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ORIGINAL ARTICLE

The expression of eukaryotic translation initiation factor 3B and its correlation with tumor characteristics as well as prognosis in non-small cell lung cancer patients: a retrospective study

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Summary

Purpose: *This study aimed to compare eukaryotic translation initiation factor 3B (EIF3B) expression between tumor tissues and non-cancerous tissues and to investigate the correlation of tumor EIF3B with clinical characteristics and prognosis in non-small cell lung cancer (NSCLC) patients.*

Methods: *The tumor samples and non-cancerous adjacent tissues of 365 operated NSCLC patients were acquired. The EIF3B expression in tumor tissues and non-cancerous tissues was detected by immunohistochemistry and was classified into four groups according to multiple staining intensity and staining density as follows; low EIF3B, high(+)EIF3B, high(++) EIF3B, and high(+++) EIF3B. The clinical characteristics were extracted from the database. The disease-free survival (DFS) and overall survival (OS) was calculated from the survival data.*

Results: *EIF3B was increased in tumor tissues (10.1% in high(+++) EIF3B, 17.5% in high(++) EIF3B, 29.9% in high(+) EIF3B, and 42.5% in low EIF3B group) compared to non-cancer tissues (2.2% in high(+++) EIF3B, 9.6% in high(++) EIF3B, 23.3% in high(+) EIF3B, and 64.9% in low EIF3B group) (p<0.001). Correlation analysis showed that tumor with higher EIF3B expression was correlated with the presence of lymph node metastasis (p=0.001) and more advanced TNM stage (p=0.026). Kaplan-Meier curves revealed that DFS and OS were worst in patients with high (+++) EIF3B expression (p<0.001). Notably, multivariate Cox's regression showed that a higher EIF3B expression was an independent predictive of decreased DFS (p=0.041) and OS (p=0.006).*

Conclusion: *EIF3B might be a potential biomarker to improve the monitoring and management of NSCLC in clinical practice.*

Key words: *eukaryotic translation initiation factor 3B; non-small cell lung cancer; tumor characteristics; disease-free survival; overall survival*

Introduction

Lung cancer (LC) is one of the most prevalent cancers worldwide, with about 2 million newly-diagnosed lung cancer patients in 2018 [1]. Moreover, it ranks first in all causes of cancer-related deaths and accounts for approximately 18.4% of cancer-related deaths globally [2]. Non-small cell lung cancer (NSCLC) is the major (85%) subtype of LC, with relatively less aggressive clinical features [3]. Although the treatment modalities of NSCLC patients (including surgery, radical radiotherapy, chemotherapy, and targeted therapies) have been greatly developed in recent years, the prognosis remains poor, with the 5-year survival rate being 15% [4,5]. Therefore, searching novel prognostic biomarkers for a better management of NSCLC patients is needed.

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Eukaryotic translation initiation factor 3B (EIF3B), a member of the EIF3 family, is a key regulator of the initiation of protein translation [6]. Previous studies have indicated that EIF3B overexpression enhances cell proliferation and suppresses apoptosis in gastric cancer cells, glioblastoma cells, and colon cancer cells [7-9]. High EIF3B expression is correlated with more advanced tumor stage and worse prognosis in gastric cancer, cervical cancer, and prostate cancer [7,10,11]. For NSCLC, the inhibition of EIF3B suppresses cell proliferation and promotes apoptosis [12]. Moreover, in our preliminary and small-scale research we found that EIF3B was overexpressed in tumor tissues compared to adjacent tissues of NSCLC patients. Therefore, we hypothesized that EIF3B might be an indicator of worse tumor characteristics and prognosis in NSCLC patients. However, the relevant clinical significance of EIF3B in NSCLC is still unclear. In this study, we enrolled 365 NSCLC patients to detect the expression of EIF3B in tumor tissues and non-cancer tissues and to explore the correlation of tumor EIF3B with tumor characteristics as well as NSCLC prognosis.

Methods

Patients

This is a retrospective study focusing on NSCLC patients who underwent resection in our hospital. A total of 365 eligible NSCLC patients were screened from database between January 2015 and December 2019. The main inclusion criteria were: (1) histologically confirmed primary NSCLC; (2) age ranging from 18 to 80 years; (3) TNM stage I-IIIA; (4) tumor tissues and adjacent non-cancer tissues excised from surgery were well-preserved; (5) the records of tumor features before resection were complete; (6) adequate follow-up data to calculate disease-free survival (DFS) and overall survival (OS). The main exclusion criteria were: (1) relapse or secondary NSCLC; (2) history of other malignancies; (3) poorly-controlled hepato-renal disorders; (4) severe abnormalities in hematological indexes.

This study was approved by the Ethics Committee of our hospital. All patients or their family members provided the written-informed consents.

Immunohistochemistry (IHC)

Formalin-fixed and paraffin-embedded tumor tissues and adjacent non-cancer tissues were cut into 4 μm sections and used for IHC assay after acquiring agreement from the Pathology Department. A primary antibody Rabbit monoclonal to EIF3B (1:100, Abcam, Cambridge, MA, USA) and a secondary antibody Goat Anti-Rabbit IgG H&L (HRP) (1:5000, Abcam, Cambridge, MA, USA) were used in IHC assay; and the procedures were conducted according to application manuals of the antibodies. The EIF3B expression was assessed by multiplying the staining intensity and staining density as previously described [13]. Briefly, the staining intensity was scored as 0 (no staining); 1 (weak staining); 2 (moderate staining) and 3 (strong staining). The staining density was evaluated based on the percentage of positively-stained cells as follows: no cells staining positive was scored as 0; 1%-25% of cells staining positive was scored as 1; 26%-50% of cells staining positive was scored as 2; 51%-75% of cells staining positive was scored as 3, and 76%-100% of cells staining positive was scored as 4. The total IHC score was ranging from 0 to 12. High EIF3B expression was defined as total IHC score>3 and low EIF3B expression was defined as the total IHC score≤3. The high EIF3B expression was further divided into groups as follows: high(+) EIF3B (IHC score 4-6), high(++) EIF3B (IHC score 7-9), and high(+++) EIF3B (IHC score 10-12)[13].

Data collection and follow-up

The demographics and major preoperative tumor features were extracted from the database of our hospital. The disease relapse, disease progression, and survival status were obtained from survival data. The last follow-up date was December 31, 2019 and the median follow-up duration was 30.0 months. DFS was defined as the duration from surgery to disease relapse, disease progression, or death and OS was defined as the duration from surgery to death.

Statistics

All statistical analyses were performed using SPSS version 22.0 (IBM, Chicago, IL, USA) and all figures were plotted using GraphPad Prism version 7.00 (GraphPad Software, La Jolla, CA, USA). Comparison of EIF3B expression between tumor tissues and non-cancer tissues was determined by McNemar test or McNemar-Bowker test. Comparison of clinical features between patients with high and low EIF3B expression was determined by x^2 test or Wilcoxon rank-sum test. DFS and OS were analyzed using the Kaplan-Meier method. Comparison of DFS and OS between groups was determined by Log-rank test. Factors predicting DFS and OS were analyzed by univariate Cox's proportional hazard regression model and factors with $p<0.05$ in the univariate Cox's regression were included in the forward stepwise multivariate Cox's regression analysis. P value <0.05 was considered significant.

Results

Clinical characteristics of NSCLC patients

The mean age of NSCLC patients (n=365) was 61.6±10.0 years There were 298 males. For grade of tumor differentiation, 67 (18.4%) patients had well-differentiated, 213 (58.4%) had moderately-differentiated, and 85 (23.3%) had poorly-differentiated tumors. For tumor size, the mean tumor size was 5.3±2.1 cm; tumor size was greater than or equal to 5 cm in 213 (58.4%) patients. For lymph node (LN) metastasis, 244 (66.8%) had no LN metastasis, while 121 (33.2%) presented with LN metastasis.

For TNM stage, there were 115 (31.5%) patients with TNM stage I, 133 (36.4%) with TNM stage II, and 117 (32.1%) with TNM stage III. For CEA, the median CEA level was 5.9 (2.7-26.9) ng/mL; 170 (46.6%) patients had normal CEA level, while 195 (53.4%) presented with abnormal CEA level. The detailed clinical characteristics of NSCLC patients were listed in Table 1.

EIF3B expression in NSCLC patients

The examples of EIF3B expression detected by IHC in tumor tissue and non-cancer adjacent tissue from NSCLC patients are shown in Figure 1A. In tumor tissues, high EIF3B expression was detected in 210 (57.5%) cases and low EIF3B expression in 155 (42.5%) cases. In non-cancer tissues, high EIF3B expression was detected in 128 (35.1%) cases and low EIF3B expression was detected in 237 (64.9%) cases. Subsequent analysis showed that EIF3B was increased in tumor tissues compared to non-cancer tissues ($p<0.001$) (Figure 1B). Moreover, further classification in tumor tissues showed that high +++ EIF3B was detected in 37 (10.1%) cases; high ++ EIF3B was detected in 64 (17.5%) cases; high + EIF3B was detected in 109 (29.9%) cases; low EIF3B expression was detected in 155 (42.5%) cases. In non-cancer tissues, high +++ EIF3B was detected in 8 (2.2%) cases; high ++ EIF3B was detected in 35 (9.6%) cases; high(+) EIF3B was detected in 85 (23.3 %) cases; low EIF3B expression was detected in 237 (64.9%) cases. Subsequent analysis showed that EIF3B was higher in tumor tissues compared to non-cancer tissues ($p<0.001$) (Figure 1C).

Table 1. Features of NSCLC patients

Features	*NSCLC patients (N=365) n (%)*
Demographic features	
Age (years), mean±SD	61.6±10.0
Gender (male/female), No.	298/67
Smoking history	202 (55.3)
Alcohol consumption	145 (39.7)
Common chronic complications	
Hypertension	132 (36.2)
Hyperlipidemia	116 (31.8)
Diabetes	58 (15.9)
Tumor features	
Differentiation	
Well	67 (18.4)
Moderate	213 (58.4)
Poor	85 (23.3)
Tumor size (cm), mean±SD	5.3±2.1
≤5	213 (58.4)
>5	152 (41.6)
LN metastasis	
Absent	244 (66.8)
Present	121 (33.2)
TNM stage	
I	115 (31.5)
II	133 (36.4)
III	117 (32.1)
CEA (ng/mL), median (IQR)	5.9 (2.7-26.9)
Normal*	170 (46.6)
Abnormal*	195 (53.4)

NSCLC: non-small cell lung cancer; SD: standard deviation; LN: Lymph node; CEA: carcinoembryonic antigen; IQR: interquartile range. * CEA abnormal level >5.0 ng/mL, CEA normal level ≤5.0 ng/mL

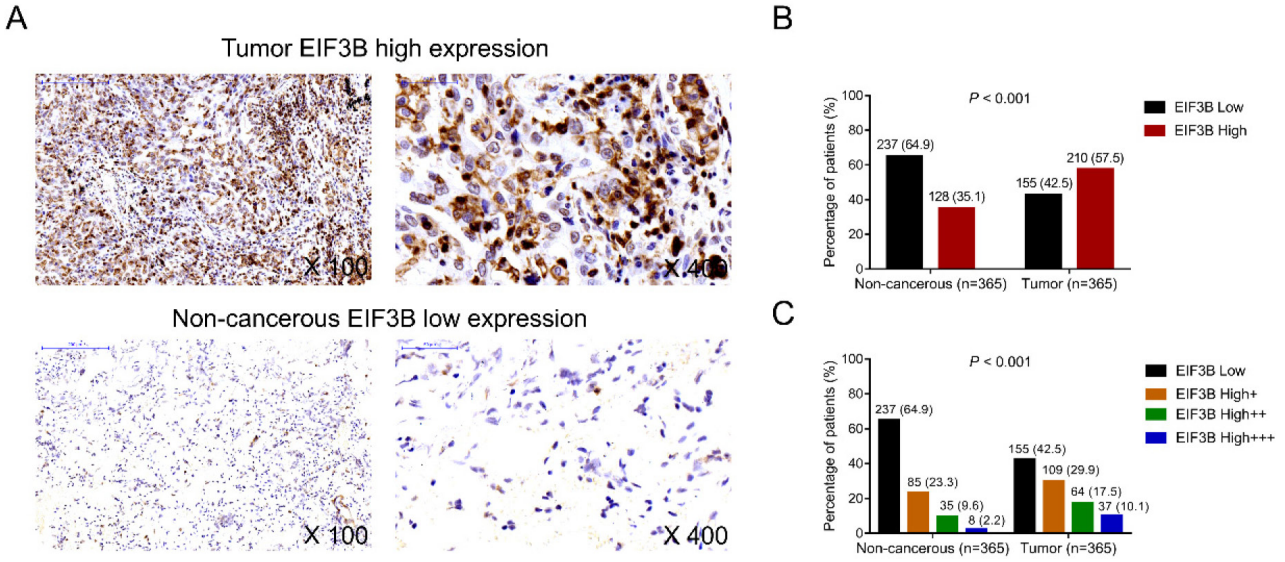

Figure 1. EIF3B expression. **A:** IHC samples of EIF3B in tumor tissue and non-cancer adjacent tissue of NSCLC patients. **B:** Comparison of EIF3B in tumor tissues and non-cancerous adjacent tissues of NSCLC patients. **C:** Further classification of EIF3B expression in tumor tissues and non-cancerous adjacent tissues of NSCLC patients. EIF3B: eukaryotic translation initiation factor 3B; IHC: immunohistochemistry; NSCLC: non-small cell lung cancer.

Correlation of tumor EIF3B with clinical characteristics of NSCLC patients

For demographic features and common chronic complications, no correlation was found in tumor EIF3B with age (p=0.663), gender (p=0.486), smoking (p=0.369), alcohol consumption (p=0.155), hypertension (p=0.182), hyperlipidemia (p=0.774), or diabetes (p=0.446) (Table 2). For tumor characteristics, tumor EIF3B was positively correlated with LN metastasis (p=0.001) (Figure 2C) and TNM stage (p=0.026) (Figure 2D), while no correlation was found in tumor EIF3B with grade of tumor differentiation (p=0.205) (Figure 2A), tumor size (p=0.160) (Figure 2B), or CEA level (p=0.097) (Figure 2E).

Table 2. Correlation of tumor EIF3B expression with demographic features and common chronic complications

Features	*EIF3B expression*		*p value*
	Low (n=155) n (%)	*High (n=210) n (%)*	
Age, years			0.663
≤65	88 (56.8)	124 (59.0)	
>65	67 (43.2)	86 (41.0)	
Gender			0.486
Female	31 (20.0)	36 (17.1)	
Male	124 (80.0)	174 (82.9)	
Smoking history			0.369
No	65 (41.9)	98 (46.7)	
Yes	90 (58.1)	112 (53.3)	
Alcohol consumption			0.155
No	100 (64.5)	120 (57.1)	
Yes	55 (35.5)	90 (42.9)	
Hypertension			0.182
No	105 (67.7)	128 (61.0)	
Yes	50 (32.3)	82 (39.0)	
Hyperlipidemia			0.774
No	107 (69.0)	142 (67.6)	
Yes	48 (31.0)	68 (32.4)	
Diabetes			0.446
No	133 (85.8)	174 (82.9)	
Yes	22 (14.2)	210 (17.1)	

Comparison was determined by x^2 test

Correlation of tumor EIF3B with DFS and OS of NSCLC patients

DFS was decreased in patients with high tumor EIF3B expression compared to patients with low EIF3B expression (p=0.003) (Figure 3A). Moreover, subgroup analysis showed DFS was shortest in patients with high +++ tumor EIF3B expression, followed by patients with high ++ tumor EIF3B expression, patients with high + tumor EIF3B expression, whereas DFS was longest in patients with low tumor EIF3B expression (p<0.001) (Figure 3B). For OS, it was decreased in patients with high EIF3B expression compared to patients with low EIF3B expression (p<0.001) (Figure 4A). Additionally, subgroup analysis revealed that OS was shortest in patients with high +++ tumor EIF3B expression, followed by patients with high ++ tumor EIF3B expression, patients with high + tumor EIF3B expression, while OS was longest in patients with low EIF3B expression (p<0.001) (Figure 4B).

Factors affecting DFS and OS of NSCLC patients

For DFS, univariate Cox's regression showed that higher EIF3B expression (p=0.003, HR=1.509), poorer tumor differentiation (p=0.012, HR=1.461),

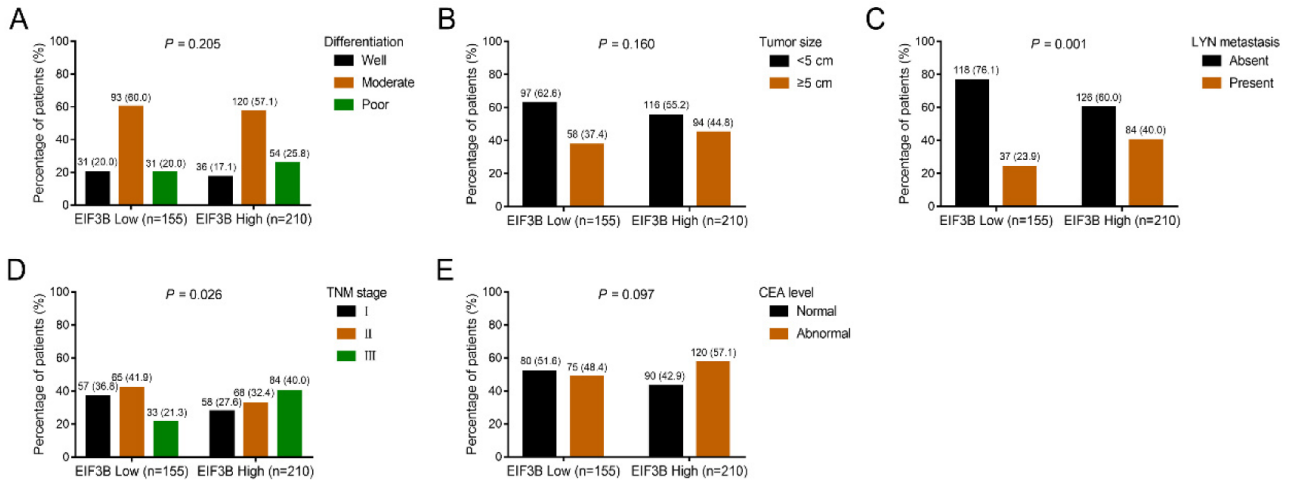

Figure 2. Association of tumor EIF3B with tumor properties. Correlation of tumor EIF3B with differentiation **(A)** tumor size **(B)** LN metastasis **(C)** TNM stage **(D)** and CEA level **(E)**. EIF3B: eukaryotic translation initiation factor 3B; LN: lymph node; CEA: carcinoembryonic antigen.

larger tumor size (>5 cm) (p=0.016, HR=1.371), LN metastasis (p<0.001, HR=2.257), more advanced TNM stage (III vs. II/I) (p<0.001, HR=2.105), and increased CEA (p=0.002, HR=1.509) were associated with decreased DFS in NSCLC patients. Furthermore, multivariate Cox regression analysis showed that higher EIF3B expression (p=0.041, HR=1.324), LN metastasis (p<0.001, HR=1.852), increased TNM stage (IIIvs.II/I) (p=0.008, HR=1.503), and elevated CEA (p=0.001, HR=1.546) were independent predictive factors for decreased DFS in NSCLC patients (Table 3).

For OS, univariate Cox regression analysis showed higher EIF3B expression (p<0.001, HR=1.776), poorer tumor differentiation (p=0.005, HR=1.586), larger tumor size (>5 cm) (p=0.013, HR=1.457), LN metastasis (p<0.001, HR=2.871), higher TNM stage (III vs. II/I) (p<0.001, HR=1.883), and increased CEA (p=0.001, HR=1.647) were associated with decreased DFS in NSCLC patients. Moreover, multivariate Cox regression analysis indicated that higher EIF3B expression (p=0.006, HR=1.565), poorer tumor differentiation (p=0.014, HR=1.502), LN metastasis (p<0.001, HR=2.842), and increased CEA (p=0.002, HR=1.635) were independent predictive factors for decreased OS in NSCLC patients (Table 4).

Discussion

EIF3B is reported to be a tumor promoter in several cancers [6]. For example, in esophageal squamous cell carcinoma cells, EIF3B increases cell proliferation and migration, suppressing apoptosis by activating the protein kinase B (Akt) pathway [14]. In ovarian cancer cells, knockdown of EIF3B by small interfering RNA promotes apoptosis, thus inhibits cell proliferation [15]. In gastric cancer cells, EIF3B enhances cell migration and invasion *via* activating epithelial-mesenchymal transition

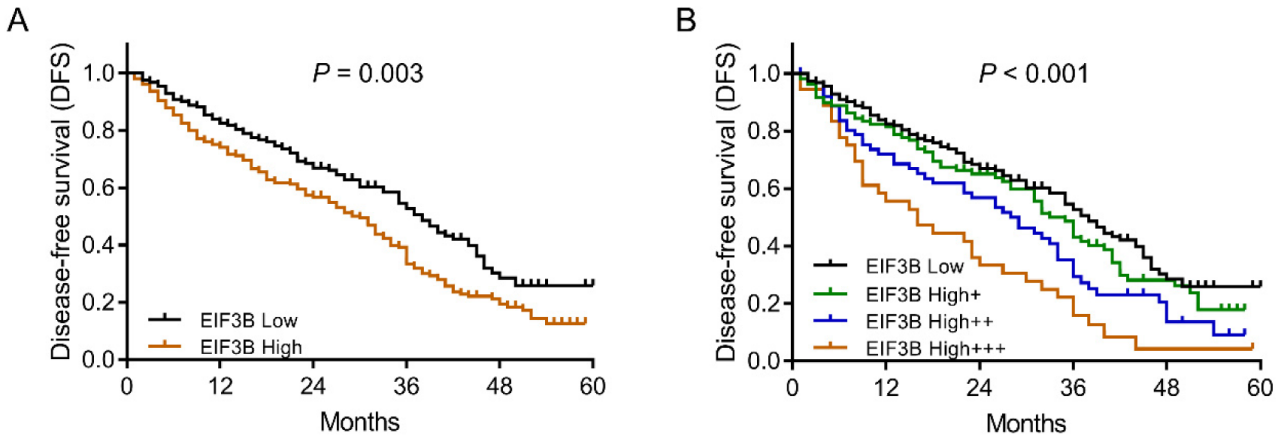

Figure 3. Association of tumor EIF3B with DFS. **A:** Comparison of DFS between patients with high tumor EIF3B expression and patients with low tumor EIF3B expression. **B:** Correlation of tumor EIF3B with DFS by further classification. EIF3B: eukaryotic translation initiation factor 3B; DFS: disease-free survival.

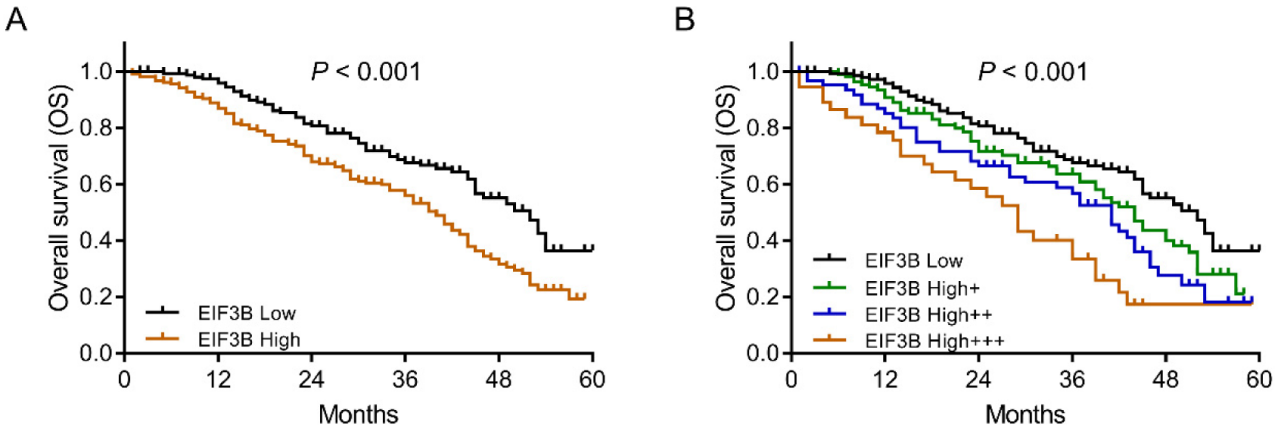

Figure 4. Association of tumor EIF3B with OS. **A:** Comparison of OS between patients with high tumor EIF3B expression and patients with low tumor EIF3B expression. **B:** Correlation of tumor EIF3B with OS by further classification. EIF3B: eukaryotic translation initiation factor 3B; OS: overall survival.

Table 3. Cox proportional hazard regression model analyses of factors affecting DFS

Features	*Cox's proportional hazard regression model*			
	p value	*HR*	*95%CI*	
			Lower	*Higher*
Univariate Cox regression				
EIF3B high	0.003	1.509	1.154	1.972
Age (>65 years)	0.081	0.792	0.609	1.029
Male	0.232	0.820	0.592	1.135
Smoking history	0.918	1.014	0.783	1.312
Alcohol consumption	0.517	1.090	0.840	1.416
Hypertension	0.382	0.886	0.677	1.161
Hyperlipidemia	0.320	1.150	0.873	1.514
Diabetes	0.233	0.801	0.557	1.153
Differentiation (poor vs. moderate/well)	0.012	1.461	1.089	1.961
Tumor size (>5 cm)	0.016	1.371	1.060	1.773
LN metastasis	<0.001	2.257	1.738	2.932
TNM stage (III vs. II/I)	<0.001	2.105	1.619	2.736
CEA abnormal*	0.002	1.509	1.159	1.963
Forward stepwise multivariate Cox regression*				
EIF3B high	0.041	1.324	1.011	1.735
LN metastasis	<0.001	1.852	1.370	2.503
TNM stage (III vs. II/I)	0.008	1.503	1.110	2.035
CEA abnormal*	0.001	1.546	1.187	2.015

*Only factors with p<0.05 in the univariate Cox regression were included in the forward stepwise multivariate Cox regression analysis. DFS: disease-free survival; HR: hazard ratio; CI: confidence interval; LN: lymph node; CEA: carcinoembryonic antigen. *CEA: abnormal level >5.0 ng/mL, CEA normal level ≤5.0 ng/mL

Table 4. Cox proportional hazard regression model analyses of factors affecting OS

Factors	*Cox proportional hazard regression model*			
	p value	*HR*	*95%CI*	
			Lower	*Higher*
Univariate Cox regression				
EIF3B high	<0.001	1.776	1.291	2.444
Age (>65 years)	0.243	0.836	0.618	1.130
Male	0.683	0.922	0.626	1.360
Smoking history	0.703	0.944	0.702	1.270
Alcohol consumption	0.278	1.179	0.875	1.589
Hypertension	0.358	0.864	0.632	1.180
Hyperlipidemia	0.207	1.224	0.894	1.674
Diabetes	0.192	0.757	0.499	1.150
Differentiation (Poor vs. moderate/well)	0.005	1.586	1.149	2.190
Tumor size (>5 cm)	0.013	1.457	1.083	1.960
LN metastasis	<0.001	2.871	2.129	3.872
TNM stage (III vs. II/I)	<0.001	1.883	1.390	2.551
CEA abnormal*	0.001	1.647	1.212	2.239
*Forward stepwise multivariate Cox regression**				
EIF3B high	0.006	1.565	1.136	2.155
Differentiation (Poor vs. moderate/well)	0.014	1.502	1.087	2.078
LN metastasis	<0.001	2.842	2.103	3.840
CEA abnormal*	0.002	1.635	1.199	2.231

*Only factors with p<0.05 in the univariate Cox regression were included in the forward stepwise multivariate Cox regression analysis. OS: overall survival; HR: hazard ratio; CI: confidence interval; LN: lymph node; CEA: carcinoembryonic antigen. *CEA abnormal level >5.0 ng/mL, CEA normal level ≤5.0 ng/mL

as well as signal transducer and activator of transcription 3 (STAT3). Further an *in vivo* study reveals that knockdown of EIF3B suppresses tumor growth and lung metastasis by activating phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway [7]. In NSCLC cells, EIF3B is overexpressed compared to normal cells; its overexpression promotes cell proliferation and inhibits apoptosis [12]. Therefore, these previous studies indicate that EIF3B is a tumor promoter that increases the proliferation, migration, and invasion in several solid tumors including NSCLC.

The clinical function of EIF3B in cancer has been reported in previous studies. For example, in cervical cancer patients, EIF3B is increased in tumor tissues compared to paired adjacent tissue and is associated with increased stage and LN metastasis [10]. In gastric cancer patients, EIF3B is enhanced in gastric cancer tissues and is positively correlated with the depth of tumor invasion, LN metastasis, and TNM stage [7]. However, information on the clinical role of EIF3B in NSCLC is quite limited. Only one previous study reveals that EIF3B is overexpressed in tumor tissues of NSCLC patients; however, it has several limitations such as its relatively small sample size and single-center sample resource [12]. In line with that previous study, we also found that EIF3B was increased in tumor tissues compared with non-cancer adjacent tissues, implying that EIF3B might be an onco-protein in NSCLC. Moreover, we investigated the correlation of tumor EIF3B with tumor characteristics. The data revealed that tumor EIF3B was associated with presence of LN metastasis and higher TNM stage. Possible explanations for our data might be due to the following factors: (1) EIF3B overexpression might promote malignant proliferation of lung fibroblasts as in NIH3T3 cells according to a previous study [11], which might promote tumorigenesis in NSCLC patients. (2) Tumor is characterized by high level of malignant proliferation and high EIF3B expression might promote malignant proliferation [11]; therefore, EIF3B was increased in tumor tissues compared to non-cancer tissues. (3) EIF3B might activate epithelial-mesenchymal transition and STAT3 pathway to promote migration and invasion in NSCLC cells as in gastric cancer cells reported by a previous study [7]; therefore, it was positively correlated with LN metastasis as well as TNM stage in NSCLC patients.

Regarding the correlation of EIF3B with the prognosis of cancer patients, a previous study revealed that EIF3B is correlated with worse DFS and OS in cervical cancer patients [10], whereas little relevant information is found in NSCLC. In the present study, DFS and OS were decreased in patients with high tumor EIF3B expression compared to patients with low tumor EIF3B expression. Meanwhile, we found that the higher the tumor EIF3B expression, the worse the DFS and OS. Moreover, high EIF3B expression was an independent predictive factor for inferior DFS and OS. Possible explanations might be due to the following factors: (1) Tumor EIF3B was correlated with the presence of LN metastasis and increased TNM stage (above-mentioned), which resulted in a worse NSCLC prognosis (2). Increased EIF3B might enhance the transcription level of m^6A modified-yes-associated protein (YAP) to induce drug resistance in NSCLC cells [16], which resulted in a worse therapeutic efficacy and deteriorated prognosis of NSCLC patients.

There were several limitations in this study. Firstly, the follow-up duration of this study was relatively short (30 months of median follow-up) and the long-term effect of tumor EIF3B on the prognosis of NSCLC patients was unclear. Secondly, metastatic or recurrent NSCLC patients were excluded from this study, which might cause selection bias and the conclusion of this study was not applicable to these patients. Finally, the molecular mechanisms of EIF3B in the regulation of survival and mobility of NSCLC cells were not investigated in this study. Therefore, further studies should be conducted to verify our results.

To conclude, EIF3B is upregulated in the tumor tissues compared to non-cancer tissues and tumor high EIF3B correlates with LN metastasis , increased TNM stage, and unfavorable prognosis in NSCLC patients, implying EIF3B is a potential biomarker to ameliorate the management and prognosis of NSCLC patients.

Conflict of interests

The authors declare no conflict of interests.

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