Original Article

Expression of *p42.3* in non-small cell lung cancer

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Background: Lung cancer is the most malignant tumor with the highest morbidity and mortality. This study aimed to investigate the role of the expression and the significance of the *p42.3* gene in non-small cell lung cancer (NSCLC).

Methods: Lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) were analyzed based on the biological information data of The Cancer Genome Atlas (TCGA). Furthermore, 142 postoperative tumor tissue and normal tissue samples (70 cases of LUAD and 72 cases of LUSC) from NSCLC patients admitted to our hospital from 2005 to 2009 were retrospectively collected. Paraffin-embedded tissues were used to make the tissue microarrays (TMA), and the expression of the p42.3 protein was detected by immunohistochemical staining.

Results: The expression of *p42.3* in both LUAD and LUSC was significantly upregulated (P<0.01) compared with the normal lung tissues. The *p42.3* expression was significantly higher than that of LUAD (P<0.01) in the LUSC group. LUSC had a lower level of *p42.3* DNA methylation and a higher level of *p42.3* DNA amplification than LUAD. The expression rate of p42.3 protein decreased in patients 70 years or older (P=0.029). High expression of the p42.3 protein was an independent factor for worse pathological differentiation (P=0.043).

Conclusions: Both genetic and epigenetic alterations contributed to dysregulated *p42.3* in NSCLC. Despite the temporary absence of TCGA-LUSC (TCGA data on LUSC) survival information, we observed that the up-regulated expression of *p42.3* in LUSC was significantly higher than that in LUAD by analyzing the public database and reviewing the real-world data. Furthermore, a high expression of p42.3 protein was significantly correlated with poor differentiation of tumor tissues. Therefore, the prognostic value of *p42.3* in LUSC deserves further study.

Keywords: *p42.3*; non-small cell lung cancer (NSCLC); bioinformatics analysis; histological grade; immunohistochemistry (IHC)

Submitted Mar 27, 2020. Accepted for publication Jun 07, 2020.
doi: 10.21037/atm-20-2928
View this article at: http://dx.doi.org/10.21037/atm-20-2928

Introduction

Lung cancer has historically been the leading cause of cancer morbidity and mortality in the world (1), while non-small cell lung cancer (NSCLC) accounts for about 85% of primary lung cancers (2).

The *p42.3* gene (*GenBank*, *DQ150361*) is a highly conserved mammalian gene with a cDNA length of about 4.0 kb. It is highly homologous to the *c9orf140* gene located on the human chromosome 9q34.3 and encodes a protein composed of 389 amino acids with a molecular weight of 42.3 kDa; therefore, it has been named the *p42.3* gene. *p42.3* is specifically expressed in a variety of tumor cell lines. The expression of *p42.3* is cell cycle-dependent, and its mRNA expression in G1 and M phases are higher than that in S and G2 phases examined by RT-PCR. Among them, the M phase has the highest expression and gradually decreases after cell division, indicating that this gene may be involved in cell cycle regulation. This gene has a regulatory effect on the key proteins involved in cell cycle regulation, including the CHK2 and cyclin B1 proteins of gastric cancer (GC) cell lines, suggesting that it may be involved in tumor development as an oncogene (3-5).

Furthermore, the overexpression of *p42.3* has been proven to be closely related to the clinical stage of malignant melanoma, the 5-year survival rate of colorectal cancer (CRC) patients, and the histological grade of glioma (6-8). However, little is known about the relationship between *p42.3* and NSCLC. Therefore, in this study, we explored the expression of *p42.3* in NSCLC by bioinformatics analysis, and discussed the relationship between p42.3 protein expression and clinicopathological characteristics in combination with clinical cases.

Methods

Bioinformatic analysis using FireBrowse

The analysis of the *p42.3* expression in the solid tumors and corresponding normal tissues was performed with data from The Cancer Genome Atlas (TCGA). The data generated by the TCGA was analyzed using FireBrowse (http://firebrowse.org/) (9).

Bioinformatic analysis using UCSC Xena browser

The level 3 data of patients with primary NSCLC in TCGA-NSCLC (TCGA data on NSCLC) were extracted using the UCSC Xena browser (https://xenabrowser.net/). The *p42.3* mRNA expression and DNA methylation in patients with primary lung adenocarcinoma (LUAD) or lung squamous cell carcinoma (LUSC) were examined using data from the TCGA-LUAD (TCGA data on LUAD) and TCGA-LUSC with the UCSC Xena browser. Kaplan-Meier curves for the overall survival (OS) rates after initial therapy were also generated using the same browser.

Bioinformatic analysis using cBioPortal for cancer genomics

p42.3 genetic alterations from the TCGA-LUAD and TCGA-LUSC were examined using the cBioPortal for Cancer Genomics (http://www.cbioportal.org/) website (10,11). Only pathways with a P value <0.05 were included.

Patients and samples

NSCLC patients (n=142, 72 LUSC patients and 70 LUAD patients) who were diagnosed and underwent surgery at Beijing Hospital between 2005 and 2009 were included. None of these patients received anti-tumor therapy before surgery. The tumor tissue and paired normal tissue paraffin specimens were assigned to the tumor group and the control group, respectively. These tissue samples were processed in tissue microarrays (TMA). The clinicopathological data of the patients were collected and collated. This study is a retrospective observational study. Only paraffin specimens from tumor tissues of patients with NSCLC that were previously preserved by the subjects were collected for the study. No intervention measures were taken for the subjects. The collection of information and the publication of research results do not contain unique information that can identify the subject. Informed consent is not required. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Review Committee of Beijing Hospital (No. 2020BJYYEC-111-01).

Immunohistochemistry (IHC)

The TMA paraffin section (4 μm thick) was baked at 65 ℃ for 60 minutes. Next, it was dewaxed in xylene, and hydrated with graded alcohol water and a phosphate-buffered saline (PBS, pH 7.2–7.4). Treatment with a 3% hydrogen peroxide solution for 10 minutes was applied to block endogenous peroxidase activity. Following these steps, we heated the TMA in a 1X citrate buffer (pH 6.0) for 10 minutes in the microwave, and natural cooling restored

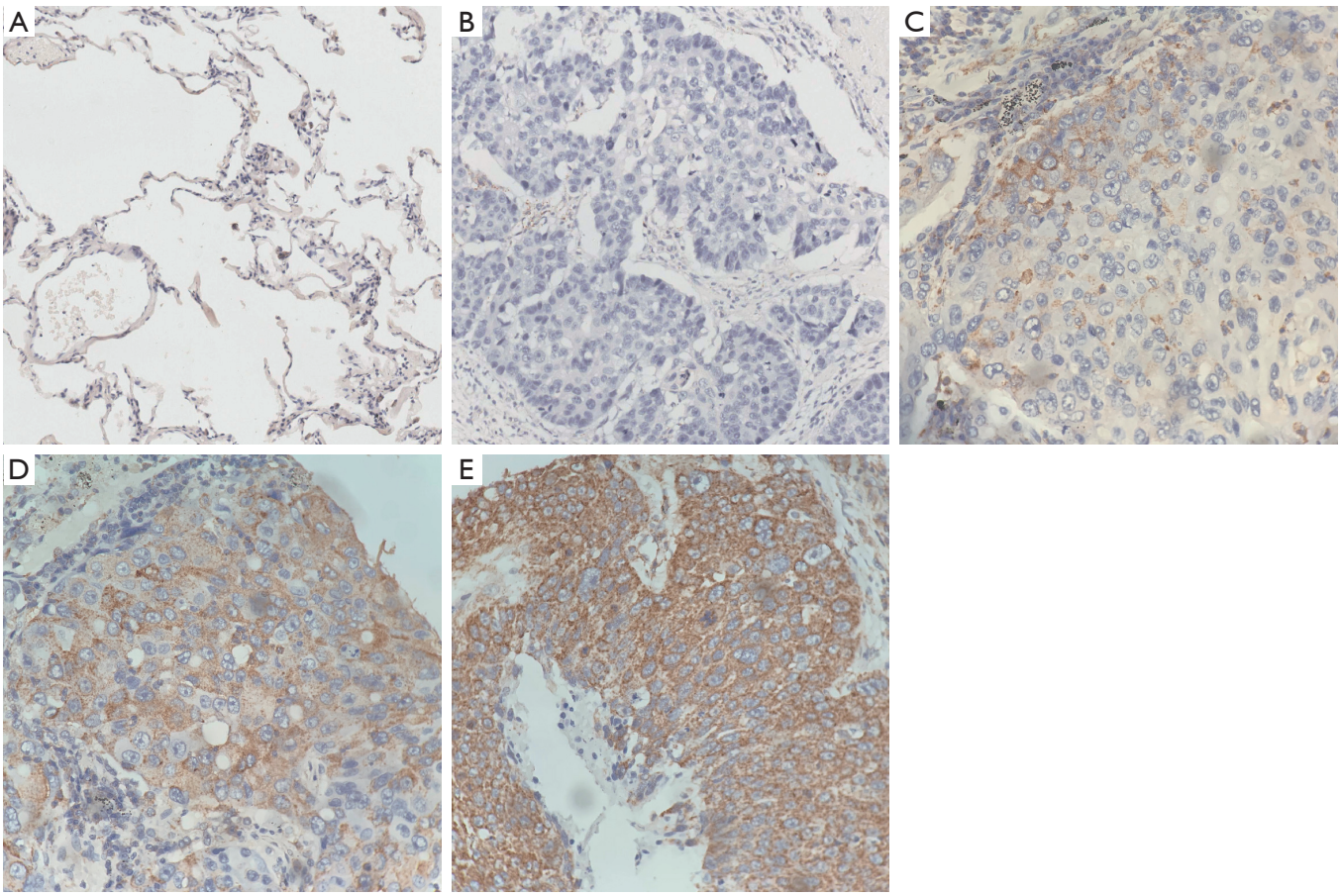

Figure 1 LUSC immunohistochemical staining results (original magnification, 200×, 400×). (A) No p42.3 protein expression in the normal alveolar tissue; (B) p42.3 (–), negative staining; (C) p42.3 (+), weak-positive staining; (D) p42.3 (++), medium expression; (E) p42.3 (+++), strong-positive. LUSC, lung squamous cell carcinoma.

the protein to its original spatial conformation. Goat serum (SP KIT-B2) was used to reduce nonspecific binding. Then, the SAPCD2 polyclonal antibody (PA5-60632) (diluted 1:3,000) was selected as the p42.3 protein antibody, and the TMA was incubated in SAPCD2 overnight at 4 ℃. After incubating with immunochromogenic reagent (Kit-5020) at room temperature for 20 minutes, we added 3,3'-diaminobenzidine (DAB) for 2 minutes. Then hematoxylin redyeing was completed with 1% hydrochloric acid ethanol differentiation, 1% ammonia regain blue, and gradient alcohol dehydration.

Following this, the histopathological evaluations were performed independently by 2 pathologists regardless of the patient's clinical data. The positive expression of p42.3 protein showed brownish yellow granules in the cytoplasm. The positive staining area ≥1% was defined as positive. The qualitative score of immune response was given according to the microscopic staining intensity in the following manner: staining intensity (–) = negative staining, no coloration of tumor cytoplasm; (+) = weak-positive staining, sparse brownish yellow granules observed in the cytoplasm of tumor cells; (++) = medium staining, the staining strength was between weak-positive and strong-positive; (+++) = strong-positive staining, deeply stained brownish yellow granules observed in the cytoplasm of tumor cells (*Figure 1*).

Histological grading method

There is no recognized, specific grading system for most lung cancers (12). The hematoxylin and eosin (HE) staining results were scored according to the tumor cell differentiation degree reference for the current clinical

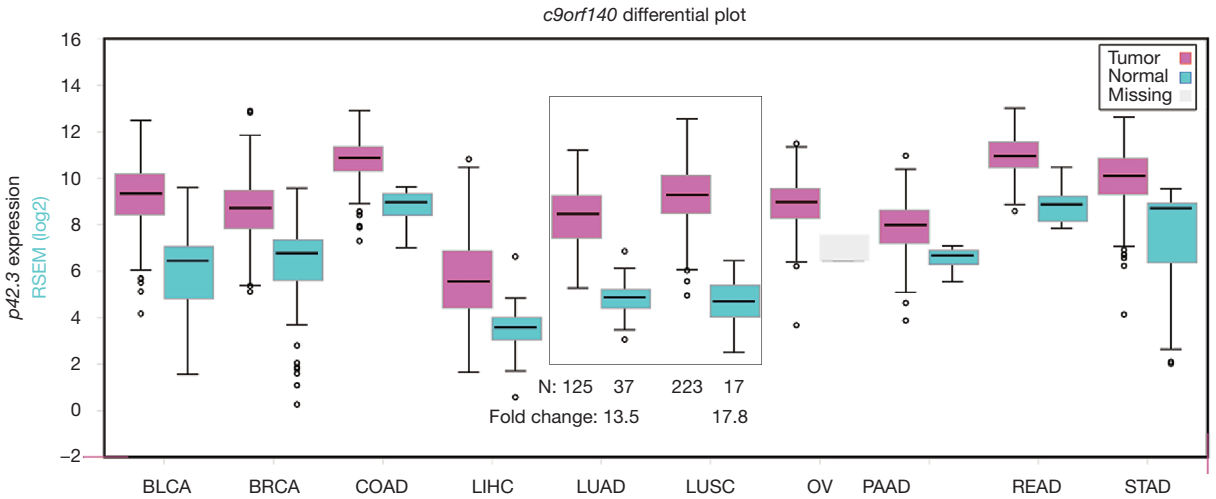

Figure 2 *p42.3* mRNA expression in different types of solid tumors and in corresponding normal tissues. BLCA, bladder urothelial carcinoma; BRCA, breast cancer; COAD, colon adenocarcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; READ, rectum adenocarcinoma; STAD, stomach adenocarcinoma.

general grading method in which a higher level of differentiation indicates that the tumor cells are closer to the normal source tissues. The grading is as follows: high differentiation (grade I), medium differentiation (grade II), and low differentiation (grade III).

Statistical analysis

The statistical analyses were performed using SPSS 22.0 (SPSS, Chicago, IL, USA). Pearson's chi-square (χ^2) test was used to compare the differences in p42.3 protein expressions between the NSCLC tumor tissues and the adjacent normal tissues, and between the LUSC and LUAD tumor tissues. The relationship between age and positive p42.3 protein expression was also evaluated using the χ^2 test. Next, the association between the p42.3 protein expression and the clinicopathological features were evaluated using Fisher's exact test. In all cases, P values <0.05 were considered to be statistically significant.

Results

Part 1: Bioinformatics analysis

p42.3 was significantly upregulated in both LUAD and LUSC compared with the normal lung tissues

We characterized *p42.3* mRNA expression in several types of solid tumors, including LUAD and LUSC, using FireBrowse for data mining. Our results indicated that *p42.3* expression in the LUAD tissues was approximately 13.5-fold higher than in the normal lung tissues. Furthermore, the LUSC tissues were about 17.8-fold higher than the normal lung tissues (*Figure 2*). For further comparisons, the *p42.3* mRNA RNA-sequencing data extracted from TCGA-LUAD and TCGA-LUSC were analyzed. Heatmaps and subsequent comparisons showed that the *p42.3* expression in the LUSC tissues was significantly higher than that in the LUAD tissues (*Figure 3A,B*).

LUSC had a lower level of *p42.3* DNA methylation and a higher level of *p42.3* DNA amplification than LUAD

We explored the potential mechanisms of *p42.3* expression dysregulation and observed that the level of *p42.3* DNA methylation was significantly lower in the LUSC patients than in the LUAD patients after comparing *p42.3* expression and its DNA methylation data (*Figure 4A*). Afterward, we examined copy number alterations (CNAs) from the TCGA-LUAD and TCGA-LUSC data. The *p42.3* mutation was observed in 0.4% of LUAD and 1.1% of LUSC cases (*Figure 4B*). Amplification was the predominant type of mutation, and it was associated with an increase of *p42.3* mRNA expression in LUAD and LUSC (*Figure 4C,D*). In addition, we visualized methylation results in *Figure 4E*.

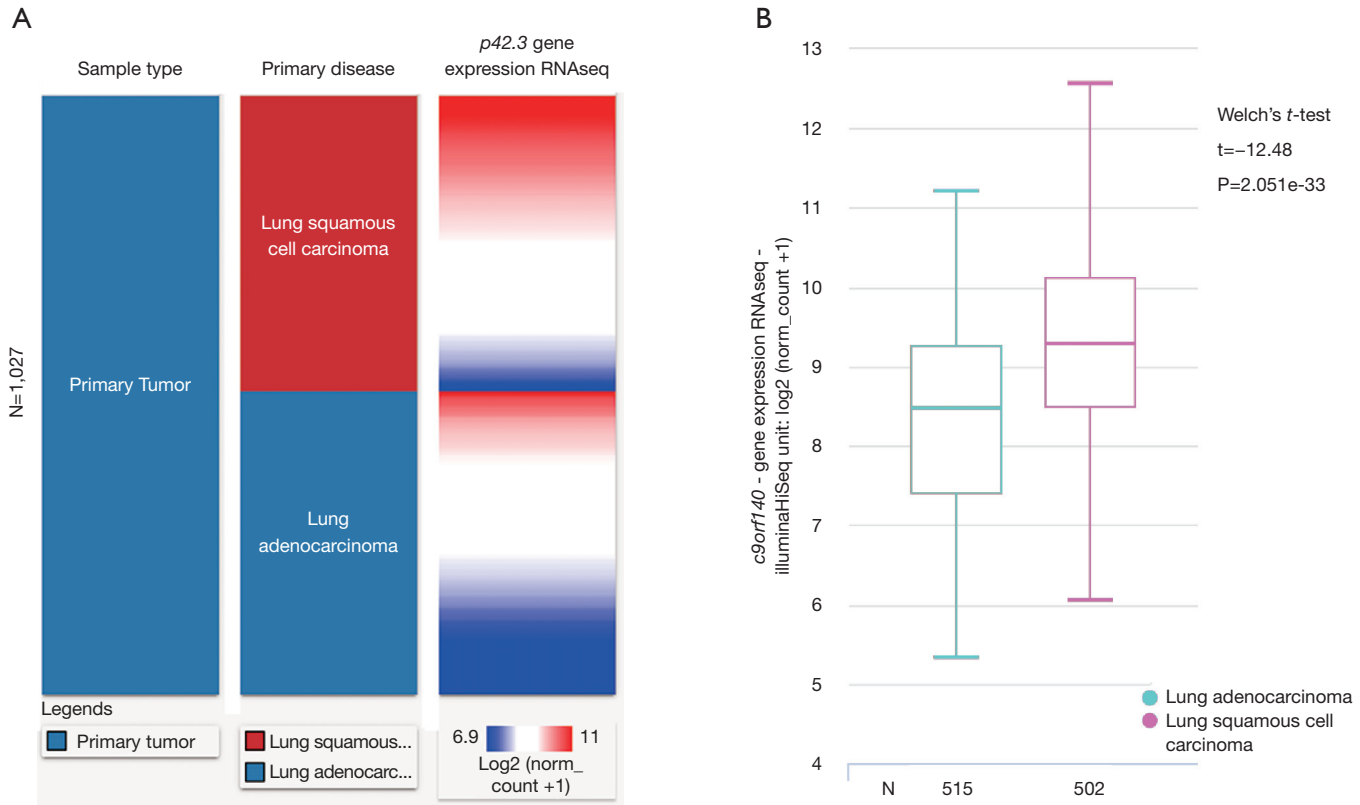

Figure 3 *p42.3* expression in LUSC and in LUAD. (A) A heatmap of *p42.3* mRNA in patients with primary LUSC or LUAD. Data were obtained from the TCGA-LUSC and TCGA-LUAD databases; (B) box plots of the *p42.3* expression in LUSC and in LUAD tissues. The analysis was performed using the UCSC Xena Browser. LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; TCGA-LUSC, The Cancer Genome Atlas data on LUSC; TCGA-LUAD, The Cancer Genome Atlas data on LUAD.

p42.3 DNA mutation was not significantly associated with worse OS in LUAD (lack of survival data in LUSC)

We investigated the associations between *p42.3* DNA mutation and the survival rates in LUAD and LUSC patients. The survival curve failed to indicate that LUAD patients with a *p42.3* amplification were associated with a worse OS rate (*Figure 5*). On the other hand, although *p42.3* amplification was more significant in LUSC patients, there was no relevant survival information in TCGA.

Part 2: Real-world research

p42.3 protein expression in NSCLC tumor tissues was significantly higher than in adjacent normal tissues

A total of 142 NSCLC patients were included in the IHC evaluation (tissue separation from the slides were excluded), which included 72 LUSC and 70 LUAD samples. IHC staining showed that p42.3 protein was mainly expressed in the cytoplasm of NSCLC with variable intensity (*Figure 1*). Furthermore, p42.3 protein expression in NSCLC tumor tissues was significantly higher than that in normal tissues (32/142, 22.5% *vs.* 0/142, 0%; P<0.01) (*Figure 6A*).

p42.3 protein expression in LUSC was significantly higher than LUAD

Then, tumor tissue samples were further divided into the LUSC and LUAD groups according to the pathological classification. According to the results of the Fisher's exact test, the p42.3 protein expression in the LUSC was significantly higher than that in the LUAD group (31/72, 43.1%, *vs.* 1/70, 1.4%; P<0.01) (*Figure 6B*). The clinicopathological features of LUSC patients in the real world were further analyzed to explore the significance of *p42.3* upregulation.

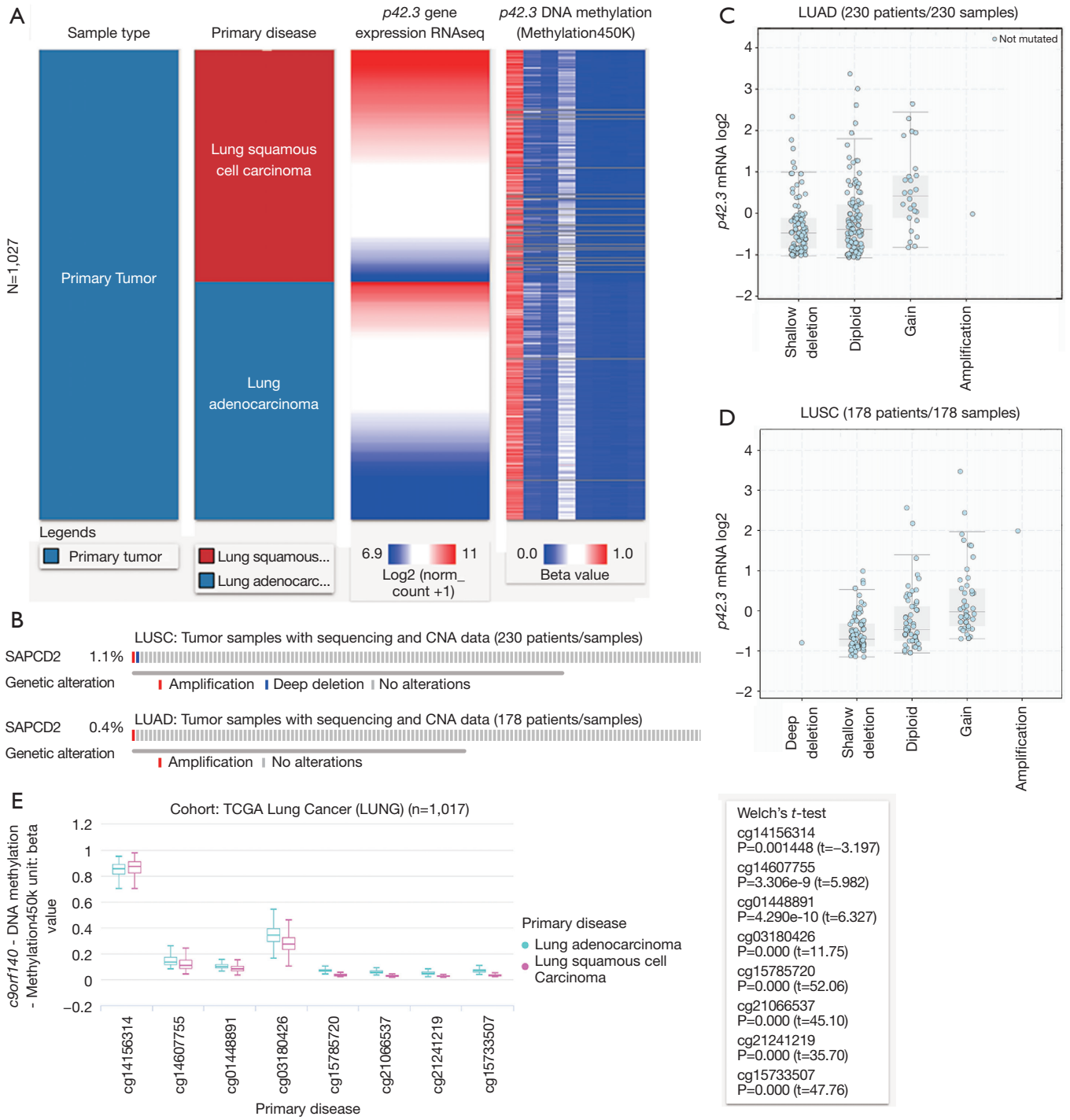

Figure 4 *p42.3* DNA methylation and CNAs in LUSC and LUAD. (A) Heatmap of *p42.3* mRNA expression and DNA methylation in patients with primary LUSC or LUAD; (B) genetic alterations of *p42.3* occurred in 230 cases of LUAD and 178 cases of LUSC; (C,D) box plots of *p42.3* expression in the LUAD (C) and in LUSC (D) tissues indicating genetic status; (E) box plots of *p42.3* DNA methylation in the LUAD and in LUSC tissues. Data were obtained from TCGA-LUSC and TCGA-LUAD databases. The analysis was performed using the UCSC Xena Browser and cBioPortal for Cancer Genomics. CNA, copy number alteration; LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; TCGA-LUSC, The Cancer Genome Atlas data on LUSC; TCGA-LUAD, The Cancer Genome Atlas data on LUAD.

Association of p42.3 protein expression with clinicopathological features in LUSC

The clinical and pathological information of 72 LUSC patients, including 68 males (94.4%, 68/72) and 4 females (5.6%, 4/72), were analyzed. At the time of surgery, the ages of the patients ranged from 31 to 77 (median age 64.4) years old. All tumors stage classifications were conducted according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition (stage I–IV; no carcinoma *in situ*) (*Table 1*). No significant correlation was found between p42.3 protein expression and gender (Fisher, P=0.58). The positive expression rate of p42.3 protein was significantly different between patients younger than 70 years and those 70 years or older (51.9%, 27/52 *vs.* 20%, 4/20; P=0.029). Due to the small sample size of stage IV cases, which might have caused statistical bias, Fisher's exact test was further used to analyze the correlations between clinical stage or histological grade and p42.3 protein expression. No significant difference was found between different clinical stages (P=0.356). However, for the patients with advanced histological grade, the IHC staining was stronger, which indicated that high p42.3 protein expression was correlated with lower differentiation (P=0.043) (*Table 2*).

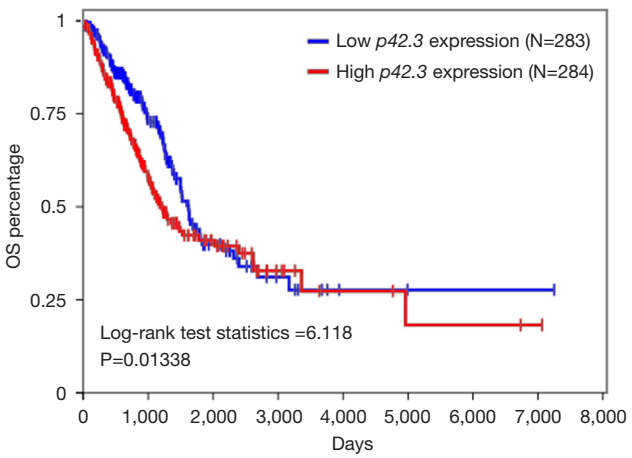

Figure 5 The association between *p42.3* expression and OS in LUAD patients. OS, overall survival; LUAD, lung adenocarcinoma.

Discussion

Based on the current data from TCGA-LUAD and TCGA-LUSC databases, the abnormal expression of *p42.3* in LUAD and LUSC tissues has been observed. Furthermore,

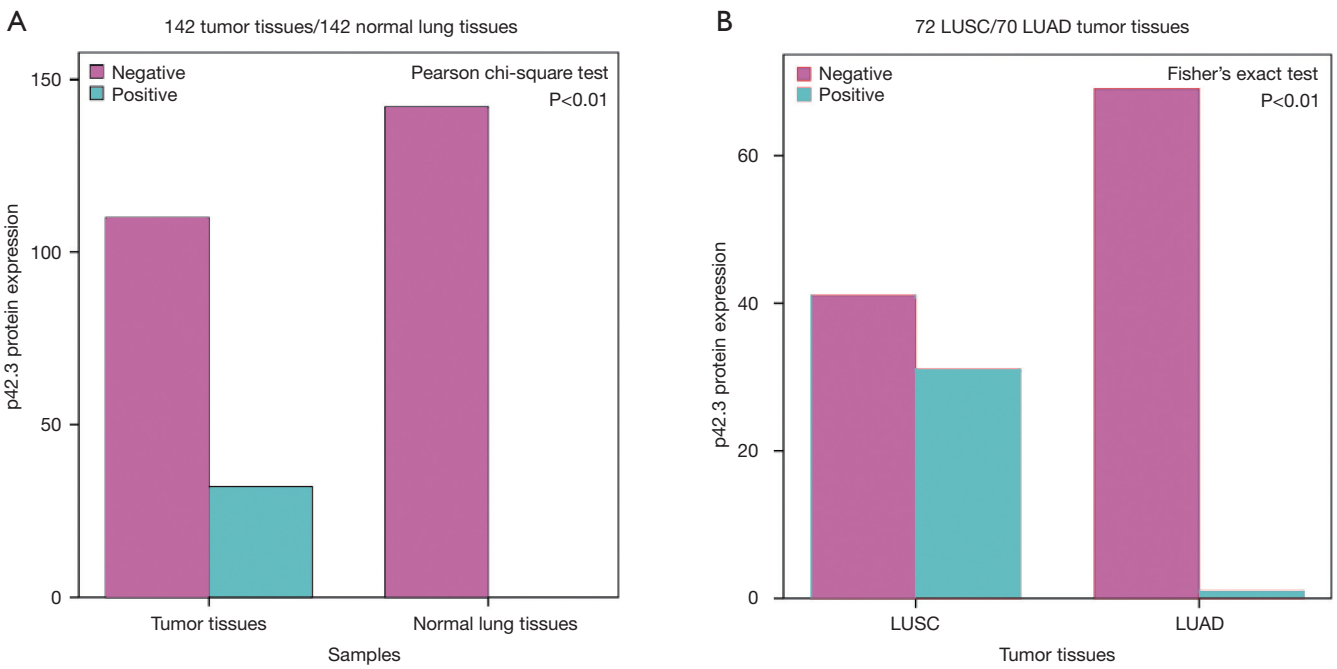

Figure 6 p42.3 protein expression of NSCLC using real-world data. (A) p42.3 protein expression in NSCLC tumor tissue and paired normal adjacent tissues; (B) p42.3 protein expression in LUSC and LUAD tumor tissues. NSCLC, non-small cell lung cancer; LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma.

we found that *p42.3* expression was significantly higher in LUSC than in LUAD. Approximately 1.1% of LUSC cases had *p42.3* amplification, compared with only 0.4% for LUAD. We also observed that some CpG loci of the *p42.3* gene had a higher methylation level in LUAD than in LUSC, which suggests that epigenetic changes are important mechanisms for *p42.3* dysregulation in NSCLC. These findings help to explain why *p42.3* expression is significantly higher in LUSC than in LUAD. Most importantly, we observed that high p42.3 protein expression correlated with worse differentiation, suggesting that *p42.3* may have an important prognostic value in LUSC.

As an oncogene, *p42.3* upregulation is also prognostic in some cancers. In the GC cell line (BGC823), *p42.3* was found to participate in malignant transformations, while the silencing of *p42.3* expression could significantly inhibit the proliferation and oncogenicity of tumor cells (3). Studies on CRC showed that the expression of *p42.3* was an independent prognostic factor in CRC patients (P=0.030). Patients with high expression of *p42.3* had a poor prognosis (P=0.033) (7). Furthermore, high *p42.3* expression in patients with primary hepatocellular carcinoma (HCC) was significantly correlated with worse differentiation (P=0.031) (13). Besides, high expression of *p42.3* was correlated with the clinical stage of melanoma patients (P=0.045) (6) and high histological grade of glioma (P<0.01) (8).

In regards to the driving mechanisms of *p42.3* expression in tumorigenesis, recent studies have shown that the *p42.3* gene might be a regulatory factor involved in the signaling pathways. It was found that in GC cell lines, p42.3 protein expression was negatively correlated with the expression of microRNA-29a (miR-29a), which directly targeted *p42.3* 3'UTR, while the knockout of the *p42.3* gene could inhibit tumor cell proliferation and induce cell cycle arrest (14). Meanwhile, miR-29a was shown to significantly inhibit the proliferation and invasion of the GC cell lines, while the expression of miR-29a in human GC lines was significantly downregulated (15).

These findings are consistent with the observations for GC, HCC, and other tumor cell lines: the silencing of the *p42.3* gene leads to a down-regulation of the cell cycle regulatory protein cyclinB1 and an up-regulation of CHK2, inducing changes in the biological processes of proliferation, invasiveness, and malignant transformation (3,13,16). The decreased expression rate of p42.3 protein in LUSC patients aged 70 years or older is consistent with the decreased metabolic rates in elderly patients. Therefore, it is speculated that the p42.3 protein may be a significant

Table 1 Correlation between p42.3 protein expression and clinicopathological features in LUSC (N=72)

Characteristics	N	p42.3		P
		+ (%)	– (%)	
Gender				0.580
Male	68	29 (42.6)	39 (57.4)	
Female	4	2 (50.0)	2 (50.0)	
Age				0.029
<70	52	27 (51.9)	25 (48.1)	
≥70	20	4 (20.0)	16 (80.0)	
Clinical stage (AJCC 8)				0.356
I	18	9 (50.0)	9 (50.0)	
II	28	14 (50.0)	14 (50.0)	
III	24	7 (29.2)	17 (70.8)	
IV	2	1 (50.0)	1 (50.0)	

LUSC, lung squamous cell carcinoma; AJCC 8, the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition.

Table 2 Correlation between p42.3 protein expression and histological grade

	N	Staining intensity				P
		– (%)	+ (%)	++ (%)	+++ (%)	
Histological grade						0.043
I	10	8 (80.0)	2 (20.0)	0 (0.0)	0 (0.0)	
II	44	28 (63.6)	9 (20.5)	6 (13.6)	1 (2.3)	
III	18	5 (27.8)	10 (55.6)	2 (11.1)	1 (5.6)	
Total	72	41 (56.9)	21 (29.2)	8 (11.1)	2 (2.8)	

regulatory factor involved in this signaling pathway. It is of great significance to further study the role of *p42.3* in NSCLC.

In conclusion, the present study confirmed that both genetic and epigenetic alterations contribute to the dysregulation of *p42.3* in NSCLC. The high expression of p42.3 protein was an independent factor of a worse pathological differentiation in LUSC. Therefore, there exists a potential for *p42.3* to be developed as a cost-effective biomarker of LUSC prognosis.

To further explore the biological functions, prognostic value, and potential mechanisms of *p42.3* in NSCLC, prospective studies with expanded sample sizes should be conducted. Meanwhile, findings from cell transfection, and cell proliferation, scratch wound healing, and migration and invasion assays will continue to be reported.

Acknowledgments

We would like to thank the State Key Laboratory of Molecular Oncology, Department of Etiology and Carcinogenesis, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College for providing the laboratory.

Funding: This work was supported by the CAMS Innovation Fund for Medical Sciences (2018-I2M-1-002) and Beijing Hospital Research Fund for Clinical medicine (BJ-2018-016).

Footnote

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-2928

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-2928). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Informed consent is not required. This study is a retrospective observational study. Only paraffin specimens from tumor tissues of patients with NSCLC that were previously preserved by the subjects were collected for the study. No intervention measures were taken for the subjects. The collection of information and the publication of research results do not contain unique information that can identify the subject. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Review Committee of Beijing Hospital (No. 2020BJYYEC-111-01). Individual consent for this retrospective analysis was waived.

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Cite this article as: Zhang X, Nie X, Long J, Yu J, Zhang P, Liu Y, Wu X, Bai Y, Mao J, Liu X, Yuan Y, Zhao H, Li L. Expression of *p42.3* in non-small cell lung cancer. Ann Transl Med 2020;8(13):819. doi: 10.21037/atm-20-2928

