low expression.

Follow-up

In this study, the primary endpoints in this study were disease recurrence and overall death. LSCC patients were typically followed and monitored through their treatment and post-treatment courses with regularly scheduled clinical and radiographic examinations. Medical record review for follow-up status of all patients was performed under direct supervision of staff head and neck surgeon. Primary tumor subsite, clinical stage, treatment, and vital status were reviewed from medical records as assessed between the initial and final patient contact

Table 1. TIP30 and P53 expression in LSCC and adjacent normal tissues

Groups	TIP30		Total	*P** value	P53		Total	*P** value
	High	Low			High	Low		
LSCC	49	56	105	< 0.001	67	38	105	< 0.001
Adjacent normal tissues	83	22	105		16	89	105	
Total	132	78	210		83	127	210	

*Two-sided x^2 test.

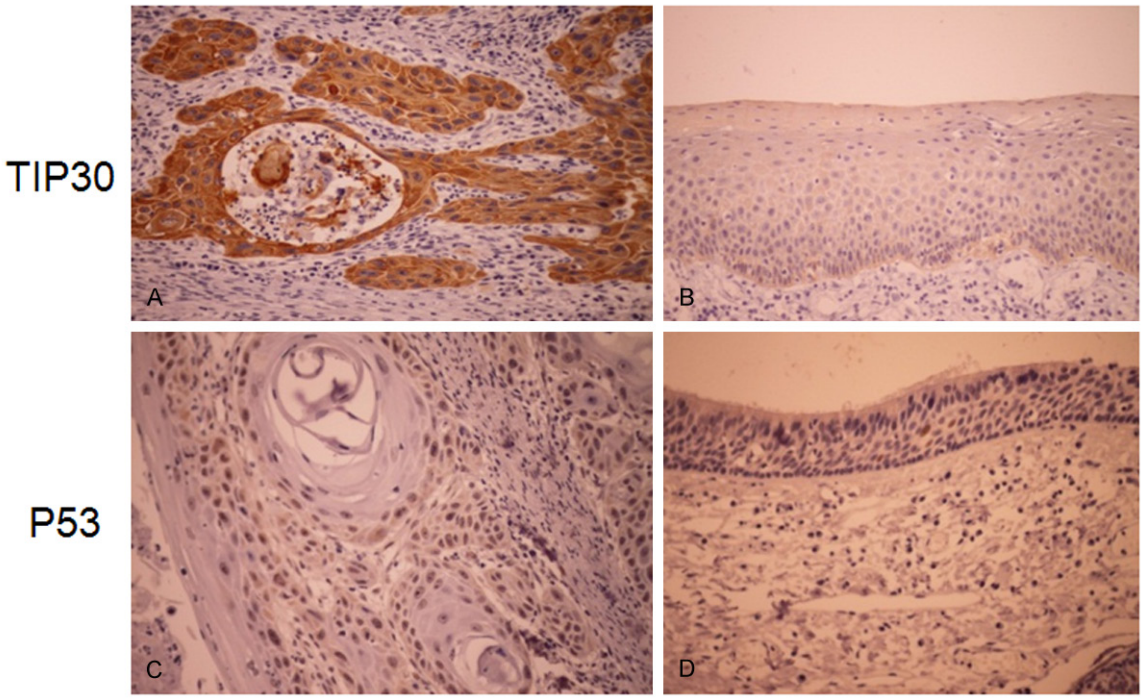

Figure 1. Immunohistochemical staining for TIP30 and P53 in LSCC (A and C) and adjacent nontumor tissues (B and D) (Original magnification, 600 ×).

recorded. Recurrent disease was defined as appearance of a new lesion of the same histology verified by biopsy (incisional, excisional, or needle biopsy), reappearance of any lesion that had disappeared, or development of tumor-related symptoms. Time to recurrence was computed from date of end of treatment to date of last follow-up or date of clinically detectable recurrent cancer (local, regional, or distant). Participants who were recurrence-free or lost to follow-up was considered censored. Over survival (OS) were defined as the time from initial diagnosis to death from any cause or date of last follow-up. Participants who were alive at the end of the study period or lost to follow-up were considered censored. After reviewing medical charts of the patients, of 105 patients, 25 patients were lost to follow up, and a total of 80 patients were available for final analysis of survival.

Statistical analysis

The differences in TIP30 and p53 expression between LSCC and adjacent nontumor tissues were analyzed using Student's *t*-test and one-way analysis of variance (ANOVA) for multiple comparisons. Pearson's correlation was used to determine the correlation between TIP30 and p53 protein expression. Chi-square test was used to analyze the significant associations between TIP30 expression and clinicopathologic parameters. The SPSS software (Windows, version 13.0) was used for statistical calculations. A significant difference was defined at $P < 0.05$.

Table 2. Association between TIP30 and P53 expressions

P53	TIP30		Total	*P**
	High	Low		
High	25	42	67	0.011
Low	24	14	38	
Total	49	56	105	

*Two-sided x^2 test.

Table 3. Associations between TIP30 expression and clinicopathologic characteristics in LSCC

Variables	N	TIP30		*P**
		High	Low	
Age (yr)				0.972
< 55	17	8	9	
≥ 55	88	41	47	
Gender				0.968
Male	92	43	49	
Female	13	6	7	
Smoking				0.507
Ever	85	41	44	
Never	20	8	12	
Alcohol				0.328
Ever	61	26	35	
Never	44	23	21	
Site				0.778
Supraglottic	36	22	14	
Glottic	55	21	34	
Infraglottic	14	6	8	
Stage				0.004
I-II	64	37	27	
III-IV	41	12	29	
Differentiation				0.000
Well	49	33	16	
Moderate/poor	56	16	40	
Lymph node metastasis				0.023
Positive	63	19	44	
Negative	42	30	12	
Treatment				0.346
Surgery only	48	20	28	
Combined	57	29	28	

*Two-sided x^2 test.

Results

Expression of TIP30 and p53 in LSCC

The TIP30 positive staining was detected in 49 (46.7%) and 83 (79.0%) of 105 cases of LSCC and adjacent nontumor tissues respectively (**Table 1**). TIP30 staining was observed in cytoplasm and cell membrane, and no nuclear staining was found in all tissues studied. The yellow-brown grana or bolus was shown in cytoplasm of positive staining cells and concentrated surrounding nuclear (**Figure 1A**, **1B**). The p53 protein expression showed a yellow-brown nuclear positive staining pattern in 67 (63.8%) tumor tissues of 105 cases and 16 (15.2%) in adjacent nontumor tissues. However, no evidence of p53 expression was found in cytoplasm (**Figure 1C**, **1D**).

Correlation between expression of TIP30 and p53

Of 67 tumors with p53 expression, 25 (51.0%) were TIP30 positive. Of 38 tumors without p53 expression, 24 (49.0%) were TIP30 positive (**Table 2**). The expression of TIP30 was negative associated with p53 expression (r = -0.249, P = 0.010).

Correlation of TIP30 expression with selected clinicopathologic characteristics in LSCC

The clinicopathologic characteristics of 105 patients with LSCC are listed in **Table 3**. The significant correlations were found between TIP30 expression and overall staging and, tumor differentiation, and lymph node metastasis (P = 0.004; P < 0.001; and P = 0.023; respectively), while such significant correlations were not observed for age, gender, tobacco, alcohol, tumor site and treatment (**Table 3**).

Association of TIP30 expression with survival of LSCC

Of 105 patients, 80 cases had information on follow-up and 25 patients were lost for follow-up. The median follow-up period for these patients was 44 months (range, 12-60 months). Of these patients, a total of 28 patients died mainly due to disease recurrence and second primary malignancy followed in frequency by death from causes unrelated to cancer. During the follow-up, 39 patients had disease recurrence. Of the patients with recurrence, 2 (5.1%) had distant recurrence, 22 (56.4%) had local recurrence, 13 (33.3%) had regional recurrence, and 2 (5.1%) had recurrence of more than one category.

As shown in **Figure 2**, the differences in overall survival (DFS) and disease free survival (OS)

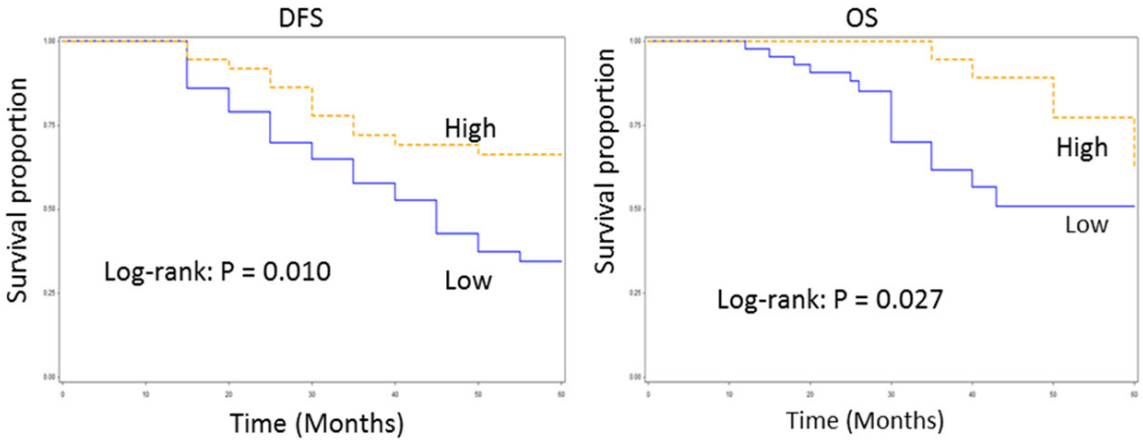

Figure 2. Kaplan-Meier estimates for DFS and OS of patients according to TIP30 expression.

Table 4. Multivariable survival analysis by TIP30 expression in 80 LSCC patients

TIP30 expression	Total (80)	Events		Survival	
		Death (all causes)	Recurrence	OS	DFS
				aHR, 95% CI	aHR, 95% CI
Low	43	20	27	1.0	1.0
High	37	8	12	0.44 (0.21-0.95)	0.42 (0.21-0.83)

*Adjusted for age, sex, smoking, alcohol, overall stage, tumor sites, differentiation, node metastasis, p53 expression, and treatment in Cox's models.

between LSCC patients with high and low expression of TIP30 were statistically significant (log-rank: $P = 0.010$ and $P = 0.027$, respectively). The LSCC patients with high expression of TIP30 had significantly better OS and DFS than those with the low TIP30 expression. Multivariable analysis showed that patients with high TIP30 expression had significantly increased risk of death overall and disease recurrence compared to those with low expression of TIP30 (HR, 0.44; 95% CI, 0.21-0.95 for overall death; HR, 0.42; 95% CI, 0.21-0.83 for recurrence) (**Table 4**).

Discussion

Laryngocarcinoma is the second malignancy in head and neck sites [16]. Approximately over 90% laryngocarcinoma is LSCC. The malignant biological characteristics, such as tumor recurrence, metastasis, drug resistance, and chemoradiotherapy resistance, lead to worse survival and poor life quality of patients with LSCC. Particularly, the metastasis and recurrence of LSCC are the primary causes of treatment failure and subsequent death in these patients despite progress in the development of diagnostic techniques for early detection and improvement in therapeutic skills. A series of genetic abnormalities may play important roles in the development, progression and prognosis of this disease. Therefore, the identification of prognostic markers, such as TIP30, is urgently needed. Such molecular biomarkers could help identify individuals at high risk of deaths/recurrence and developing LSCC for potentially optimizing patient's stratification for targeted therapies and cancer screening and prevention as well as personalized treatment strategies, leading to both improved survival and better quality of life.

Several studies have demonstrated that TIP30, a tumor suppressor gene, inhibited tumor cell growth and metastasis by promoting apoptosis and inhibiting angiogenesis [1-3, 8, 17]. TIP30 has an unusual cellular function as an inhibitor of nucleocytoplasmic transport. TIP30 mutant had similar functions of oncogenes. For example, the TIP30-deficient mice results in spontaneous tumorigenesis, such as HCC, ulreter carcinoma, urinary bladder and carcinoma,

leiomyoma, angiosarcoma and other tumors with a relatively long latency, as well as rapid immortalization of murine mammary epithelial cells [8]. Furthermore, the TIP30-null mammary epithelial cells undergo immortalization in vitro [18]. Forced expression of TIP30 in variant SCLC [1], mouse melanoma, breast carcinoma [4], HCC [19] and gastric carcinoma cell lines [5] leads to inhibition of metastatic behavior in vitro and/or metastasis in vivo. These studies indicated that TIP30 could be not only a metastasis suppressor, but also a tumor suppressor [8].

Recent studies have also indicated that TIP30 expression is associated with metastasis and clinicopathologic characters in gastric cancer [5], colorectal cancer [6], lung cancer [7], HCC [19] and breast cancer [20]. However, to best our knowledge, there is no reported study on association of tumor TIP30 expression with prognosis of patients with LSCC. In this study, we have investigated the association of TIP30 expression in LSCC tumors with P53 protein, survival and other clinicopathologic characteristics of LSCC. We found that TIP30 expression was restricted to cytoplasm and cell membrane, and no nuclear staining was found in all tissues studied. The stained positive cells were well-distributed and had a concentrated phenomenon around nuclear. These observations are in consistent with the findings of previous studies [8, 19, 20]. TIP30 expression was significantly inversely associated with overall staging, tumor differentiation and lymph node metastasis. However, such significant associations of TIP30 expression with age, gender, smoking, alcohol use, tumor sites, and treatment were not found.

The number of positive TIP30 expression in LSCC was more common in patients with stage I-II than those with stage III-IV. In contrast, the number of negative TIP30 expression in patients with stage III-IV was higher than those with stage I-II, indicating an elevated TIP30 expression of LSCC in stage I-II but decreased in stage III-IV. The patients with well-differentiated LSCC indicated relatively higher TIP30 expression compared with those with poorly-differentiated LSCC. The LSCC patients with high TIP30 expression had less lymph node metastasis than those with low TIP30 expression. Moreover, LSCC patients with lower expression of TIP30 had a higher recurrence rate and poorer prognosis. Therefore, TIP30 might involve in the development, progression, metastasis, and prognosis of LSCC and serve as a novel prognostic biomarker for patients with LSCC. Before clinically practical application, this marker should be further confirmed in prospective clinical trials with a larger number of such patients.

Various genetic and epigenetic alterations may result in the aggressiveness of cancer cells, which lead to deregulation of the intracellular signaling pathways, in which some oncogenes are activated or other tumor-suppressor genes inactivated [21]. p53, a tumor suppressor, regulates cellular homeostasis through induction of cell cycle arrest, apoptosis, cell senescence and is frequently mutated in most human malignant tumors [9]. The mutant p53 not only loses normal regulation functions of cell proliferation and differentiation but also inhibits cell apoptosis, which promotes malignant transformation. The p53 mutant has been considered as an early important incident in malignant transformation of head and neck cancers [22, 23]. Similarly, TIP30 is a novel tumor-suppressor gene that executes its antitumor effect by promoting apoptosis [1-2, 24]. Studies have showed that TIP30 promoted tumor cell apoptosis and inhibited tumorigenesis by enhancing endogenous p53 mRNA and protein expression and suppressing Bcl-2/Bcl-xL expression [25], while TIP30 mutants down-regulated the endogenous expression of p53 mRNA and protein [26]. Therefore, TIP30 might be an upstream regulator of p53 and induce apoptosis through both p53-dependent and -independent pathways [25]. Shi *et al* speculated that TIP30 might phosphorylate the p53 C- or N- terminus in advance to enhance the p53-dependent pathway, meanwhile, TIP30 might also trigger apoptosis through other pathways that occur independently of the p53/Bax pathway [27]. Deficiency of TIP30 might allow tumor cells to bypass the tumor-suppression effect of p53, thereby contributing to carcinogenesis. *Zhao et al* showed evidence that TIP30 greatly enhanced p53 expression and its transcriptional activity under oxidative stress, which was probably through stabilization of p53 mRNA in hepatocellular carcinoma [28]. TIP30 induced apoptosis and mitochondrial dysfunction were blocked by silencing of p53 expression. The nuclear import of mRNA-binding protein HuR was blocked upon TIP30 introduction, which

might be due to the interruption of the association of HuR with importin β2. The elevated cytoplasmic HuR bound to p53 mRNA 3'-untranslated region, resulting in prolonged half-life of p53 mRNA, thereby TIP30 induced apoptosis and mitochondrial dysfunction through stabilization of p53 mRNA in hepatocellular carcinoma cells [28]. There was a poor prognosis in breast cancer patients with low expression of TIP30, but TIP30 expression was not correlated with that of p53 [20]. Our results show that TIP30 and p53 expression in the LSCC is negatively correlated, and that the low expression of TIP30 has a higher recurrence rate and poorer prognosis. TIP30, thus, may represent a new prognostic marker in the development, metastasis and prognosis of LSCC. However, further larger studies and molecular mechanisms underlying mutually roles of TIP30 and p53 in LSCC are needed.

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Disclosure of conflict of interest

None.

Abbreviations

LSCC, laryngeal squamous cell carcinoma.

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