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ORIGINAL RESEARCH

Increased Expression of TAP Is Predictive of Poor Prognosis in Patients with Non-Small Cell Lung Cancer

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Background: The most common cancer among humans is lung cancer. Non-small cell lung cancer (NSCLC) comprises the majority of these cases. In the development and progression of cancers across the spectrum, tumor abnormal protein (TAP) plays crucial roles. Additionally, in the advancement of the bladder and colorectal cancers, the involvement of glycoproteins like TAP is present. However, it is worth noting that current literature has yet to clarify the clinical significance of the TAP in NSCLC.

Methods: In the present study, to evaluate the relative level of TAP, we utilized a TAP detection agent in 154 cases of NSCLC and normal patients who underwent surgical resection anytime from March 2013 to January 2019 at the People's Hospital of Chizhou.

Results: Our results demonstrated that in NSCLC patients, the expression level of TAP was significantly higher than in normal patients. Moreover, after surgery, TAP expression was significantly downregulated in NSCLC patients. TAP expression is associated with an array of factors, which include the patient's sex, history of smoking use, tumor size, pTNM, distant cancer, metastasis of lymph nodes, invasive and aggressive indicator pleural invasion, and differentiation degree of NSCLC. Additionally, TAP has no association with the patient's age, history of drinking, location of the tumor, hypertension, and diabetes. In NSCLC patients, a poor overall survival rate within 5 years is significantly correlated with the increased TAP expression. For NSCLC patients, an independent prognostic factor is the TAP, which is confirmed using the multivariate survival analysis.

Conclusion: In the malignant progression of NSCLC, our results demonstrate how the promoting role of the upregulated TAP expression takes place. Hence, a therapeutic aim for NSCLC and a potential biomarker for NSCLC progress is a TAP.

Keywords: tumor abnormal protein, TAP, lung, cancer, prognosis, predictive

Introduction

Currently, the most common new type of cancer is lung cancer, which is also the leading cause of cancer-related deaths. Majority of these cases are classified as non-small cell lung cancer (NSCLC).[1,2] The NSCLC mortality and recurrence rates have not significantly declined amid the developments in oncology and multidisciplinary treatments.

Unfortunately, one of the main reasons is at the time of the diagnosis, patients are already at the advanced stage. As a result, it is vital to generate effective and efficient approaches to predict tumor genesis and development. Recent literature has brought light to numerous proteins that have a close association to TAP's

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progression and occurrence but (USSR) named Kostyantin, A. and Galakhin, discovered the tumor abnormal protein (TAP).[3,4] During the metabolism of cancer cells, they emit complex abnormal glycoproteins and calcium-histone proteins that comprise the TAP.[5] Essentially, TAP is the result of changes in the glycosylation of cancer cells. The presence of TAP indirectly indicates the number and extent of cell cancerization. After reaching a certain volume, these substances are discharged into the blood while more of them continue to exist in the peripheral blood. In early cancer detection, an important indicator is the increased TAP expression in the blood. However, there exists a crucial need for the biological function of TAP to be further investigated. The mutations in oncogenes and tumor-suppressor genes in cells produce TAP. Additionally, tumor growth contributes to TAP upregulation. In numerous types of carcinomas, such as breast, colon, ovarian, endometrial, stomach and lung cancers, a biomarker like TAP is upregulated.[6] In the development, progression, and metastasis of the tumor, the involvement of TAP is evident. As a result, it is considered to be an important indicator in tumor prognosis. Additionally, it is important to note that in the context of tumorigenesis and progression of NSCLC, there is still a need to further investigate the role of TAP. In this study, we aim to evaluate TAP expression levels between NSCLC and normal patients. Additionally, our study covers the analysis of the correlation between the expression of TAP and clinicopathological characteristics of patients with NSCLC. These characteristics include age, sex, history of smoking use and drinking, hypertension, diabetes, tumor size and location, pTNM, Lymph node metastasis, distant metastasis, pleural invasion, differentiation degree, and 5-year overall survival.

Materials and Methods

Patients and Samples Collection

The Ethical Committee of ChiZhou People's Hospital in Anhui Province, China approved this study. This study was conducted in accordance with the Declaration of Helsinki. We also obtained signed informed consents from all the patients. For the control group of the study, we included healthy patients. We collected NSCLC and non-tumor blood samples from patients who underwent surgical resection anytime from March 2013 to January 2019 at the People's Hospital of Chizhou. The inclusion criteria required that all the NSCLC patients did not undergo any preoperative radiotherapy and/or chemotherapy. The histopathological evaluation confirmed the results (8th edition of the TNM Classification for Lung Cancer). We collected and retained the follow-up data of all 154 NSCLC patients. Our definition for the overall survival (OS) is the period between the diagnosis and the date that the patient was last known to be alive or the patient's date of death. Table 1 provides a summary of all the clinicopathological characteristics.

TAP Detection

Detection Methods

From the first and second drops of a patient's blood from his/her fingertips, we collected whole blood samples and prepared the specimen on glass slides accordingly. After the samples have naturally dried, we used them for TAP detection along with the TAP detection reagent (Biosharp Biotech, Hefei, China). Then, we performed the condensation staining reaction. Upon the completion of the reaction and drying of the stain, we executed a microscopic examination to observe the results.

Determination of TAP Detection Results

The existence of TAP in the blood is demonstrated by its reaction with the reagent that produces a condensation product that is crystal-like. On one hand, the condensation particle area for TAP-positive is ≥225 μm^2. On the other hand, the condensation particle area for TAP weakly positive or critical type is between 121 and 225 μm^2. For TAP-negative, there was no evident observation of crystal-like condensation product. In the study, the condensation particle area was>225 μm^2 in the high, and<225 μm^2 was not observed in the low expression group.

Statistical Analysis

We repeatedly ran the experiments in this study for at least three times. We expressed all the statistical data as the mean ± standard error of the mean (SEM). To perform our statistical analysis, we utilized the SPSS 18.0 software package (SPSS, Chicago, IL, USA). Using the independent-samples *t*-test, we compared the differences in the TAP expression between the two groups of patients. Concerning the mean value, the classification of the TAP expression levels in the NSCLC blood samples was the low expression and high expression. Furthermore, to evaluate the relationship between the TAP expression and the clinicopathological parameter of NSCLC, our study used the chi-square test. Then, to examine and compare the

Table 1 Clinical Association Between TAP Expression and Clinicopathological Variables in NSCLC Patients

Variable	Number	TAP		χ^2 Test P value
		Low Expression	High Expression	
Age				0.724
≤60	61	43	18	
>60	93	68	25	
Sex				0.001
Male	79	48	31	
Female	75	63	12	
Smoking				0.000
No	112	90	22	
Yes	42	21	21	
Drinking				0.072
No	131	98	33	
Yes	23	13	10	
Hypertension				0.268
No	93	62	29	
Yes	61	47	14	
Diabetes				0.830
No	143	103	40	
Yes	10	7	3	
Tumor size				0.000
≤3cm	125	101	24	
>3cm	29	10	19	
Tumor location				0.896
LUL	40	31	9	
LLL	13	7	6	
RUL	55	40	15	
RML	17	11	6	
RLL	29	22	7	
pTNM				0.000
I	119	108	11	
II–IV	35	3	32	
Lymph node metastasis				0.000
No	128	108	20	
Yes	26	3	23	
Distant metastasis				0.000
No	144	111	33	
Yes	10	0	10	
Pleural invasion				0.000
No	103	85	18	
Yes	51	26	25	
Differentiation degree				0.000
No	90	76	14	
Yes	64	35	29	

prognoses, we worked with the Kaplan-Meier method and Log rank test. Finally, to study the independent prognostic factors for survival among the NSCLC patients, we utilized the analytical tools, such as the univariate and multivariate Cox proportional hazards. Our statistical significance is set at P-value<0.05.

Results

In NSCLC Blood, TAP Is Upregulated – After Surgery, TAP Is Downregulated

Initially, we used 154 cases of blood samples extracted from NSCLC and non-tumor patients to compare TAP expression between the two groups. Then, we used a TAP detection reagent to further evaluate these TAP expression levels. The results suggest that in NSCLC blood, TAP expression significantly increased than in non-tumor blood (Figure 1A and B). We also conducted examinations on TAP's expression in NSCLC patients who underwent surgery. Figure 1B illustrates how there was a significant decrease in the TAP expression level in NSCLC patients after surgery, as indicated by the tap detection reagent. Therefore, after surgery, the upregulation of TAP is evident in NSCLC patients.

TAP Expression Is Associated with the Patient's Sex, History of Smoking Use, Tumor Size, pTNM, Distant Cancer, Metastasis of Lymph Nodes, Invasive and Aggressive Indicator Pleural Invasion, and Differentiation Degree of NSCLC

We assessed the relationship between TAP expression and the clinicopathological characteristics of NSCLC to broaden the understanding of the role of TAP in NSCLC. Concerning the mean value, the classification of the TAP expression levels in the NSCLC blood samples was the low expression and high expression. Table 1 highlights the significant association of high TAP expression levels to clinicopathological factors, such as sex, tumor size, pTNM, distant cancer, metastasis of lymph nodes, invasive and aggressive indicator pleural invasion, and differentiation degree of NSCLC. Additionally, as seen in Table 1, TAP has no association with the patient's age, history of drinking, location of the tumor, hypertension, and diabetes. These outcomes underline the involvement

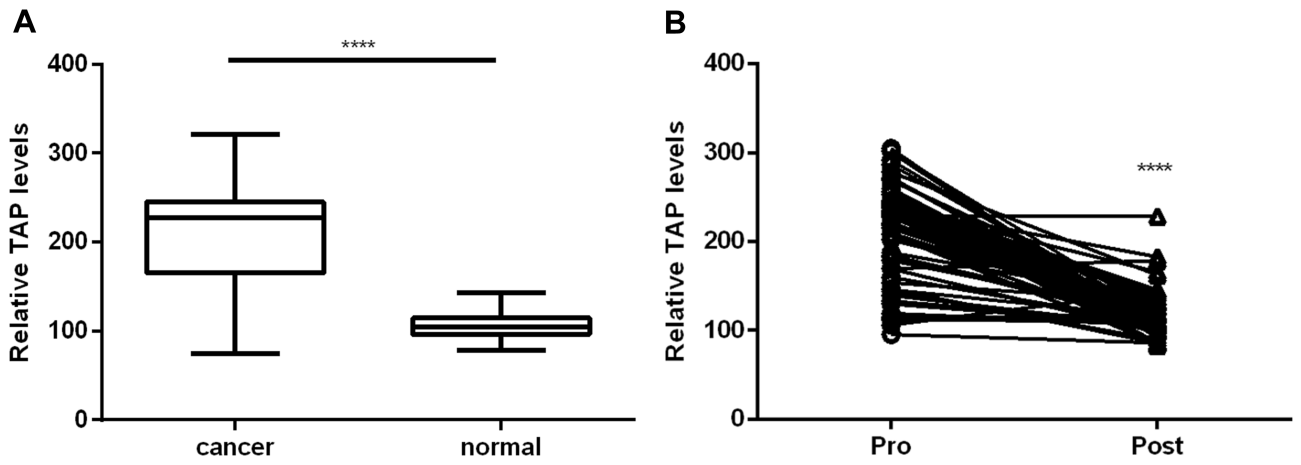


Figure 1 Relative expression of TAP in NSCLC patients and normal patients. (**A**) Expression levels of TAP in a total of 154 NSCLC blood and non-tumor blood were measured by TAP detection reagent. (**B**) A line connects two points from pre-operation to post-operation with a decreased trend, suggesting that the expression level of TAP is downregulated in NSCLC patients after surgery. (****p<0.0001).

of increased TAP expression levels in the progression of the NSCLC malignancy.

Among NSCLC Patients, High TAP Expression Levels are Predictive of Their Poor Prognosis

Our in-depth analysis covered the assessment of the association between the TAP expression and survival period of NSCLC patients, which obtained results that showed a worse prognosis for NSCLC patients with high TAP expression levels than those with low TAP levels (Figure 2). To study the independent prognostic factors for survival among the NSCLC patients, we utilized the analytical tools, such as the univariate and multivariate Cox proportional hazards. The significant association of the overall survival of NSCLC patients with the tumor size, pTNM, lymph node metastasis, distant metastasis, pleural invasion, differentiation degree, and TAP expression reflected in the univariate analysis data (Table 2). For the prognosis of NSCLC patients, another independent prognostic factor is the TAP expression (Table 3). For the overall survival (OS) of NSCLC patients, these are not independent prognostic factors: the tumor size, pTNM, lymph node metastasis, distant metastasis, pleural invasion, and differentiation degree (Table 3). Furthermore, our results confirm that high TAP expression levels can predict the poor prognosis of NSCLC patients accordingly.

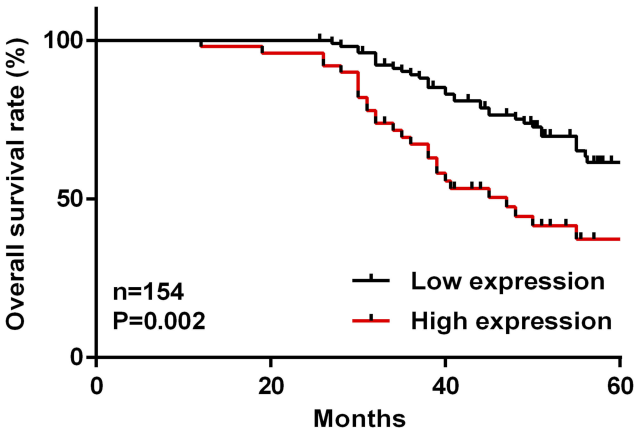


Figure 2 Kaplan-Meier postoperative survival curve for patterns of patients with NSCLC and TAP expression. NSCLC patients with High TAP expression (n=50) showed shorter survival time than those with low TAP expression (n=104).

Table 2 Univariate Analysis of Prognostic Factors of NSCLC

Variable	Hazard Ratio	p value
TAP expression (Low/High)	0.248	0.008
Age (≤60/>60)	1.002	0.992
Gender (Male/Female)	0.851	0.499
Smoking (Yes/No)	0.699	0.165
Drinking (Yes/No)	1.471	0.199
Hypertension (Yes/No)	0.710	0.152
Diabetes (Yes/No)	1.184	0.660
Tumor size (≤3cm/>3cm)	0.276	0.000
Tumor location (LUL/LLL/RUL/RML/RLL)	1.054	0.535
pTNM (I/II–IV)	0.163	0.000
Lymph node metastasis (Yes/No)	0.159	0.000
Distant metastasis (Yes/No)	0.165	0.000
Pleural invasion (Yes/No)	3.016	0.000
Differentiation degree (Moderate/Poor)	0.467	0.001

Table 3 Multivariate Analysis of Independent Prognostic Factors of NSCLC

Variable	Hazard Ratio	p value
TAP expression (Low/High)	0.505	0.043
pTNM (I/II–IV)	0.798	0.706
Tumor size (>3cm/<3cm)	0.707	0.332
Lymph node metastasis (Yes/No)	0.544	0.194
Distant metastasis (Yes/No)	0.674	0.336
Pleural invasion (Yes/No)	1.653	0.075
Differentiation degree (Moderate/Poor)	0.826	0.473

Discussion

Recent studies have collected evidence on the critical role that TAP plays in the development and progression of cancer, as well as the regulation of cell proliferation, apoptosis, differentiation, and development.[7–9] In gastric cancer patients, the upregulation of TAP was significant compared to healthy volunteers. Also, progression-free survival (PFS) is evident among patients with high TAP levels.[10] By combining the clinical signs and symptoms, TAP examination could be utilized in the diagnosis of urothelial carcinoma of the bladder. Additionally, it could also detect urothelial carcinoma of the bladder.[11] In colorectal cancer (CRC) patients, the detection of TAP has high levels of sensitivity and specificity. Also, in the course of chemotherapy and clinical monitoring of CRC patients, TAP detection is used as a new independent indicator.[12] In the advancements of the diagnostics and therapeutics of cancers in humans, it is crucial to study the precise roles of specific TAP.

In this research, we utilized 154 peripheral blood samples of NSCLC patients and evaluated the TAP expression accordingly. In NSCLC and healthy patients, the remarkable upregulation of TAP was evident in the TAP detection reagent data. After the surgery of NSCLC patients, their TAP expression levels also decreased. These outcomes suggest that in the development of NSCLC, TAP is released in the blood. Furthermore, our in-depth analysis found that high TAP expression levels were significantly related to the patient's sex, history of smoking use, tumor size, pTNM, distant cancer, metastasis of lymph nodes, pleural invasion, and differentiation degree of NSCLC. However, we found that TAP had no association with the patient's age, history of drinking, location of the tumor, hypertension, and diabetes. Men have higher TAP than women, which may have something to do with the high proportion of men who smoke. Our speculation includes the possible impact of TAP on the prognosis of NSCLC patients given the general association of invasive and metastatic tumor cells with poorer prognosis of cancer patients.

We evaluated the association between the expression of TAP and the overall survival (OS) of NSCLC patients to evaluate the legitimacy of our speculation. In contrast with patients that have low TAP expression, our data confirm the worse prognosis of NSCLC patients with high TAP expression. Also, an independent prognostic factor is the TAP expression among NSCLC patients. Similarly, a higher TAP level was found in breast cancer patients than patients with a benign diagnosis ($P<0.001$). On one hand, TAP was not associated with estrogen receptor, progesterone receptor, her-2 expression, tumor size, and pathological degree. On the other hand, TAP was significantly associated with the patient's age, metastasis of lymph nodes, and TNM stage.[13] The outcome of recent studies suggests that for the diagnosis of lung cancer and evaluation of progression among lung cancer patients, TAP could be utilized as an indicator.[14] We could sensitively distinguish abnormal sugar chains associated with malignant tumors in the digestive tract using TAP detection. As a result, numerous signals related to the tumor could be obtained. In malignant tumors of the subclinical stage, we could detect TAP.[15–17] As verified by previous studies, the detection of TAP expression could be up to 2 years earlier than the revelation of clinical signs, symptoms, and malignant lumps.[18] Our recommendation for future research is in-depth coverage on the exact regulatory role and mechanism of TAP in the proliferation, migration, and invasion of NSCLC cells. The significance will revolve around the rising need of patients that are TAP-positive for therapeutic interventions, as well as for cancer prevention and treatment. Encouraging results have been found in cancer vaccines that are based on glycans.[19,20] Apart from lung cancer, the existence of TAP expression is evident in the stomach, colorectal, thyroid, and bladder tumors.[9–12,21] Our research findings add to the general overview of TAP's role in a tumor's development and progression.

In conclusion, our data suggest the significant upregulation of the TAP expression in the NSCLC blood and downregulation following a surgery. The TAP expression has a significant relationship with the patient's sex, history of smoking use, tumor size, pTNM, lymph node metastasis, distant metastasis, pleural invasion, and differentiation degree of NSCLC patients. More importantly, a predictive

factor of a worse prognosis in NSCLC patients is an increased TAP expression. Taking all these data into consideration, in the malignant progression of NSCLC, we would like to shed light on the promoting role of TAP and its potential to become an NSCLC prognostic biomarker.

Disclosure

The authors report no conflicts of interest in this work.

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