JOURNAL OF COMPUTATIONAL BIOLOGY
Volume 27, Number 6, 2020
© Mary Ann Liebert, Inc.
Pp. 948–957
DOI: 10.1089/cmb.2019.0241

High Expression of *FGF5* Is an Independent Prognostic Factor for Poor Overall Survival and Relapse-Free Survival in Lung Adenocarcinoma

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ABSTRACT

Lung cancer is not only a serious disease but also a public problem threatening human health all over the world. Nonsmall cell lung cancer—which accounts for the majority of lung cancer—is mainly composed of lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC). *FGF5* is a gene located in q21.21. In the past years, research on *FGF5* is mainly focused on hair length and hereditary spherocytosis. In our study, bioinformatics analysis of *FGF5* was performed through multiple databases. Expression of *FGF5* was compared between tumor and normal tissues, association between gene expression and clinical outcomes was investigated in LUAD and LUSC separately, and potential signaling pathways were predicted. *FGF5* expression was upregulated in lung cancer tissues compared with normal tissues. What is more, the high *FGF5* expression group had significantly lower proportions of lymph node negative (N0) patients (77/144, 53.5%, vs. 253/358, 70.7%, $p = 0.000$), and is associated with worse overall survival (OS) ($p < 0.0001$) and relapse-free survival (RFS) ($p = 0.024$) in LUAD patients, which could not be seen in LUSC. The following analysis confirmed that high *FGF5* expression could be an independent prognostic factor for poor OS (HR: 0.431, 95% CI: 0.312–0.597, $p = 0.001$) and RFS (HR: 0.678, 95% CI: 0.471–0.977, $p = 0.037$) in LUAD, but not in LUSC. Coexpression genes related to *FGF5* were explored and potential pathways were investigated for further research. *FGF5* is a tumor-associated gene that upregulated in lung cancer tissues, and could be an independent prognostic factor that have potential value for further research.

Keywords: bioinformatics, FGF5, lung cancer, NSCLC, survival analysis.

1. INTRODUCTION

GREAT IMPROVEMENT HAS BEEN MADE in the treatment of lung cancer in recent years, but the survival status is still poor. The 5-year survival rate of lung cancer is just 19% (Siegel et al., 2019). Many scholars believe that lung cancer is a complex disease which can hardly be controlled by single target therapy; it is important to explore new pathological mechanisms and develop new targets for the disease. Nonsmall cell lung cancer (NSCLC) constitutes the main part of lung cancer, and is mainly composed of lung squamous

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cancer (LUSC) and lung adenocarcinoma (LUAD). With worldwide tobacco uptake and cessation activities, lung squamous cancer incidence declined twice as fast in males compared with females (Ahmedin et al., 2012). But the incidence of LUAD was still stable and had replaced LUSC as the most common pathological type of NSCLC.

Public database provides us with a convenient and fast way to research oncology, such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) database. Large pieces of information about cancer patients and compared with normal people could be found in these databases, including gene expression level, clinical features, and outcomes.

FGF5 is an encoded gene belonging to the fibroblast growth factor family, the protein encoded by *FGF5* is fibroblast growth factor 5, which is an important component in transducing signals from fibroblast growth factor receptors 1 to 4 (FGFR1–4) (Mckeehan et al., 1998). Past research indicated that *FGF5* is associated with hair length and some other disease such as hereditary spherocytosis (Hébert et al., 1994). Intriguingly, in recent years, oncological value of *FGF5* has been gradually revealed: overexpression of *FGF5* could be seen in some solid tumors such as hepatocellular carcinoma (Feng et al., 2015), colorectal cancer (Mitchell et al., 2014), and breast carcinoma (Huang et al., 2018), and expression of *FGF5* was associated with poor survival outcome. In lung cancer, to our best knowledge, seldom research has reported the oncological value of *FGF5*. In this study, bioinformatics analysis was performed to investigate the prognostic value of *FGF5* in LUSC and LUAD, and explore the possible pathways *FGF5* might be involved in.

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2. METHODS

2.1. Expression analysis

The expression level of *FGF5* in two kinds of lung cancer (LUSC and LUAD) and normal tissues was obtained from TCGA database through UCSC Xena Browser (Cline et al., 2013) (https://xenabrowser.net). Patients were grouped in different pathological stages and compared with normal tissues separately.

2.2. Survival analysis

Data of clinical features were obtained from TCGA database through UCSC Xena browser, including living status, overall survival (OS), relapse-free survival (RFS), age at initial diagnosis, gender, and smoking history. The survival analysis results were validated by Kaplan–Meier Plotter browser (Gyorffy et al., 2013) (http://kmplot.com/analysis/index.php?p=service&cancer=lung).

2.3. Coexpression gene analysis and protein–protein interaction analysis

Coexpression genes of *FGF5* were obtained by Cbioportal (Ethan et al., 2012) (www.cbioportal.org/index.do) and Ualcan (Chandrashekar et al., 2017) browser (http://ualcan.path.uab.edu/analysis.html). Only the genes with the Spearman or Pearson rank >0.4 could be selected for study. These genes were sent to GlueGo (Bindea et al., 2009) in Cytoscape (Shannon et al., 2003) for KEGG pathway analysis. *FGF5* and coexpression genes were performed to String browser (Szklarczyk et al., 2019) for protein–protein interaction analysis.

2.4. Statistical analysis

Excel was used to prepare the obtained data, statistical analysis was mainly performed through SPSS23.0. Expression status was compared by T-test, and χ^2-test was used to explore the association between *FGF5* expression and the clinical data. The *FGF5* expression was divided into high and low groups, and the cutoff value was determined by receiver operating characteristic curve through Medcalc V15.0 software. Kaplan–Meier was used to analyze the OS and RFS in two expression groups. Univariate and multivariate analyses were used to identify the prognostic value

3. RESULTS

3.1. Compared with normal tissues, upregulation of FGF5 *expression could be seen in lung cancer*

With the use of Xena browser, expression data of LUAD, LUSC, and normal tissues were obtained, results showed a significantly upregulated expression of *FGF5* in lung cancer tissues, both in LUAD and in LUSC (Fig. 1A, B). Further analysis showed that, compared with normal tissues, *FGF5* expression was significantly elevated in almost every independent stage (Fig. 1C–I), except stage IV in LUSC (Fig. 1J).

3.2. High FGF5 *expression was associated with poor survival outcome, which had potential prognostic value*

Tables 1 and 2 showed the relationship between *FGF5* expression and clinical feature, for LUAD patients, compared with low expression group, high *FGF5* expression patients had a smaller proportion of early stage (stage I/II) (96/144, 66.7% vs. 300/362, 82.3%, $p=0.000$) and lymph node negative (N0) (77/144, 53.5% vs. 253/358, 70.7%, $p=0.000$) status. What is more, significantly more patients died in the high-expression group of *FGF5* (69/144, 47.9% vs. 114/358, 31.8%, $p=0.001$) (Table 1). We could seldom explore a similar phenomenon in LUSC patients (Table 2). Through Kaplan–Meier analysis, high expression of *FGF5* in LUAD patients was associated with worse survival outcome, both in OS ($p=0.000$) and RFS ($p=0.024$) (Fig. 2A, B). However, no statistical difference could be observed in LUSC (OS: $p=0.204$, RFS: $p=0.106$, Fig. 2C, D). Results were verified by Kaplan–Meier plotter, probe 208378_x_at was selected in our research, and similar results were obtained (Fig. 2E, F): high expression of *FGF5* was associated with worse OS in LUAD patients ($p<0.000$) but not in LUSC patients ($p=0.18$).

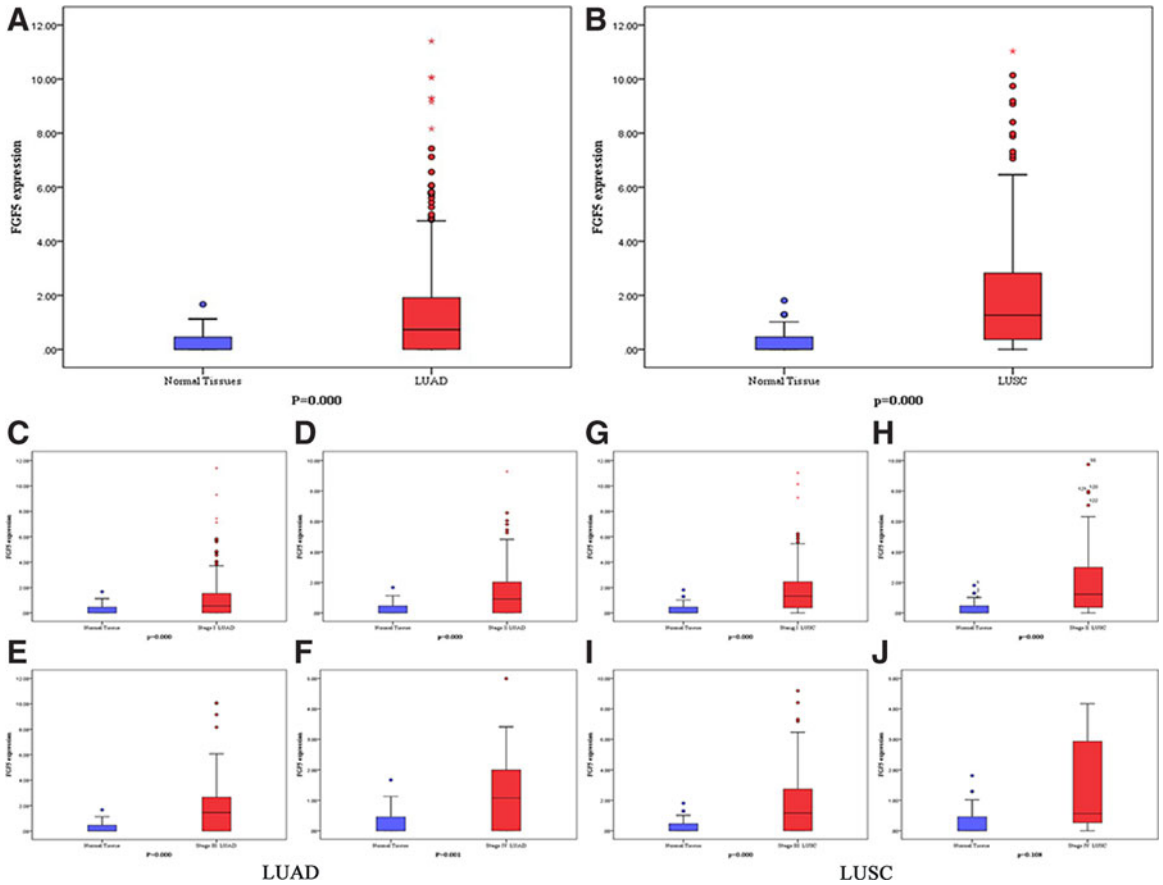

FIG. 1. Expression of FGF5 in LUAD (**A**) and LUSC (**B**) compared with normal tissues; expression of FGF5 in different stages in LUAD (**C, D, E, F**) and LUSC (**G, H, I, J**) compared with normal tissues. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

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Table 1. Association Between FGF5 Expression and Clinical Features of Lung Adenocarcinoma Patients

Parameters	*FGF5 expression Low,* N = *367*	*FGF5 expression High,* N = *147*	χ^2	p
Age				
<66	171	79	2.740	0.098
>66	184	61		
DIS	12	7		
Gender				
Male	167	70	0.189	0.664
Female	200	77		
Clinical stage				
I/II	300	96	15.904	0.000
III/IV	62	48		
DIS	5	3		
Smoking history				
Lifelong nonsmoker	51	24	0.500	0.480
Smoker	306	119		
DIS	10	4		
Status				
Living	244	75	11.453	0001
Dead	114	69		
DIS	9	3		
T stage				
T1/T2	324	121	3.217	0.073
T3/T4	41	25		
DIS	2	1		
N stage				
N0	253	77	13.486	0.00
N1/N2/N3	105	67		
DIS	9	3		
M stage				
M0	244	102	0.473	0.492
M1	16	9		
DIS	107	36		

DIS, discrepancy.

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Then the following univariate analysis showed an association between high *FGF5* expression and poor survival, as well as the association between advantage stage and poor survival. Multivariate analysis confirmed that high *FGF5* expression and advantage pathological stage could be an independent prognostic factor for poor OS (HR: 0.431, 95% CI: 0.312–0.597, $p = 0.001$) and RFS (HR: 0.678, 95% CI: 0.471–0.977, $p = 0.037$) in LUAD patients (Table 3). However, a similar result was not found in LUSC (Table 4).

3.3. FGF5 *participates in different pathways in lung adenocarcinoma compared with lung squamous cell carcinoma*

Coexpression genes were obtained in two different platforms in our study. Results showed that there were 85 genes related to *FGF5* in LUAD, and 43 genes in LUSC (Supplementary Material). The heatmap of the top 25 coexpression genes in LUAD and LUSC is shown in Figure 3.

To further explore the possible pathways these genes might be participated in, KEGG pathway analysis was performed through ClueGo in Cytoscape. Results showed that *FGF5* and its coexpressed genes were enriched in some pathways such as protein digestion and absorption, phagosome, PI3K-Akt signaling pathway, proteoglycans in cancer, Ras signaling pathway, ECM–receptor interaction, hypertrophic cardiomyopathy (HCM), hematopoietic cell lineage, dilated cardiomyopathy, NF-kappa B signaling pathway, phospholipase D signaling pathway, and melanoma in LUAD (Fig. 4A), whereas they were enriched in cytokine–cytokine receptor interaction, PI3K-Akt signaling pathway, focal adhesion, proteoglycans in cancer, pertussis, regulation of actin cytoskeleton, ECM–receptor interaction, HCM, hematopoietic cell

Table 2. Association Between FGF5 Expression and Clinical Features of Lung Squamous Cell Carcinoma Patients

Parameters	*FGF5 expression Low,* N = *315*	*FGF5 expression High,* N = *187*	χ^2	p
Age				
≤68 years	166	89	1.644	0.200
>68 years	141	96		
	8	2		
Gender				
Male	228	144	1.184	0.277
Female	86	43		
DIS	1	0		
Clinical stage				
I/II	252	154	0.243	0.622
III/IV	59	32		
DIS	4	1		
Smoking				
Nonsmoker	10	8	0.495	0.482
Smoker	300	171		
DIS	5	8		
Status				
Living	183	99	1.645	0.200
Dead	125	86		
DIS	7	1		
T stage				
T1/T2	257	150	0.205	0.651
T3/T4	57	37		
DIS	1	0		
N stage				
N0	196	123	0.369	0.544
N1/N2/N3	113	63		
DIS	6	1		
M stage				
M0	254	157	0.016	0.898
M1	5	2		
DIS	56	28		

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lineage, dilated cardiomyopathy, rheumatoid arthritis, allograft rejection, graft-versus-host disease, type I diabetes mellitus, Rap1 signaling pathway, shigellosis, melanoma, arrhythmogenic right ventricular cardiomyopathy, bacterial invasion of epithelial cells, TGF-beta signaling pathway, protein digestion and absorption, toll-like receptor signaling pathway, toxoplasmosis, vascular smooth muscle contraction, pathways in cancer, Systemic lupus erythematosus, cell adhesion molecules, phagosome, and calcium signaling pathway in LUSC (Fig. 4B).

The gene *FGF5* was enriched mainly in melanoma, PI3K-Akt signaling pathway, and Ras signaling pathway in LUAD, and Rap1 signaling pathway, melanoma, regulation of actin cytoskeleton, and PI3K-Akt signaling pathway in LUSC; results showed that *FGF5* participated in different pathways between LUAD and LUSC. Then the protein–protein interaction network was analyzed, proteins that were closely related to the *FGF5* expression were observed (Fig. 4C).

4. DISCUSSION

FGF5 is a gene located in the q21.21 of human chromosome. The protein expressed by *FGF5* gene is fibroblast growth factor-5 (*FGF5*), which is composed of 18 polypeptides and belongs to fibroblast growth factor family. *FGF5* participates in many activities of embryonic development and normal physiological

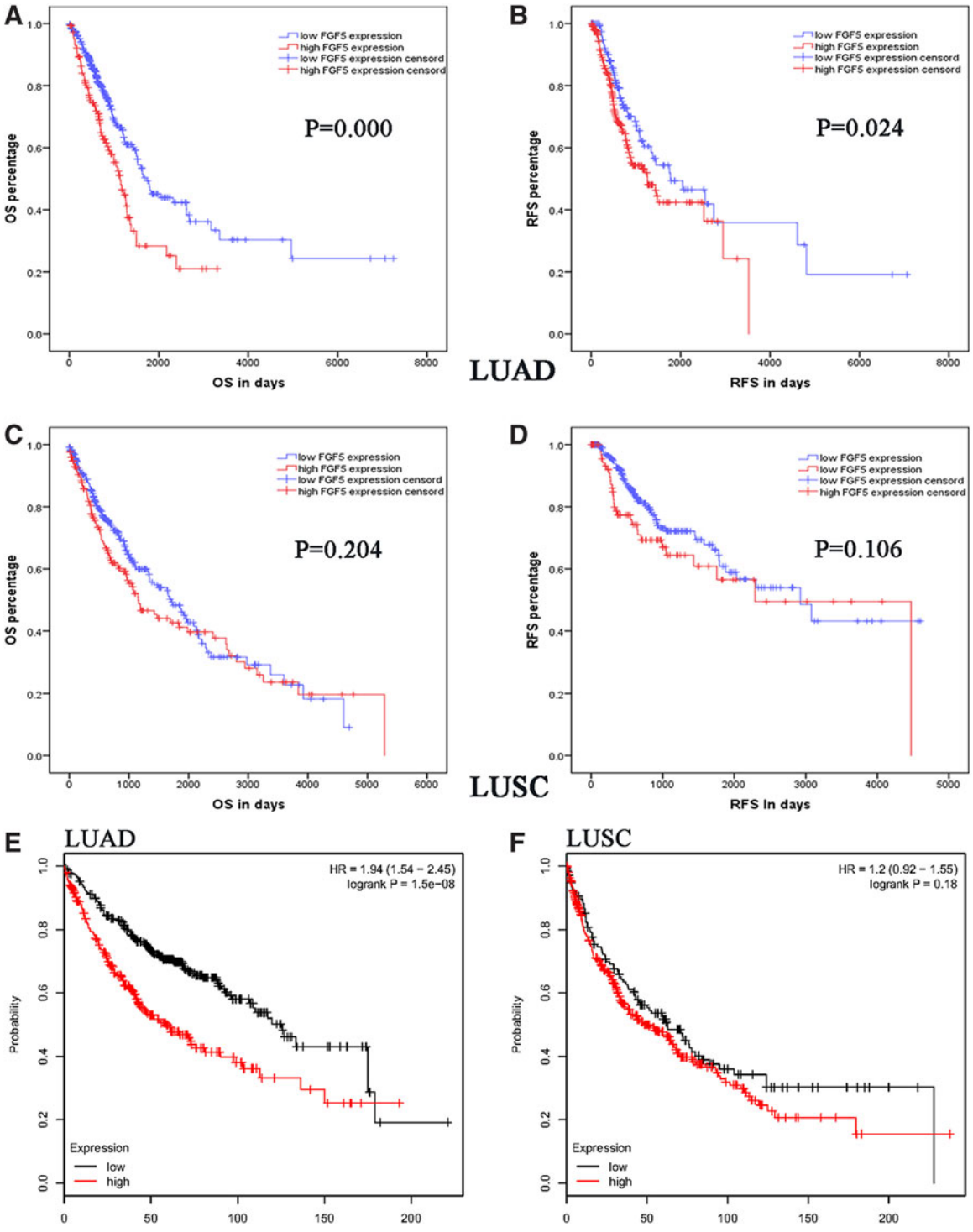

FIG. 2. Survival curve of different FGF5 expression groups. **(A, B)** Display the survival curve of LUAD patients in different FGF5 expression groups, **(C, D)** Show the survival curve of LUSC patients in different FGF5 expression groups. **(E, F)** Show the verification of overall survival in different FGF5 expression groups in LUAD and LUSC.

activities of adults, such as stem cell generation, migration, proliferation, and tube formation. Ren et al. (2018) observed the abnormal *FGF5* expression in hypertension patients and found the relationship between *FGF5* expression and blood pressure. Higgins et al. (2014) explored the important value of *FGF5* in hair growth in humans. In the past, the study of FGF5 is mainly limited to non-neoplastic diseases. In recent years, the role of *FGF5* in tumorigenesis and development has been discovered. Some scholars believed

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Table 3. Univariate and Multivariate Analyses of Overall Survival/Relapse-Free Survival in Lung Adenocarcinoma Patients

	Univariate analysis				*Multivariate analysis*			
Parameters	p	*HR*	*95% CI (lower/upper)*		p	*HR*	*95% CI (lower/upper)*	
OS								
Age >65 years vs. ≤65 years	0.116	0.785	0.580	1.062				
Female vs. male	0.397	0.878	0.649	1.187				
Smoking history 2/3/4/5 vs. 1	0.808	1.053	0.693	1.601				
Clinical stage III/IV vs. I/II	0.000	0.403	0.292	0.555	0.000	0.431	0.425	0.804
FGF5 expression high vs. low	0.000	0.533	0.388	0.730	0.001	0.431	0.312	0.597
RFS								
Age >65 years vs. 65 years	0.097	0.751	0.535	1.054				
Female vs. male	0.765	1.054	0.748	1.484				
Smoking history 2/3/4/5 vs. 1	0.400	0.812	0.499	1.319				
Clinical stage III/IV vs. I/II	0.032	0.644	0.430	0.964	0.055	0.672	0.448	1.008
FGF5 expression high vs. low	0.024	0.658	0.458	0.947	0.037	0.678	0.471	0.977

OS, overall survival; RFS, relapse-free survival. Smoking history: 1, never smoke; 2, current smokers; 3, former smokers >15 years; 4, former smokers ≤15 years; 5, former smokers without specified duration.

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that *FGF5* not only participates in the carcinogenic process of melanoma, but also could promote the growth of melanoma in some subgroups (Ghassemi et al., 2017). *FGF5* is an important factor that promotes the malignant progression by autocrine and paracrine effects in astrocytic brain tumors (Allerstorfer et al., 2008). Silencing *FGF5* expression could suppress NSCLC cell growth and invasion by regulating the VEGF pathways and cell cycle (Zhou et al., 2018). Fang et al. (2015) observed that *FGF5* plays an important role to suppress the proliferation and metastasis of hepatocellular carcinoma. However, the expression of *FGF5* and its relationship with oncological outcomes in NSCLC remain unclear.

In our study, *FGF5* expression in two different types of lung cancer was compared with normal tissues, and significant upregulation was observed both in LUAD and in LUSC. Next, *FGF5* expression of lung

Table 4. Univariate and Multivariate Analyses of Overall Survival/Relapse-Free Survival in Lung Squamous Cell Carcinoma Patients

	Univariate analysis				*Multivariate analysis*			
Parameters	p	*HR*	*95% CI (lower/upper)*		p	*HR*	*95% CI (lower/upper)*	
OS								
Age >65 years vs. ≤65 years	0.123	0.805	0.612	1.060				
Female vs. male	0.316	0.848	0.615	1.170				
Smoking history 2/3/4/5 vs. 1	0.221	1.666	0.736	3.722				
Clinical stage III/IV vs. I/II	0.007	0.642	0.466	0.885	0.007	0.642	0.466	0.885
FGF5 expression high vs. low	0.205	0.835	0.632	1.103				
RFS								
Age >65 years vs. 65 years	0.629	1.107	0.733	1.672				
Female vs. male	0.174	0.712	0.436	1.161				
Smoking history 2/3/4/5 vs. 1	0.076	2.497	0.910	6.850				
Clinical stage III/IV vs. I/II	0.004	0.490	0.300	0.799	0.004	0.490	0.300	0.799
FGF5 expression High vs. low	0.108	0.698	0.451	1.081				

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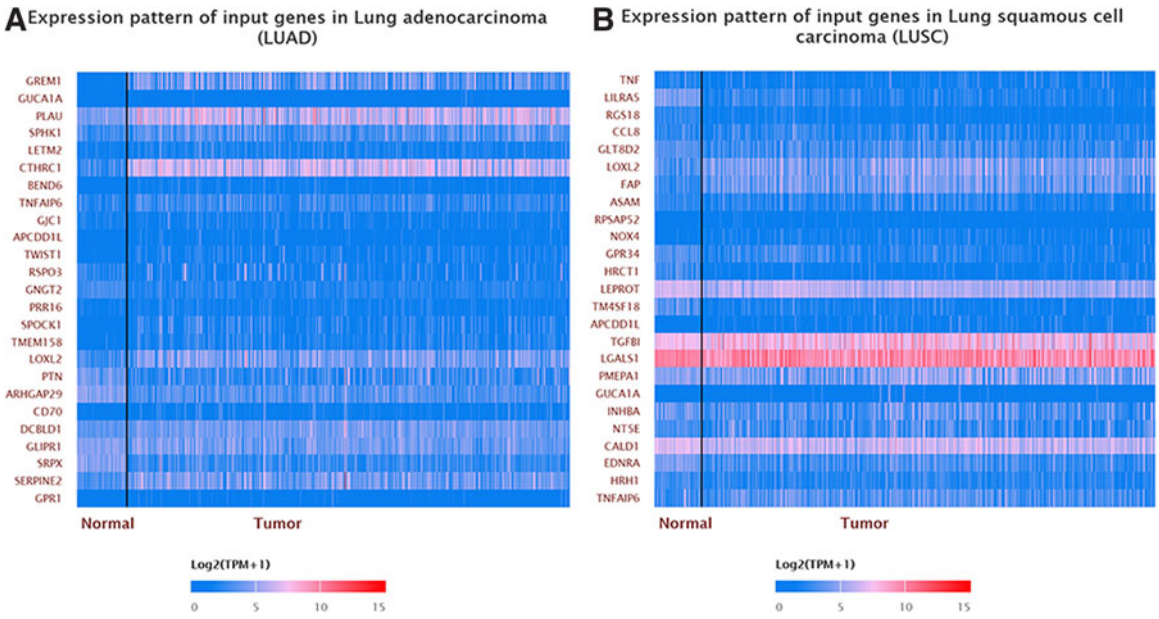

FIG. 3. Heatmap for top 25 coexpression genes in LUAD (**A**) and LUSC (**B**).

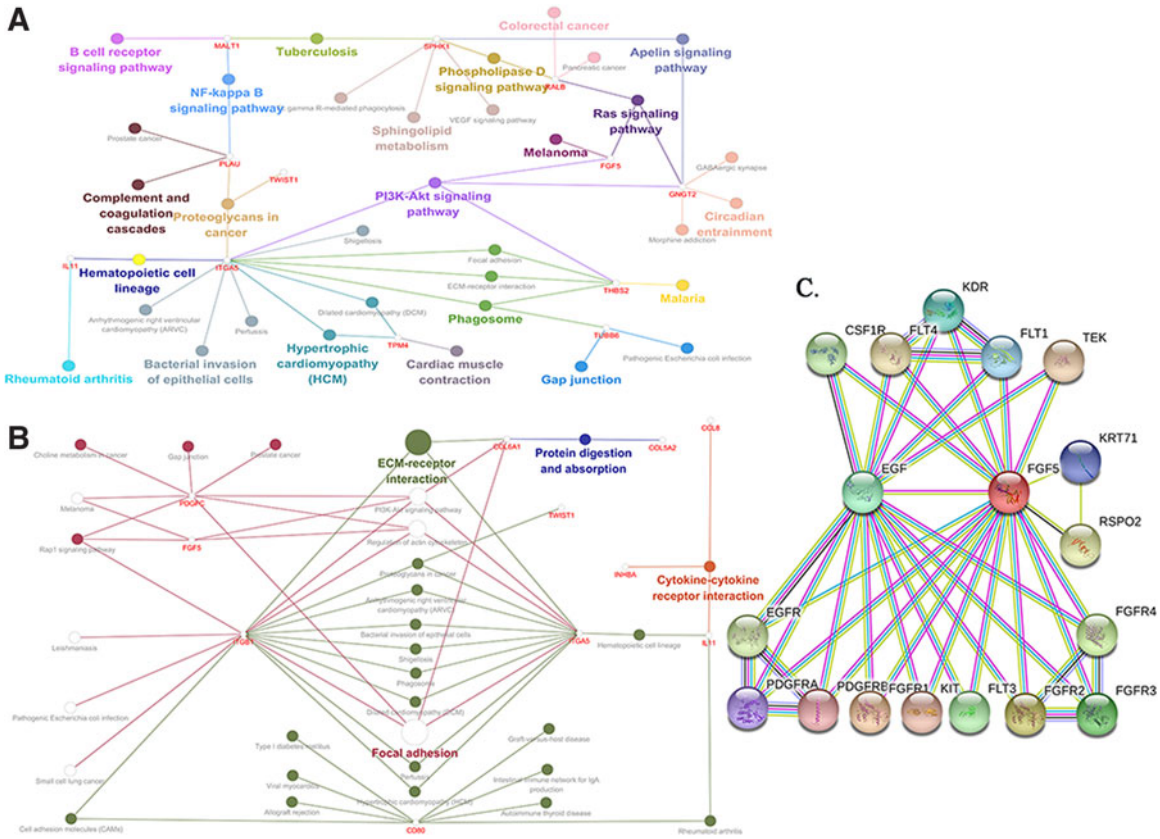

FIG. 4. KEGG analysis for FGF5 coexpression genes and PPI network. **(A)** Shows the KEGG pathway in LUAD patients, 82 coexpression genes were obtained from 2 different platforms. **(B)** Shows the KEGG pathway in LUSC patients, 42 coexpression genes were obtained from 2 different platforms. **(C)** Shows PPI network of fibroblast growth factor 5, the filter value of PPI was set at 0.8, and 17 proteins were closely related to fibroblast growth factor 5. PPI, protein–protein interaction.

cancer at different pathological stages was analyzed. Except stage IV LUSC cases, upregulation expression of *FGF5* could be seen at all the other stages. As a carcinogenic gene in other tumors, we speculate that fibroblast growth factor 5 may play a role in promoting the occurrence and development of lung cancer.

Lymph node metastasis is one of the important factors affecting prognosis of lung cancer patients (Dai et al., 2016). Patients with lymph node metastasis had a later pathological stage and a poorer survival compared with lymph node negative (stage N0) patients. Lymph node metastasis can be inferred by imaging examination, but the most accurate diagnostic method is pathological diagnosis by invasive examination (Call et al., 2018). In our study, there was a significant difference in the expression of *FGF5* between patients with lymph node negative and lymph node positive status. High *FGF5* expression was associated with lymph node metastasis. Therefore, we believe that *FGF5* expression can not only be an independent prognostic factor for LUAD patients, but can also act as a potential predictor of lymph node metastasis. High expression of *FGF5* suggests poor prognosis and greater likelihood of lymph node metastasis. For this reason, we believe that FGF5 has certain research potential in noninvasive diagnosis of LUAD.

To further investigate the possible signaling pathways in which *FGF5* might be involved in, *FGF5* coexpressed genes in LUAD and LUSC were subjected to KEGG pathway analysis.

To explore the potential pathways in which *FGF5* might participate in, KEGG was analyzed with the *FGF5* coexpressed genes in LUAD and LUSC. Some pathophysiological pathways are common in LUAD and LUSC such as PI3K-Akt signaling pathway, proteoglycans in cancer, and Rap1 signaling pathway. *FGF5* may promote the development of tumors in these aspects. Through protein–protein interaction analysis, many proteins once closely related to epidermal growth factor (EGF) have been found to be associated with *FGF5*. As we know, the main mechanism of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) is MAPK/PI3K pathway (Liu et al., 2018). We speculate that *FGF5* might be another potential target for anticancer therapy: designing TKI drugs for this target has similar antineoplastic effects compared with EGFR pathways perhaps, which may provide hope for EGFR-negative patients. Nevertheless, we should also be aware that targeting *FGF5* therapy may be cross-resistant with classical EGFR-TKI drugs.

5. CONCLUSION

As a tumor-associated gene, *FGF5* was upregulated in two types of lung cancer in our study, and could be an independent prognostic factor that has potential value for further research; pathways analysis indicated that *FGF5* participates in various pathophysiological pathways, the oncological value of which deserves further study verification.

AUTHOR DISCLOSURE STATEMENT

The authors declare that no competing financial interests exist.

FUNDING INFORMATION

Clinical Technology Innovation Project of Beijing Municipal Administration of Hospitals provided financial support for this study (Grant No. XMLX201702).

SUPPLEMENTARY MATERIAL

Supplementary Material

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