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C-terminal binding protein-2 is a prognostic marker for lung adenocarcinomas

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Abstract

C-terminal binding protein-2 (CtBP2) a transcriptional corepressor, has been reported to involve in tumorigenesis and progression and predict a poor prognosis in several human cancers. However, few studies on CtBP2 in lung cancer tissues have been performed. In the present study, we first explored the *CtBP2* gene expression profile from the the cancer genome atlas (TCGA) datasets, then western blot analysis and immunohistochemistry were performed to investigate and verified whether lung adenocarcinoma (LUAD) tissues exhibit deregulated CtBP2 expression. We evaluated the correlations between CtBP2 expression and the clinicopathological characteristics, and Kaplan–Meier survival analyses were performed to estimate the effect of CtBP2 expression on prognosis of LUAD patients. The results revealed that CtBP2 expression was significantly upregulated in LUAD tissues compared with normal lung tissues. Furthermore, increasing CtBP2 expression in LUAD was significantly associated with tumor differentiation ($P = .028$), tumor node metastasis (TNM) stage ($P = .042$). CtBP2 expression was significantly correlated with LUAD patients' survival ($P = .028$). In conclusion, the present study revealed that CtBP2 protein is a novel prognostic marker for LUAD. A further large-scale study is needed to confirm the present results.

Abbreviations: CtBP2 = C-terminal binding protein-2, EMT = epithelial-mesenchymal transition, IHC = immunohistochemical, LUAD = lung adenocarcinoma, LUSC = lung squamous cell carcinoma, NSCLC = non-small cell lung cancer, PVDF = polyvinylidene difluoride, TCGA = the cancer genome atlas, TNM = tumor node metastasis.

Keywords: c-terminal binding protein-2, lung adenocarcinoma, lung cancer, tumor marker

1. Introduction

Lung cancer is a major public health problem for leading cause of cancer death.[1] In recent years, the incidence and mortality of lung cancer are steadily increasing. Non-small cell lung cancer (NSCLC) accounts for over 80% of all lung cancersRef2.[2] For most patients present with advanced-stage disease when they are diagnosed; therefore, the prognosis of lung cancer is poor and the overall 5-year survival rate is only 15%.[1,3] Mechanisms involving in developing of lung cancer and treatment options for lung cancer have received intense investigation over the last decade.

The C-terminal-binding protein (CtBP) was originally identified as a cellular phosphoprotein that interacts with a C-terminal domain of adenovirus E1a protein involved in negative modulation of oncogenic transformation.[4,5] In vertebrates, CtBP protein contains 2 highly homologous isoforms (CtBP1 and CtBP2), which widely expresses during animal developmental processes. Several studies suggested that CtBP was required for the repressive action of various transcription factors.[6,7] Many studies reported that CtBPs were abnormal expression in several human malignant tissues, such as prostate cancer, melanoma, esophageal cancer, and breast cancer.[8–11] Additionally, a genome-wide association study revealed that CtBP2 expression was positively associated with the risk of prostate cancer-Ref12.[12] CtBP2, mediated repression of tumor suppressor genes, was demonstrated involving in tumorigenesis and tumor progression, and as a predicting factor for cancer metastasis.[8,13,14] However, there is still no study on the CtBP2 expression in human lung cancer, the relationship between CtBP2 and relevant clinical significance of lung cancer till now.

In the present study, we found that CtBP2 was overexpressed in NSCLC, and closely correlated with various clinical features and NSCLC progression. Overall, our results suggest that CtBP2 might be a potential biomarker for tumorigenesis and a prognostic indicator of NSCLC, and targeting CtBP2 might represent novel strategies for NSCLC therapeutic.

2. Materials and methods

2.1. Patients and tissue samples

A total of 129 tumor samples from patients with NSCLC were obtained undertaken tumor resection at the Tongji Hospital of Huazhong Science and Technology University and Hubei Cancer Hospital from September 2012 to January 2015, and all the cases

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The authors report no conflicts of interest in this work.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Table 1

Relationships between CtBP2 expression and clinicopathological parameters in LUAD patients.

Clinicopathological characteristics	Total n	CtBP2 expression		*P*-value
		Low, n	High, n	
Age, yr				
≤60	40	23	17	.71
>60	32	17	15	
Gender				
Male	50	31	19	.61
Female	22	15	7	
Smoking habits				
Never smoked	30	22	8	.69
Smoker	42	29	13	
Tumor differentiation				
Well	18	14	4	.028
Moderately/poorly	54	26	28	
Tumor size (cm)				
≤3 cm	26	18	8	.22
>3cm	46	25	21	
p-TMN stage				
I	15	11	4	.042
II, III	57	25	32	
Lymphatic invasion				
Yes	49	21	28	.15
No	23	14	9	

CtBP2 = C-terminal binding protein-2, LUAD = lung adenocarcinoma.

were pathologically confirmed. The patient cohort included 72 lung adenocarcinoma (LUAD) and 57 lung squamous cell carcinoma (LUSC). No patients had received preoperative chemotherapy or radiotherapy. A total of 45 lung tissues that were obtained from patients with bullae of lung, inflammatory pseudotumor, bronchiectasis served as the control group, which were confirmed no cancer cells by postoperative pathology. For Western blot (WB) and quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) analysis, the fresh tissues were snap-frozen in liquid nitrogen and stored at −80°C immediately after surgical removal. Part of these tissues were formalin-fixed and paraffin-embedded for immunohistochemical staining study. This study was approved by the ethics committee of Affiliated Tongji Hospital of Huazhong Science and Technology University. The main clinicopathological variables of the patients are shown in Table 1.

2.2. Real-time RT-qPCR analysis

Total RNA was isolated from the specimens using TRIzol Reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. RNA concentration and purity were measured using the NanoDrop 2000 Spectrophotometer (Thermo Scientific, Wilmington, DE). Ratios of A260/280 nm were between 1.9 and 2.1. Total RNA reverse transcription was conducted using PrimeScript RT reagent Kit (TaKaRa) according to the manufacturer's instructions. Real-time quantitative PCR was performed using SYBR Premix TaqTM (Takara, Beijing) with the Mx3000P system (Stratagene, LaJolla, CA). The cycle parameters were set as follows: an initial 1-minute incubation at 95°C, followed by 40 cycles of 95°C for 5 seconds, 60°C for 20 seconds, and 72°C for 15 seconds. After amplification, the threshold cycle was automatically calculated by the Mx3000P system, and the melting curve was formed for to each primer to evaluate whether the presence of 1 gene-specific peak and the absence of primer dimer. Relative expression levels were normalized to glycerine aldehyde phosphate dehydrogenase (GAPDH) and calculated using the $2^{-\Delta\Delta Ct}$ method. The experiments were performed in triplicate and repeated at least 3 times. Primers used were as follows:

CtBP2-F: ATCCACGAGAAGGTTCTAAACGA;
CtBP2-R: CCGCACGATCACTCTCAGG-3.
GAPDH-F: CGCTAACATCAAATGGGGTG
GAPDH-R: TTGCTGACAATCTTGAGGGAG

2.3. WB analysis

Tissue samples were harvested into lysis buffer containing complete protease inhibitor cocktail and protein concentration were measured using a BioRad protein assay. Equal amounts of protein (50–100 μg/lane) were was separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and performed for WB analysis as described previously.[15] Then, the protein was transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore), and then PVDF was blocked nonspecific binding with 5% skim milk in Tris-Buffered Saline and Tween (TBST) for 1 hour at room temperature. The membranes were incubated with CtBP2 (1:800, Abcam) overnight. Then, anti-rabbit horseradish peroxidase (HRP)-conjugated secondary antibodies (ABclonal) were used to detect protein using an enhanced chemiluminescence Assay Kit (Millipore). The band intensity was quantified using Image J software (1.44 P, Wayne Rasband), the relative band intensity of target proteins was normalized against β-actin bands.

2.4. Immunohistochemistry and analyses

Tissues were fixed in 10% neutral buffered formalin, and then paraffin-embedded which were cut transversely at a thickness of 4 μm. The paraffin sections were deparaffinized in xylene, rehydrated in graded ethanol solutions, and then, antigen retrieval was performed by heating to 121°C for 2 minutes immersed in 10 mmol/L citrate buffer (pH 6.0) with an autoclave. Afterward, the sections treated with 0.3% hydrogen peroxide in methanol for 15 minutes to remove endogenous peroxidase activity. To block nonspecific protein binding, sections were incubated with 10% normal goat serum for 30 minutes. Sections were incubated with anti-CtBP2 antibody (diluted 1:400; Abcam) overnight at 4°C. Negative control slides were also processed in parallel using a nonspecific immunoglobulin IgG (Boster, Wuhan, China) at the same concentration as the primary antibody. After washing, slides were incubated with peroxidase-anti-peroxidase method (Dako, Hamburg, Germany) for 30 minutes at room temperature. The chromogenic reaction was visualized by light microscope. The slides were then counterstained with hematoxylin stains, dehydrated, and coverslipped.

The immunostained sections were scored in a blinded manner without any knowledge of the clinical information of the patients. Ten nonoverlapping highpower fields (×200) were selected randomly in per slide. For statistical analysis of CtBP2 staining, the each slide was scored by semiquantitative scoring system for both the intensity of the stain and the percentage of positive cells. The intensity of staining was coded as follows: 0 (negative or poor staining), 1 (moderate staining), and 2 (strong staining). The

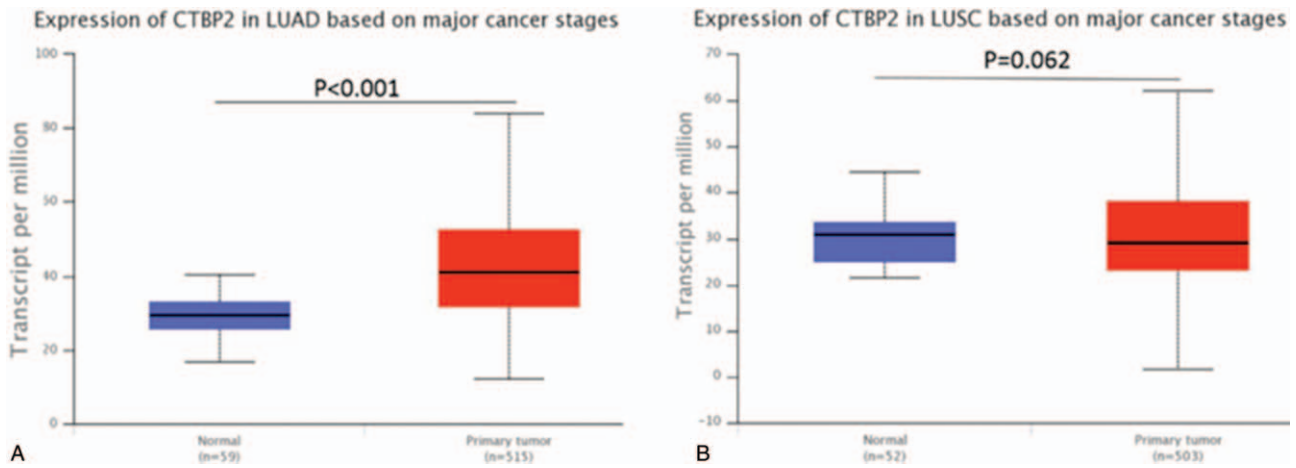

Figure 1. The expression profile of *CtBP2* gene in NSCLC based on the TCGA datasets. (A) The expression of *CtBP2* gene was higher in the LUAD patients than in the normal lung tissues. (B) The expression profile of *CtBP2* gene in the LUSC patients. CtBP2 = C-terminal-binding protein 2, LUAD = lung adenocarcinoma, LUSC = lung squamous carcinoma.

percentage of cells was scored as follows: 1 (0%–25% tumor cells stained), 2 (26%–50% tumor cells stained), 3 (51%–75% tumor cells stained), and 4 (>75% tumor cells stained). Then, we multiplied the 2 scores and classified them into 2 groups: high expression (>6 scores) and low expression (≤6 scores).

2.5. Gene expression profile

We explored the *CtBP2* gene expression profile from the TCGA datasets (https://cancergenome.nih.gov/). TCGA was a public functional genomics data repository in which accepted array and sequence-based data.

2.6. Statistical analysis

The data are presented as average ± standard deviation, Survival curves were estimated by the Kaplan–Meier method. Two-sided $P < .05$ was considered statistically significant. Statistical analyses were performed using the SPSS version 21.0 statistical software package (SPSS, IBM). Figures were constructed using the GraphPad Prism 5.0 software program (La Jolla, CA).

3. Results

3.1. CtBP2 positive expression rate is higher in LUAD tissues than normal lung tissues

First, we used TCGA datasets (https://cancergenome.nih.gov/) to explore CtBP2 expression in lung cancer tissues. As a result of the data the TCGA database, we found that CtBP2 expression levels in LUAD group were significantly increased than that in lung tissues of the normal lung; however, the CtBP2 expression levels in LUSC tissues were almost equal to the normal lung tissues (Fig. 1). We next used immunohistochemical (IHC) staining to further examined CtBP2 expression in 72 LUAD tissues, 40 LUSC tissues, and 45 normal lung tissues. Representative IHC staining revealed that CtBP2 was predominantly located in the nucleus (Fig. 2A). CtBP2 showed markedly overexpression in LUAD tissues, even it showed higher expression in poorly differentiated LUAD tissues than in well-differentiated ones. The high expression rate of CtBP2 in all LUAD patients was 93.4%, while the high expression rate of CtBP2 in the control group was 0.00%. However, in LUSC group, the CtBP2 expression levels were higher than the normal group, but there was no statistical difference. These findings are consistent with those of the public data which revealed that CtBP2 is highly expressed in malignant LUAD tissues and increases with ascending tumor cell differentiation.

3.2. CtBP2 protein expression is higher in LUAD tissues than normal lung tissues

We extracted RNA from the fresh LUAD tissues and normal lung tissues, and compared to normal group, the result of RT-PCR for CtBP2 was upregulated in LUAD tissues, as shown in Figure 2B. Furthermore, we also performed WB analysis of CtBP2 protein expression in fresh LUAD tissues and normal tissues. The WB results showed that expression of CtBP2 in LUAD tissue (0.48 ± 0.25) was significantly higher than in normal lung tissue (0.43 ± 0.13) ($P = .0082$) (Fig. 3C and D).

3.3. Correlation between the expression of CtBP2 and clinicopathological characteristics of NSCLC

The correlations between the CtBP2 expression and the clinicopathological characteristics in the 72 cases of LUAD are shown in Table 1. High expression of CtBP2 in LUAD was significantly associated with tumor differentiation ($P = .028$), TNM stage ($P = .042$). By contrast, no statistically significant relationships were found for age, gender, smoking habits, tumor size, and lymphatic invasion.

We further explore the association between high CtBP2 expression in NSCLC and the clinicopathological characteristics from the TCGA datasets. As shown in Figure 3. Whatever, in the LUAD or LUSC group, no statistically significant relationships were found for patients, age, gender, and race. But the interesting thing was that CtBP2 expression levels were lower in the smoker of LUAD patients than in the nonsmoker of LUAD patients ($P = .018$), even the LUAD patients had reformed smoking habit over 15 years ($P = .037$). According to TNM stage, as tumor

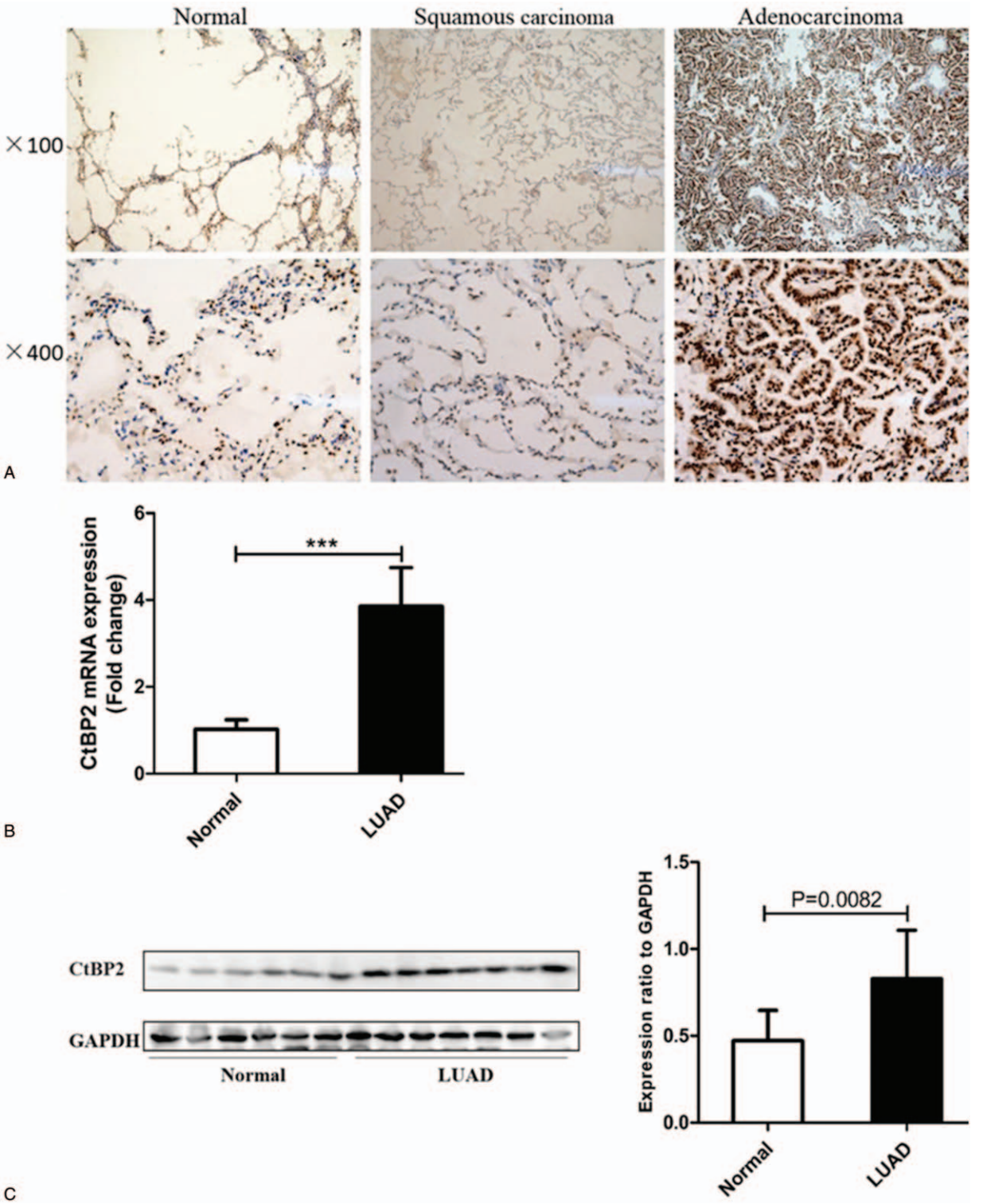

Figure 2. Immunohistochemical staining, RT-qPCR and Western blotting analysis for CtBP2 in representative samples of normal lung tissue, LUAD tissues, and LUSC tissues. (A) Representative IHC staining revealed that CtBP2 was predominantly located in the nucleus staining of the normal lung tissue, LUAD tissues and LUSC tissues (magnification, × 100, above; magnification, × 400, below). (B) RT-qPCR analysis showed that the mRNA levels of CtBP2 were higher in LUAD tissues (n = 9) than in normal lung tissues (n = 9) ($^{***}P < .001$). (C and D) Western blotting analysis showed that the protein levels of CtBP2 were higher in 7 representative LUAD tissues than in 6 normal lung tissues. CtBP2 = C-terminal-binding protein 2, LUAD = lung adenocarcinoma, LUSC = lung squamous carcinoma.

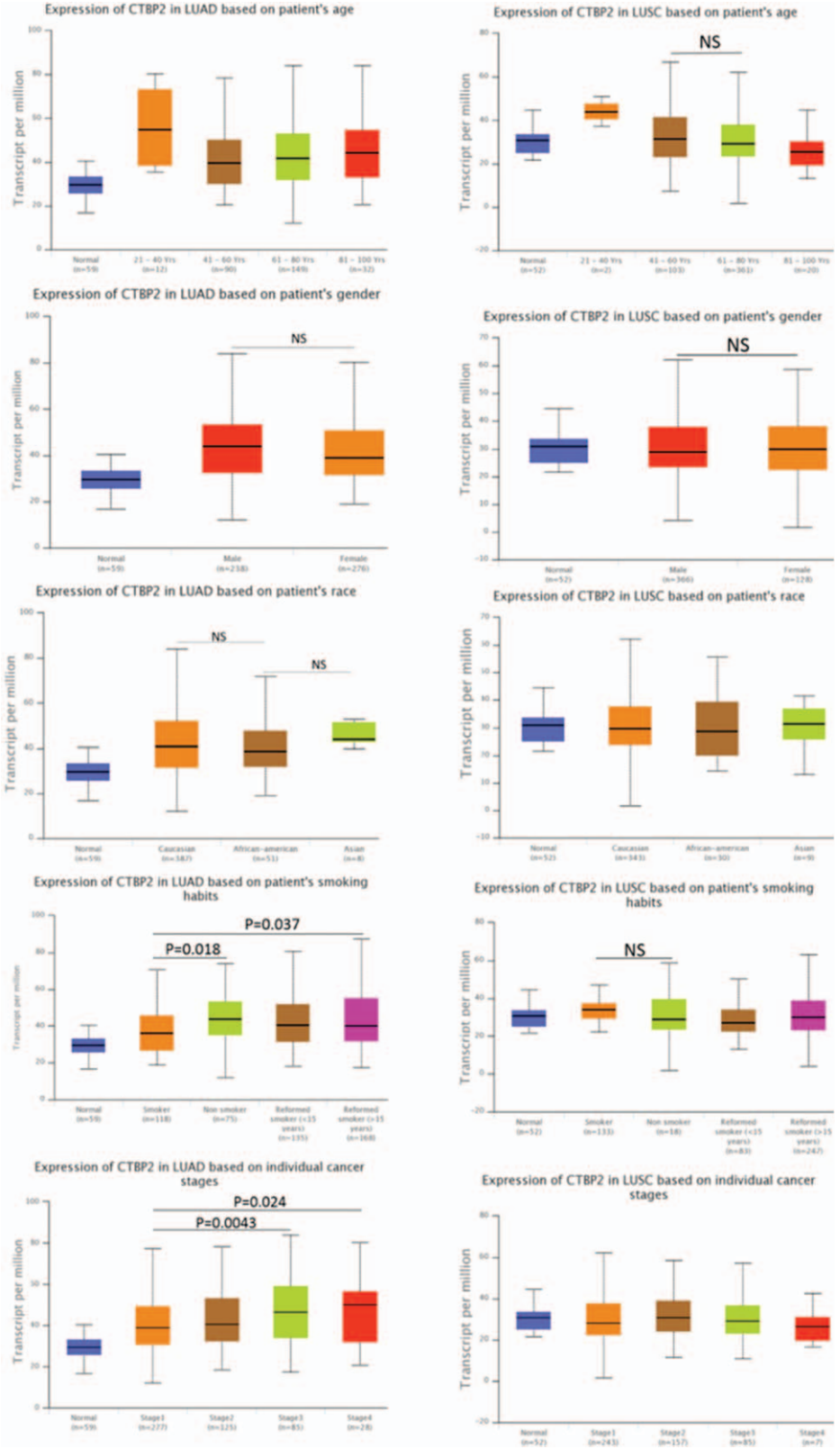

Figure 3. Correlation between the expression of CtBP2 and clinicopathological characteristics of NSCLC. CtBP2 = C-terminal-binding protein 2, NSCLC = non-small cell lung cancer.

Table 2

Relationships between CtBP2 expression and EMT markers E-cadherin and vimentin.

Markers	CtBP2 expression intensity		Total	*P*-value
	High expression (n = 33)	Low expression (n = 39)		
E-cadherin; n (%)				.45
Positive	14 (35%)	26 (65%)	40	
Negative	19 (59.4%)	13 (40.6%)	32	
Vimentin; n (%)				.13
Positive	22 (57.9%)	19 (48.7%)	38	
Negative	11 (32.4%)	20 (51.3%)	34	

CtBP2 = C-terminal binding protein-2, EMT = epithelial-mesenchymal transition.

malignancy growing, CtBP2 expression levels also gradually increased, CtBP2 protein expression levels in stage I of the LUAD were significantly lower than stage III ($P = .0043$) and stage IV ($P = .024$) of the LUAD ($P = .024$).

3.4. Relationship between CtBP2 expression and epithelial–mesenchymal transition (EMT)-related markers, E-cadherin, and vimentin expression

IHC staining of E-cadherin and vimentin was analyzed with the intensity of these markers expression. CtBP2 expression was not correlated with the loss of E-cadherin ($P = .47$) or gain of vimentin ($P = .35$; Table 2).

3.5. High CtBP2 expression is associated with poor prognosis of LUAD patients

Based on the IHC analyses of CtBP2 expression in LUAD patients from our hospital, we used Kaplan–Meier survival curves for LUAD patients with high or low expression of CTBP2, as shown in Figure 4A, which indicated that the low CtBP2 expression group exhibited a significantly longer survival time than the high CtBP2 expression group ($P = .028$), as well, we found the same result from large simple data (TCGA datasets), which showed LUAD patients with CtBP2 low expression group had better prognoses (Fig. 4B and C). We further used univariate and multivariate analyses to evaluate CtBP2 as prognostic factors for overall survival in LUAD, which showed that CtBP2 expression was a risk factor for LUAD patients outcomes. Besides the levels of CtBP2 expression, other candidate parameters entered the multivariate analysis were shown in Table 3. It was found that CtBP2 expression failed to be an independent risk factor for poor prognosis of LUAD patients.

4. Discussion

CtBP family proteins function have been well characterized as transcriptional co-repressors for many transcription factors.[16] The CtBPs was first discovered involved in tumorigenesis in studies of the E1A oncogene.[17] Increasing evidences have confirmed that CtBP2 play important roles during development and oncogenesis, including differentiation, cell proliferation, and apoptosis.[17,18] CtBP2 as a transcription regulatory protein, its molecular function owned receptor signaling complex scaffold activity, and biological process was signal transduction and cell communication, which consequently regulates diverse cellular processes.[7,16,19]

Recently, CtBP2 abnormal expression has reported in multiple human cancers, included prostate cancer, gliomas, breast cancer, and gastric cancer.[13,14,20,21]

In the present study, using IHC, RT-PCR, and WB analyses tissues from LUAD patients in our hospital, and large sample size data from the public database TCGA showed that CtBP2 expression was upregulated in LUAD tissues. Whereas, CtBP2 expression was no obvious change in LUSC tissues, which demonstrated the CtBP2 exhibited a tissue specific expression and the possibility that the CtBP2 function is different between LUAD and squamous cell carcinoma. Therefore, LUSC patients

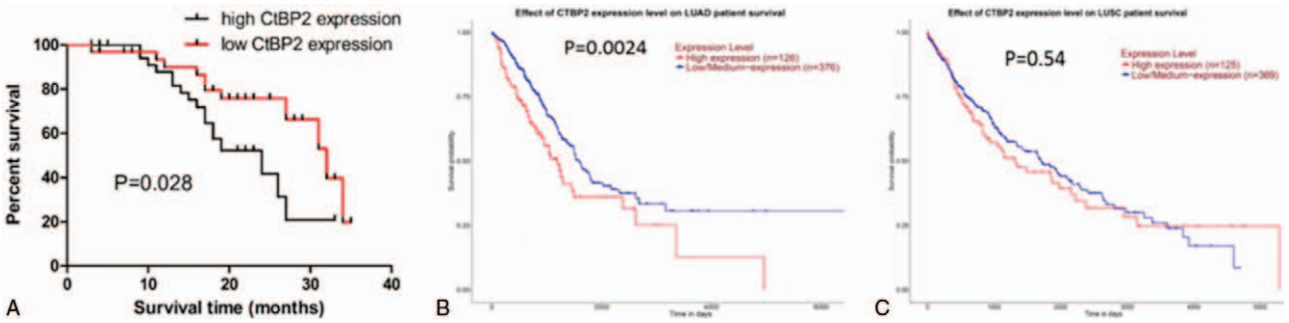

Figure 4. Analysis of LUAD patients survival prognosis using the Kaplan–Meier method. (A) The CtBP2 high-expression group (black line) had significantly worse prognoses than the CtBP2 low-expression group (red line) ($P < .05$), the LUAD patients data from the hospital. (B) The overall survival of LUAD patients was significantly higher than for the CtBP2 low-expression group (blue line) than the high-expression group (red line) ($P < .01$), the data from the TCGA datasets. (C) The overall survival of LUSC patients was not significantly higher than for the CtBP2 low-expression group (blue line) than the high-expression group (red line) ($P > .05$), the data from the TCGA datasets. CtBP2 = C-terminal-binding protein 2, LUAD = lung adenocarcinoma, LUSC = lung squamous carcinoma.

Table 3

Univariate and multivariate analyses of the effects of CtBP2 expression on lung adenocarcinoma patients.

	Univariate analysis		Multivariate analysis	
Factors	***P*-value**	**HR**	**95%CI**	***P*-value**
CtBP2 expression High versus low	<.001*	2.17	1.28–3.52	<.001*
Gender Female versus male	.37	/	/	/
Age (yr) >60 versus ≤60	.57	/	/	/
Smoking status Yes versus no	.63	/	/	/
Tumor differentiation Moderate, poor versus well	.07	/	/	/
Tumor size >3 cm versus ≤3 cm	.035*	1.45	1.12–2.28	.027*
p-TMN stage Stage II, III versus Stage I	.018*	1.31	1.12–3.52	.037*
Lymphatic invasion Yes versus No	.012*	0.076	0.83–1.97	.13

CI = confidence interval, CtBP2 = C-terminal binding protein-2, HR = hazard risk.
* Denotes statistically significant correlations.

were excluded for further analysis from the present stud0y. Immunostaining showed that CtBP2 was predominantly localized in the nuclei. By evaluating the association between CTBP2 expression and clinicopathological variables, it was demonstrated that CtBP2 overexpression was closely associated with malignant behaviors and poor prognosis. The high expression of CtBP2 in LUAD was significantly associated with differentiation and TNM stage. These findings are consistent with those of previous studies.[14,22] As we know, smoking is the primary risk factor for lung cancer, linked to approximately 80% to 90% of lung cancers[23]; however, we found that CtBP2 expression levels were lower in the smoker of LUAD patients than in the non-smoker of LUAD patients and LUAD patients had reformed smoking habit over15 years. Therefore, the mechanism of smoking effect on the CtBP2 expression needs further research.

Recently years, EMT has been reported to be associated with more aggressive tumor behavior and prognosis in malignant tumors.[24,25] The characters of EMT is a loss of cell adhesion, markers such as E-cadherin, and increased cell mobility due to cells gaining a mesenchymal phenotype, markers such as vimentin.[24,25] Zheng et al reported that CtBP2 is an independent prognostic marker that promotes GLI1 induced EMT in hepatocellular carcinoma.[26] Also, Yang et al demonstrated that CtBP2 promotes cell proliferation and migration in breast cancer via suppression of E-cadherin of $p16^{INK4A}$.[27] We evaluated the relationship between CtBP2 expression and the EMT-related markers E-cadherin and vimentin. But there was no significant correlation between CtBP2 expression and EMT markers e-cadherin and vimentin. The possibility cause of the CtBP2 involving in the EMT process is different between LUAD and hepatocellular carcinoma. Therefore, further studies to investigate the role of CtBP2 involving in the EMT process are required through in vivo experiment.

Additionally, previous studies have demonstrated that the overexpression CtBP2 protein correlated with poor prognosis of patients with various types of tumors.[20,22,26] At the present study revealed that high CtBP2 expression in LUAD patients was significantly associated with poorer survival of patients. However, we did not study the detailed mechanism underlying transcriptional regulation of CtBP2 in LUAD.

There are several limitations in present study. First, the sample size was small, and a retrospective single-center study may result in some selection bias. So need large-scale clinical data to clarify clinical significance in detail. Second, this study did not support and explain the of molecular mechanisms CtBP2 involving in oncology behavior at the cellular level. Further studies are needed to investigate the biological effect mechanism of CtBP2 role on the tumor progression. In brief, we revealed that CtBP2 expression was increased in LUAD patients compared with normal lung tissue and that high CtBP2 expression was associated with poor prognosis in LUAD patients. The results of this study indicated that CtBP2 may present a potential diagnostic marker and a novel therapeutic target in the treatment of LUAD.

Author contributions

All authors contributed to data collection and analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.
Conceptualization: Qi Huang.
Investigation: Zhengkai Xiang.
Software: Fei Xiong.
Supervision: Baoguo Yan.
Validation: Baoguo Yan.
Visualization: Qi Huang.
Writing – original draft: Binfeng Li.

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