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Correlated low IGF2BP1 and FOXM1 expression predicts a good prognosis in lung adenocarcinoma

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ABSTRACT

IGF2BP1 and FOXM1 are shown to be critical in the regulation of caner progression. However, the prognostic value of IGF2BP1 in lung adenocarcinoma and its relationship with FOXM1 still remains unclear. In this study, the expression and biological significance of both IGF2BP1 and FOXM1 were evaluated in 188 lung adenocarcinoma, at mRNA and protein levels. We showed that mRNA and protein levels of IGF2BP1 and FOXM1 were upregulated in lung adenocarcinoma compared to adjacent non-cancerous tissues. High IGF2BP1 expression was correlated with a poor prognosis for lung adenocarcinoma patients. Moreover, IGF2BP1 expression was positively associated with FOXM1 expression. Meanwhile, the findings indicated that low IGF2BP1 combined with low FOXM1 expression, was negatively correlated with pathological stage and lymph node metastasis, predicted good outcomes for lung adenocarcinoma patients. Additionally, low IGF2BP1 and FOXM1 expression status, is an independent prognostic factor for lung adenocarcinoma after surgical resection. We demonstrate that low IGF2BP1 and FOXM1 expression can serve as a potential factor for the clinical diagnosis and prognosis of lung adenocarcinoma, and targeted inhibition of IGF2BP1 and FOXM1 might be an alternative strategy for the management of lung adenocarcinoma.

1. Introduction

Lung cancer is the most prevalent human cancer and the first most common cause of cancer-related cancer death in recent years [1]. With the steady reductions in smoking and remarkable advances in early detection, the lung cancer incidence is declining continuously. However, due to the recurrence and metastasis of cancer, the 5-year overall survival is still low (about 18%) [2]. Therefore, effective diagnostic strategies that predict cancer recurrence and metastasis were gaining more attention from researchers.

Accumulating evidence has shown that IGF2BP1 and FOXM1 are responsible for cancer progression in human cancers. IGF2BP1 serves as a post-transcriptional fine-tuner regulating the expression of some essential mRNAs, non-coding RNAs or miRNAs that are required for the control of tumor cell proliferation and growth, invasion, and chemoresistance, associating with a poor overall survival and metastasis in various types of human cancers [3,4]. Meanwhile, FOXM1 acts as an oncogene that affects cell migration, invasion, epithelial-mesenchymal transition, recruitment of tumor-associated macrophages, angiogenesis, stem cell renewal, DNA damage repair and cellular senescence, further promoting tumour initiation, progression, metastasis, angiogenesis and drug resistance [5,6]. However, the prognostic value of IGF2BP1 in lung adenocarcinoma has not been clearly investigated. Additionally, whether IGF2BP1 expression is correlated with FOXM1 expression remains unknown.

In the present study, we investigated the expression and biological significance of IGF2BP1 and FOXM1 in lung adenocarcinoma, at mRNA and protein levels. We suggested that IGF2BP1 expression was upregulated in lung adenocarcinoma relative to that in adjacent non-cancerous tissues, and was positively correlated with a poor prognosis for lung adenocarcinoma patients. Additionally, we also found that IGF2BP1 was positively associated with FOXM1 expression, which was also elevated in lung adenocarcinoma compared to adjacent non-cancerous tissues. Moreover, patients with low IGF2BP1 combined with low FOXM1 had the best outcomes, and the expression status was an independent prognostic factor for lung adenocarcinoma patients.

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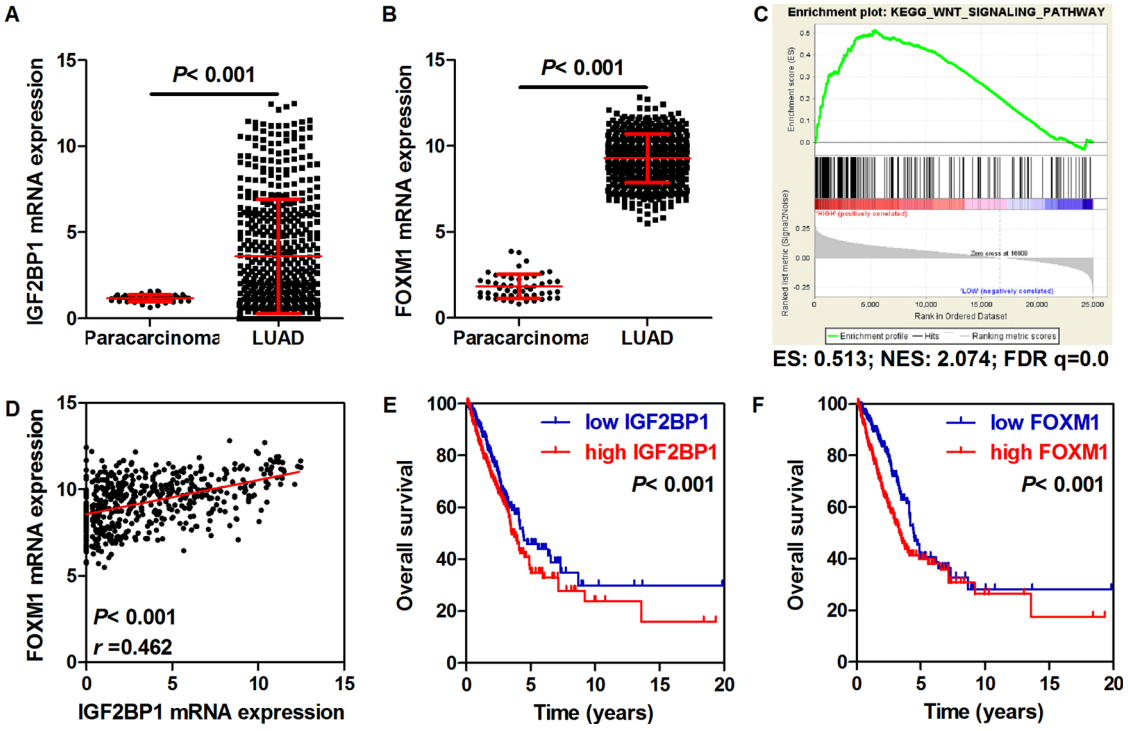

Fig. 1. The bioinformatics analysis of IGF2BP1 and FOXM1 in lung adenocarcinoma tissues and adjacent non-cancerous tissues based on TCGA LUAD mRNA-seq data. (A) Comparison of IGF2BP1 expression between lung adenocarcinoma and adjacent non-cancerous tissues. (B) Comparison of FOXM1 expression between lung adenocarcinoma and adjacent non-cancerous tissues. (C) Gene set enrichment analysis based on TCGA database showed that IGF2BP1 is involved in Wnt signaling. (D) The relationships between IGF2BP1 and FOXM1 expression. (E) Kaplan-Meier survival analysis of lung adenocarcinoma patients with low and high IGF2BP1 expression. (F) Kaplan-Meier survival analysis of lung adenocarcinoma patients with low and high FOXM1 expression.

2. Materials and methods

2.1. Bioinformatics analysis

RNA-Seq data of Lung adenocarcinoma (LUAD) was downloaded from TCGA (http://cancergenome.nih.gov/). The data included 515 lung adenocarcinoma patients, of which 59 patients were with paired non-cancerous tissues.

2.2. Patients and tissues

The protocols were approved by the Ethical Committee of Quanzhou First Hospital. Overall, 188 lung adenocarcinoma and 50 adjacent non-cancerous subjects with available clinical information and paraffin-embedded blocks were enrolled in this study. All the patients received tumor resection and tissues were obtained from patients during the surgeries. The follow up period of the patients was from 5 to 10 years. All clinicopathological features, including age, gender, pathological stage and prognostic data were retrospectively collected from the patients' medical records. All the procedure were conducted in accordance with the approved protocols.

2.3. Immunohistochemistry (IHC)

The tissue sections were dewaxed and dehydrated. The antigen retrieval was then conducted, and endogenous peroxidase activity was blocked in 3% hydrogen peroxide for 5 min. The slides were then cooled and blocked in normal goat serum for 10 min at room temperature, followed by incubation with primary antibodies for either IGF2BP1 (1:300, Abcam, USA, ab82968) or FOXM1 (1:250, Abcam, USA, ab232649) for 60 min at room temperature. Finally, the slides were incubated with the secondary antibody for 30 min at room temperature, and visualized using 3, 3′-diaminobenzidine and hematoxylin. Testis tissue was used as positive control. PBS was used as a substitute for primary antibody for negative control.

2.4. Evaluation and scoring

The staining of sections were blindly assessed and scored by two independent pathologists. The staining was scored according to the intensity and percentage of the stained sections. Staining intensity was defined as 0 (no staining), 1 (weakly staining), 2 (moderately staining), and 3 (strong staining). The percentages were estimated as follows: 1 ($\leq$ 25%), 2 (26%–50%), 3 (51%–75%), and 4 (76%–100%). The final scores were calculated as intensity score $\times$ percentage score. For statistical analysis, a score $\leq$ 6 was regarded as low expression, and $>$ 6 as high expression.

2.5. Statistical analysis

All the data analysis was performed using SPSS software (version 21.0, SPSS Inc., Chicago, USA). A nonparametric test was used to investigate the differential expression of genes between the two groups of patients. Kappa test and Spearman rank correlation analysis were performed to explore the correlation between IGF2BP1 and FOXM1. The relationships between the clinicopathlogical features and gene expression were evaluated using Pearson $\chi 2$ test. Kaplan-Meier survival curves were plotted to elucidate the relationships between gene expression and overall survival of the lung adenocarcinoma patients. Univariate and multivariate survival analysis were conducted with the Cox proportional hazards regression model to identify factors correlated with overall survival of the patients. The hazard ratio (HR) and 95% confidence intervals (95% CI) were calculated for each factor. All tests were two-sided and $P < 0.05$ was considered statistically significant.

Table 1
IGFBP1 expression in lung adenocarcinoma tissues and adjacent non-cancerous tissues.

Group	Cases(n)	IGFBP1 expression		*P* value
		Low	High	
Lung adenocarcinoma	188	103 (54.8%)	85 (45.2%)	0.007
Adjacent non-cancerous tissues	50	38 (76.0%)	12 (24.0%)	

Table 2
FOXM1 expression in lung adenocarcinoma tissues and adjacent non-cancerous tissues.

Group	Cases(n)	MYH9 expression		*P* value
		Low	High	
Lung adenocarcinoma	188	109 (58.0%)	79 (42.0%)	0.002
Adjacent non-cancerous tissues	50	41 (82.0%)	9 (18.0%)	

3. Results

3.1. IGF2BP1 and FOXM1 mRNA levels are upregulated in lung adenocarcinoma and confers poor prognosis of patients

To clarify the role of IGF2BP1 and FOXM1 in lung adenocarcinoma, we investigated their mRNA expression in lung adenocarcinoma based on the TCGA LUAD dataset. RNA-seq data from lung adenocarcinoma tissues and adjacent non-cancerous tissues showed that IGF2BP1 and FOXM1 expression were significantly elevated in lung adenocarcinoma tissues compared with adjacent non-cancerous tissues ($P < 0.001$, Fig. 1A–B), indicating their oncogenetic roles in lung adenocarcinoma. Gene set enrichment analysis based on TCGA database showed that IGF2BP1 is involved in Wnt signaling (Fig. 1C). Interestingly, IGF2BP1 expression was positively correlated with FOXM1 expression ($r = 0.462$, $P < 0.001$, Fig. 1D). Moreover, survival analyses suggested that IGF2BP1 and FOXM1 were positively correlated with a poor prognosis of lung adenocarcinoma patients (Fig. 1E–F).

3.2. Clinicopathological features of the lung adenocarcinoma patients

To verify the findings obtained from bioinformatics analysis, we further explored IGF2BP1 and FOXM1 expression by immunohistochemistry in 188 lung adenocarcinoma cases. The clinicopathological features of 188 lung adenocarcinoma patients were shown in Table 1. The patients age ranged from 20 to 84 years and the median age was 60 years. Most patients (56.9%) were male, the ratio of male patients to female patients was 1.321. Based on the 8th edition AJCC Staging System, 124 of the lung adenocarcinoma patients were in

Table 3
Correlation between IGF2BP1 expression and the clinicopathological features of lung adenocarcinoma patients.

Characteristics	Total	IGF2BP1 expression		*P* value
		Low, n (%)	High, n (%)	
Age (years)				
≤Median	97	56 (57.7%)	41 (42.3%)	0.402
>Median	91	47 (51.6%)	44 (48.4%)	
Gender				
Male	107	55 (51.4%)	52 (48.6%)	0.284
Female	81	48 (59.3%)	33 (40.7%)	
Smoking status				
No	161	92 (57.1%)	69 (42.9%)	0.113
Yes	27	11 (40.7%)	16 (59.3%)	
Family history				
No	152	82 (53.9%)	70 (46.1%)	0.634
Yes	36	21 (58.3%)	15 (41.7%)	
T stage				
T1-T2	124	75 (60.5%)	49 (39.5%)	0.029
T3-T4	64	28 (43.8%)	36 (56.2%)	
N stage				
N0	91	65 (71.4%)	26 (28.6%)	< 0.001
N1-N3	97	38 (39.2%)	59 (60.8%)	
Pathological grade				
I-II	119	60 (50.4%)	59 (49.6%)	0.114
III	69	43 (62.3%)	26 (37.7%)	
Vascular invasion				
No	166	100 (60.2%)	66 (39.8%)	0.918
Yes	22	13 (59.1%)	9 (40.9%)	

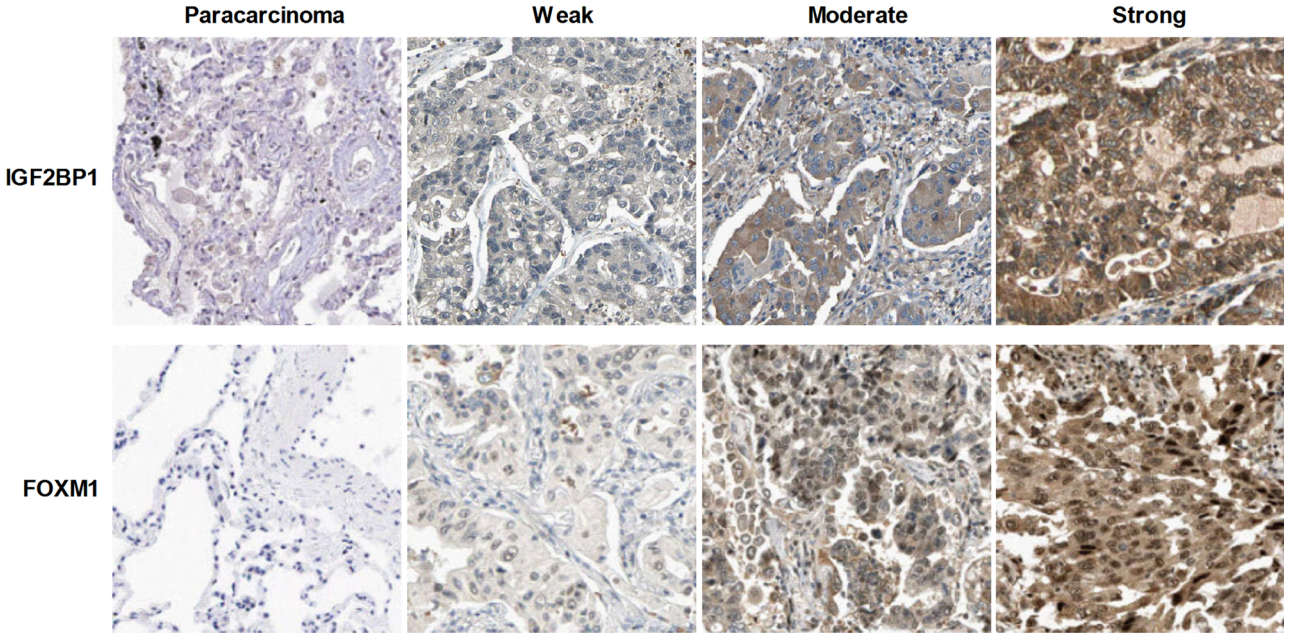

Fig. 2. Representative images of IGF2BP1 and FOXM1 staining in lung adenocarcinoma tissues and adjacent non-cancerous tissues (original magnification ×400).

Table 4
IGF2BP1 and FOXM1 protein levels in lung adenocarcinoma tissues.

FOXM1 expression	IGF2BP1 expression		Total	*Kappa*	*P* value
	Low	High			
Low	71 (69.1%)	38 (44.3%)	109	0.244	0.001
High	32 (30.9%)	47 (55.7%)	79		
Total	103	85	188		

T1 and T2 stages, 64 of them in T3 and T4 stages. Therein, 97 patients had lymph node metastasis.

3.3. Correlation between the expression of IGF2BP1, FOXM1 and clinicopathological features of lung adenocarcinoma patients

Immunohistochemistry analysis showed that patients presented different IGF2BP1 and FOXM1 expression ranging from weak staining to strong staining (Fig. 2). Immunohistochemistry showed that IGF2BP1 and FOXM1 expression were significantly elevated in lung adenocarcinoma tissues compared with adjacent non-cancerous tissues (Table 1–2). In addition, we found that IGF2BP1 expression was positively correlated with T stage and lymph node metastasis ($P = 0.029$ and $P < 0.001$, respectively), but not other parameters of the patients, including age and gender (Table 3). Intriguingly, further analysis suggested that IGF2BP1 expression was positively correlated with FOXM1 expression in lung adenocarcinoma (*kappa* = 0.244, $P = 0.001$, Table 4).

3.4. Low IGF2BP1 combined with low FOXM1 expression predicts the good prognosis in lung adenocarcinoma

Next, we conducted the survival analysis to explore the association between IGF2BP1, FOXM1 expression and overall survival of the 188 lung adenocarcinoma patients. Survival analysis indicated that low IGF2BP1 expression correlated with good prognosis for lung adenocarcinoma patients (median survival 42 months *versus* 31 months) (Log-Rank, $P = 0.015$, Fig. 3A). Additionally, we assigned the patients into two groups, the one group was named as low IGF2BP1/low FOXM1, and the another group was named as others including low IGF2BP1/high FOXM1, high IGF2BP1/high FOXM1 and high IGF2BP1/low FOXM1. The association between clinicopathological features of lung adenocarcinoma patients and the expression status of IGF2BP1 combined with FOXM1 in the two groups were analyzed and the data were summarized in Table 5. Low IGF2BP1/low FOXM1 status was negatively correlated with T stage and lymph node metastasis, but not other clinicopathological features of the lung adenocarcinoma patients. The survival analysis suggested that low IGF2BP1/low FOXM1 status contributed to a good prognosis in lung adenocarcinoma (median survival 60 months *versus* 29 months) (Log-Rank, $P < 0.001$, Fig. 3B).

Table 5
Relationship between IGF2BP1/FOXM1 combined status and clinicopathological features of lung adenocarcinoma patients.

Characteristics	Tatal	Low IGF2BP1/Low FOXM1	Others*	*P* value
Age (years)				
≤Median	97	34 (35.1%)	63 (64.9%)	0.428
>Median	91	37 (40.7%)	54 (59.3%)	
Gender				
Male	107	43 (40.2%)	64 (59.8%)	0.431
Female	81	28 (34.6%)	53 (65.4%)	
Smoking status				
No	161	59 (36.6%)	102 (63.4%)	0.439
Yes	27	12 (44.4%)	15 (55.6%)	
Family history				
No	152	54 (35.5%)	98 (64.5%)	0.193
Yes	36	17 (47.2%)	19 (52.8%)	
T stage				
T1-T2	124	56 (45.2%)	68 (54.8%)	0.004
T3-T4	64	15 (23.4%)	49 (76.6%)	
N stage				
N0	91	47 (51.6%)	44 (48.4%)	<0.001
N1-N3	97	24 (24.7%)	73 (75.3%)	
Pathological grade				
I-II	119	40 (33.6%)	79 (66.4%)	0.123
III	69	31 (44.9%)	38 (55.1%)	
Vascular invasion				
No	166	63 (38.0%)	103 (62.0%)	0.885
Yes	22	8 (36.4%)	14 (63.6%)	

* Others: low IGF2BP1/high FOXM1, high IGF2BP1/high FOXM1 and high IGF2BP1/low FOXM1.

We further performed the univariate and multivariate survival analysis to correlate the IGF2BP1/low FOXM1 expression status, the clinicopathological features and overall survival of the lung adenocarcinoma patients. As shown in Table 4, low IGF2BP1/low FOXM1 status, early T stage (T1 + T2), and negative lymph node metastasis (pN0) conferred longer overall survival of lung adenocarcinoma patients. Moreover, the multivariate Cox proportional hazard analysis revealed that low IGF2BP1/low FOXM1 status (HR = 0.522, 95% CI 0.281−0.957, $P = 0.026$) and N stage (HR = 0.322, 95% CI 0.220−0.470, $P = 0.005$), acted as independent prognostic factors for lung adenocarcinoma patients (Table 6).

4. Discussion

Studies suggested that IGF2BP1 and FOXM1 are important indicators of poor patient survival in human cancers. However, IGF2BP1 expression and its association with FOXM1 expression in lung adenocarcinoma is not fully understood. In the present study, IGF2BP1 and FOXM1 expression, and their biological significance in lung

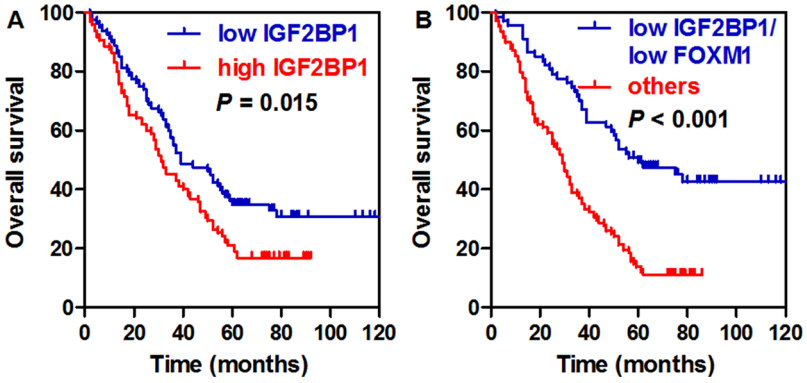

Fig. 3. Kaplan-Meier survival analysis of lung adenocarcinoma patients based on IGF2BP1, and IGF2BP1 combined with FOXM1 expression detected by immunohistochemistry.

Table 6
Univariate and multivariate survival analysis of clinicpathological variables of lung adenocarcinoma patients.

	Overall survival					
	univariate analysis			Multivariate analysis		
Clinical parameters	HR	95% CI	*P value*	HR	95% CI	*P value*
IGF2BP1/FOXM1 expression Low IGF2BP1/Low FOXM1 *vs.* Others	0.427	(0.276-0.699)	< 0.001	0.501	(0.207-0.849)	0.021
Age (years) ≤Median *vs.* >Median	0.694	(0.378-1.305)	0.484			
Gender Male *vs.* Female	1.711	(0.630-3.602)	0.315			
Smoking status No *vs.* Yes	0.919	(0.504-1.751)	0.801			
Family history No *vs.* Yes	0.711	(0.346-1.460)	0.532			
T stage T1-T2 *vs.* T3-T4	0.336	(0.216-0.561)	0.003	0.553	(0.125-1.110)	0.079
N stage N0 *vs.* N1-N3	0.137	(0.013-0.302)	< 0.001	0.218	(0.177-0.413)	< 0.001
Pathological grade I-II *vs.* III	2.090	(0.855-1.336)	0.204			
Vascular invasion No *vs.* Yes	0.210	(0.163-0.421)	< 0.001	0.357	(0.206-0.575)	0.006

*Others: low IGF2BP1/high FOXM1, high IGF2BP1/high FOXM1 and high IGF2BP1/low FOXM1.

adenocarcinoma were explored. IGF2BP1 and FOXM1 expression were upregulated in lung adenocarcinoma, at mRNA and protein levels. High IGF2BP1 protein levels conferred the poor prognosis for lung adenocarcinoma patients. Moreover, we showed that IGF2BP1 expression was positively correlated with FOXM1 expression in lung adenocarcinoma patients. In addition, low IGF2BP1 expression with low FOXM1 expression was associated with the best prognosis of lung adenocarcinoma patients.

IGF2BP1 is a RNA-binding factor that recruits target transcripts to cytoplasmic protein-RNA complexes (mRNPs). IGF2BP1 plays important roles in physiological and in pathological conditions. Immunohistochemistry analysis suggested that IGF2BP1 enhances tumorigenic activity and is correlated with poor prognosis in esophageal adenocarcinomas [7], breast cancer [8], liver cancer [9,10], gastrointestinal cancer [11], ovarian cancer [12,13], and retinoblastoma, [14]. While only few studies indicated that IGF2BP1 inhibits cancer progression [15]. However, IGF2BP1 was only shown to be associated with tumor progression in patients with lung cancer at mRNA levels [16]. In this work, we showed that both mRNA and protein levels of IGF2BP1 were upregulated in lung adenocarcinoma by bioinformatics and immunohistochemical analysis. Similarly, in this study, we found that IGF2BP1 protein levels were positively correlated with pathological stage, metastasis and poor prognosis of lung adenocarcinoma patients.

To clearly identify the oncogenic role of IGF2BP1 in lung adenocarcinoma, we focused on TCGA data mining to search mRNAs that are significantly correlated with IGF2BP1 expression. Therein, FOXM1, which has been reported as a tumor driver in lung cancer [17], was positively correlated with IGF2BP1 expression. Previous studies suggested that FOXM1 was the downstream effector of Wnt signaling [18]. Gene set enrichment analysis based on TCGA database showed that IGF2BP1 is involved in Wnt signaling. Therefore, we focused on the relationship between IGF2BP1 and FOXM1. FOXM1 is a transcription factor of the Forkhead family that is required for cell proliferation of normal cells and is regarded as a classical oncogene in human cancers [5,19–21]. In the present work, we found that IGF2BP1 expression was positively associated with FOXM1 expression by bioinformatics and immunohistochemical analysis, indicating both of them played pro-tumoral roles in lung adenocarcinoma. Importantly, we showed that patients with low IGF2BP1 combined with low FOXM1 expression had a good prognosis in lung adenocarcinoma. Further analysis suggested that low IGF2BP1 with low FOXM1 expression status negatively correlated with T stage and lymph node metastasis, and could serve as an independent prognostic factor for lung adenocarcinoma patients, suggesting the oncogenic role of FOXM1 in cancer metastasis, which was consistent with the previous findings that FOXM1 was involved in regulation of lung cancer metastasis [22,23].

Taken together, our work adds to the wealth of knowledge on the oncogenetic roles of IGF2BP1 and FOXM1 in lung adenocarcinoma. We also demonstrate that IGF2BP1 in combination of FOXM1 can serve as a potential factor for the clinical diagnosis and prognosis of lung adenocarcinoma, and targeted inhibition of IGF2BP1 and FOXM1 might be an alternative strategy for the management of lung adenocarcinoma.

Conflict of interest

The authors declare that no conflict of interest exists.

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