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IL-17F expression correlates with clinicopathologic factors and biological markers in non-small cell lung cancer

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ABSTRACT

Interleukin-17 F (IL-17F) is a pro-inflammatory cytokine that participate in inflammatory responses. Studies showed that IL-17F is likely involved in tumor development, but the biological function of IL-17F in non-small cell lung cancer (NSCLC) is unclear. The aim of this study was to explore the biological role of IL-17F in NSCLC and investigate its correlation with biological markers CD31, P53, Ki-67 and E-cadherin. Paraffin-embedded tumor tissues from 55 NSCLC patients were collected to detect proteins expression using immunohistochemistry (IHC). 12 normal lung tissues samples were used as control. IHC results showed that the expression of IL-17F in NSCLC cells (61.8%) was significantly higher compared with normal lung tissues (25.0%) ($P < 0.05$). The expression of IL-17F was positively associated with tumor differentiation and negatively associated with lymph node metastasis and TNM staging (P all < 0.05). Multivariate analysis showed that IL-17F expression was an independent factor associated with TNM staging ($P < 0.01$). Pearson's correlation analysis showed a negative correlation between IL-17F and CD31 expression and a positive correlation between IL-17F and E-cadherin expression (P all < 0.05). There was no relationship between IL-17 F and P53 or Ki-67 expression in NSCLC tissues ($P > 0.05$). These data suggest that IL-17 F may be considered as a potential marker for predicting the progression of NSCLC.

1. Introduction

Lung cancer is the most common cause of cancer-related death in the worldwide. In China, the incidence, mortality and tendency of lung cancer has rapidly increased during the past decades [1]. The majority of lung cancer is non-small cell lung cancer (NSCLC) and accounts for over 80% of all cases. Although various new therapeutic methods have certain effects on NSCLC at the early stage, the recurrence and metastasis are still the main factors of poor prognosis [2]. Recent studies showed a strong correlation between chronic inflammation and NSCLC, and inflammatory cytokines have emerged as important factors in the development and metastasis of NSCLC [3,4].

Interleukin-17 (IL-17) is a novel family of pro-inflammatory cytokines that participate in both acute and chronic inflammatory responses. IL-17 family consists of six closely related members, including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25) and IL-17F. Among IL-17 family, IL-17F shares the strongest amino acid sequence (56% amino acid identity) with IL-17A, whereas IL-17E shares 16% identity to IL-17A. Although IL-17F is structurally related to IL-17A and they bind to a heterodimeric receptor complex composed of IL-17RA and IL-17RC, but their binding affinities are different. IL-17A has higher affinity to IL-17RA, whereas IL-17F has higher affinity to IL-17RC [5]. IL-17A is not only widely involved in autoimmune disease, allergic responses and host defense against bacterial and fungal infections, but also contributes to the tumor progression by activating inflammatory signaling pathways [6–11]. The high level of IL-17A in the serum or tumor cells of cancer patients showed significant correlations with metastasis and poor prognosis, such as breast cancer, hepatocellular carcinoma and lung cancer [8–11]. IL-17F mainly participates in the defense against bacteria and inflammation in epithelial tissues. The inflammatory effect of IL-17F is obviously weaker than IL-17A [6], and its role in tumorigenesis has not been as well investigated as IL-17A. It

Abbreviations: IL-17F, Interleukin-17 F; NSCLC, Non-small cell lung cancer; IHC, Immunohistochemistry; MVD, Microvessel density; EMT, Epithelial-mesenchymal transition

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is reported that IL-17F is also involved in inflammation-related cancer [12]. Tong et al. reported that IL-17F may play a protective role in colon cancer progression [13]. On the contrary, Krejsgaard et al. reported that IL-17F expression correlates with increased risk of cutaneous T-cell lymphoma progression [14]. In addition, several studies have reported the close relationships between polymorphisms of IL-17F and cancer risk, including cervical cancer, gastric cancer and lung cancer [15–18]. Up to now, the biological role of IL-17F in NSCLC is still unclear.

This is the first study to explore the clinical significance of IL-17F expression in tumor cells of NSCLC patients, and its correlation with biological markers CD31, P53, Ki-67 and E-cadherin. Our findings will clarify the biological role of IL-17F in NSCLC development, and provide a new target for NSCLC immunotherapy.

2. Materials and methods

2.1. Patients and clinical samples

A total of 55 formalin-fixed, paraffin-embedded samples (FFPE) tumor samples were obtained from patients who were diagnosed with the primary NSCLC and underwent surgical resection. 12 normal lung tissues samples from patients undergoing lobectomy for other reasons (pulmonary bulla, bronchiectasis and lung trauma) were used as control in this study. All samples were obtained from the General Hospital of China National Petroleum Corporation (CNPC) in Jilin between January 2009 and December 2013. All patients had complete clinical pathology information from the pathology reports, with neither radiotherapy nor chemotherapy before operation. TNM classification was adopted by the international lung cancer staging criteria of the International Union against Cancer (UICC, 2009, 7th edition). The clinicopathologic factors of NSCLC patients are provided in Table 1. This study was approved by the General Hospital of CNPC ethics committee.

2.2. Immunohistochemical staining

FFPE tissues sections (4 μm-thick) were performed for immunohistochemical (IHC) staining. In brief, tissues sections were first deparaffinized in xylene and rehydrated in a series of graded alcohols then treated in citrate buffer pH6.0 or Tris/EDTA buffer 8.0 for heat-induced antigen retrieval. Endogenous peroxidase activity was blocked by incubation with 3% hydrogen peroxide for 10 min. Sections were subsequently incubated with the primary antibodies overnight at 4°C, respectively. The information and concentration of primary antibodies are summarized in Table 2. After washing, sections were incubated in the two-step immunohistochemistry detection system (PV-9000, Beijing, ZSGB-BIO, China) according to manufacturer protocol and visualized using DAB kit (ZSGB-BIO, Beijing, China). Finally, sections were counterstained with hematoxylin solution, dehydrated and mounted.

Table 1
The clinicopathologic factors of NSCLC patients.

Factor	Value
Number of patients (%)	55(100)
Age (years)	
Range	39 ~ 78
Mean	60.5
≥60	28 (50.9)
< 60	27 (49.1)
Gender (No., %)	
Male	34 (61.8)
Female	21 (38.2)
Tumor size (cm)	
≤3 cm	25 (50.0)
> 3 cm	30 (54.5)
Histology (No., %)	
Squamous carcinoma	35 (63.6)
Adenocarcinoma	20 (36.4)
Differentiation (No., %)	
Well- moderate	32 (58.2)
Poor	23 (41.8)
Lymph node metastasis	
Yes	24 (43.6)
No	31 (56.4)
TNM staging	
I	27 (49.1)
II + III	28 (50.9)

Table 2
Antibodies for the immunohistochemical analysis.

Antibodies	Item number	Supplier	Clonality	Isotype	Dilution
IL-17F	NBP2-21684	Novus	Monoclonal	Mouse-IgG1	1:1000
CD31	SC-53411	Santa	Monoclonal	Mouse-IgG1	1:50
P53	ZM-0405	ZSGB	Monoclonal	Mouse-IgG2a	Ready to use
Ki-67	ZA-0502	ZSGB	Monoclonal	Rabbit-IgG	Ready to use
E-cadherin	ZM-0092	ZSGB	Monoclonal	Mouse-IgG1	Ready to use

2.3. Histology scoring

All stained slides were assessed using the double-blind method. The expression of IL-17F, E-cadherin and P53 were scored as follows. A total of 5 high-power fields (400 × magnification) were observed and 100 tumor cells were counted in each field. Cytoplasmic and nuclear staining was assessed for IL-17F, while nuclear and membranous staining was assessed for P53 and E-cadherin, respectively. Staining intensity: 0 = absent, 1 = weak, 2 = moderate, 3 = strong; positive area: 0 = < 5%, 1 = 5–25%, 2 = 25–50%, 3 = 50–75% and 4 > 75%. Values for staining intensity and positive area were multiplied to give the final score: negative for 0–2, weak positive for 3–4, moderate positive for 6–8, strong positive for 9-12. The final score > 2 was considered positive [19]. Ki-67 labeling index (LI) was assessed for nuclear staining and scored as follows: low, LI < 10%; moderate, 10% ≤ LI < 30%; high, LI ≥ 30%. LI ≥ 10% was considered positive [20].

MVD (microvascular density) was assessed for CD31-positive cells. For each high-power field (200 × magnification), the number of positively stained blood vessels was counted at the most vascularized area (hot-spots). The mean count from five hot-spots was regarded as MVD-CD31 [21].

2.4. Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences version 17.0 (SPSS, IBM, Chicago, IL, USA). The Chi-square test was used to analyze the difference between IL-17F expression in NSCLC and normal lung tissues, and also to evaluate the associations between IL-17F expression and patients' clinicopathologic factors. Multivariate analysis was performed by multiple linear regression analysis. Pearson's correlation test was performed to assess the correlation between the expression of IL-17F and biological markers. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Expression and location of IL-17F in NSCLC and normal lung tissues

IHC staining showed that IL-17F protein was mainly located in the cytoplasm (20 cases, 58.8%; Fig.1A) and the nucleus (14 cases, 41.2%; Fig.1B) of tumor cells, and also in some immune cells and vascular endothelial cells between the tumor islands (Fig.1C). In normal lung tissues, IL-17F protein was nearly absent or only weakly expressed in

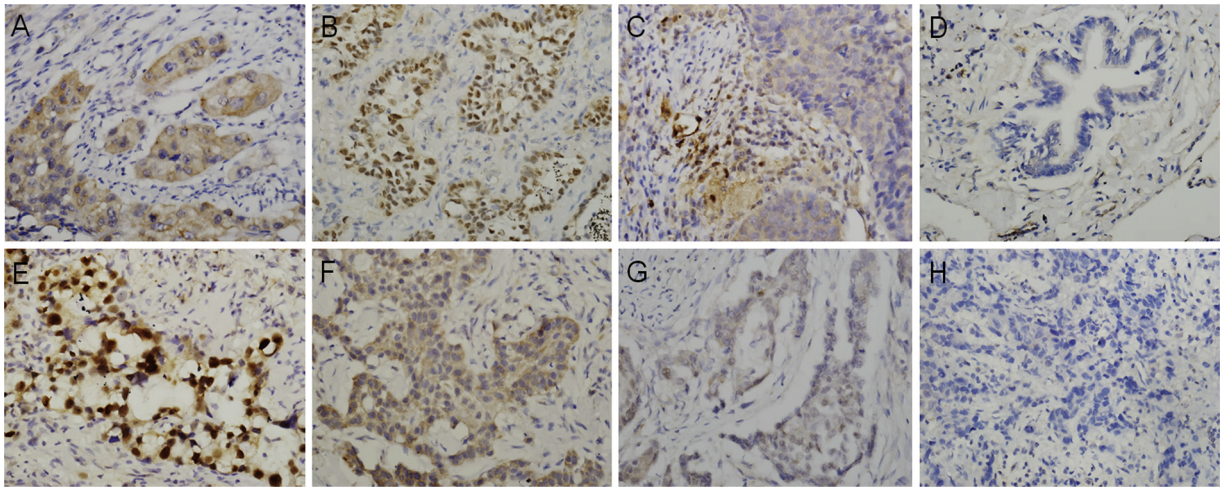

Fig. 1. IHC staining of IL-17F in NSCLC and normal lung tissues.
(A) The cytoplasmic expression of IL-17F protein in NSCLC cells. (B) The nuclear expression of IL-17F protein in NSCLC cells. (C) The positive expression of IL-17F in some immune cells and vascular endothelial cells. (D) The negative expression of IL-17F in normal bronchial mucosa endothelial cells. (E) Strong IL-17F staining in NSCLC cells with TNM stage I. (F) Moderate IL-17F staining in NSCLC cells with TNM stageII. (G) Weak IL-17F staining in NSCLC cells with stage III. (H) Negative IL-17F staining in NSCLC cells with TNM stage III. Original magnification (400 ×)

Table 3
Comparison of IL-17F expression in NSCLC and normal lung tissues.

		IL-17F expression						
Groups	n	0-2 scores	3-4 scores	6-8 scores	9-12 scores	Positive rate (%)	χ^2	*p*-value
NSCLC	55	21	16	10	8	61.8	5.400	0.020*
Normal	12	9	3	0	0	25.0		

* $P < 0.05$ was statistically significant.

the epithelium cells of bronchial mucosa (Fig.1D). IL-17F expression was positive in 34 of 55 (61.8%) NSCLC tissues and in 3 of 12 (25.0%) normal lung tissues, the difference between the two groups was highly significant ($P = 0.020$), as shown in Table 3.

3.2. Association between IL-17 F expression and clinicopathologic factors in NSCLC

The Chi-square test showed a significant increase expression of IL-17F in well-moderate differentiation when compared with poor differentiation ($P = 0.018$). Moreover, the expression of IL-17F was negatively associated with lymph node metastasis and TNM staging ($P = 0.032$; $P = 0.017$). There were no significant relationships between IL-17F expression and other factors, such as age, gender, tumor size and histological subtype ($P > 0.05$), as shown in Table 4. In addition, we did not observe the association between the location of IL-17F (cytoplasm or nucleus) and clinicopathologic factors (data not shown). Multivariate linear regression analysis further showed that IL-17F expression was an independent factor correlated with TNM staging ($P = 0.003$; Table 5 and Fig.1E-H).

3.3. Correlation between IL-17F expression and biological markers in NSCLC

Table 6 showed the correlation between IL-17F expression and biological markers CD31, P53, Ki-67 and E-cadherin.

CD31 staining and microvessel density (MVD) were assessed for angiogenesis in NSCLC tissuess. Compared to the normal lung tissues, $CD31^+$ vascular endothelial cells were highly distributed in peri-tumoral stroma region (6.04 ± 2.12 *vs* 47.31 ± 14.65; Fig. 2). 76.2% of high MVD-CD31 samples were observed in IL-17 F negative samples, and Pearson's correlation analysis showed a negative correlation between IL-17 F expression and MVD-CD31 ($r = -0.314$, $P = 0.019$; Fig. 3A-B).

Table 4
The association between IL-17F expression and clinicopathologic factors in NSCLC.

		IL-17F expression				
Clinicopathological factors	n	Positive (%)	3-4 scores	6-12 scores	χ^2	*p*-value
Age						
≥60	28	18(64.3)	9	9	0.147	0.701
<60	27	16(59.3)	7	9		
Sex						
Male	34	20(58.8)	9	11	0.338	0.561
Female	21	14(66.7)	7	7		
Tumor size						
≤3 cm	25	16(64.0)	6	9	0.092	0.761
>3 cm	30	18(60.0)	10	9		
Histology						
Squamous carcinoma	35	21(60.0)	10	11	0.135	0.714
Adenocarcinoma	20	13(65.0)	6	7		
Differentiation						
Well- moderate	32	24(75.0)	11	13	5.633	0.018*
Poor	23	10(43.5)	5	5		
Lymph node metastasis						
Yes	24	11 (45.8)	7	4	4.610	0.032*
No	31	23 (74.2)	9	14		
TNM staging						
I	27	21 (77.8)	7	14	5.723	0.017*
II + III	28	13 (46.4)	9	4		

* $P < 0.05$ was statistically significant.

IHC staining showed that P53 and Ki-67 protein were both highly expressed in the nucleus of NSCLC cells and decreased in normal

Table 5
Multivariate linear regression analysis for IL-17F correlated with differentiation, lymph node metastasis, and TNM staging.

Clinicopathological factors	β	95% CI	p-value
Differentiation	0.157	−0.228 ~ 0.912	0.234
Lymph node metastasis	−0.390	−1.806 ~ 0.137	0.091
TNM staging	−0.713	−2.465 ~ -0.547	0.003*

* $P < 0.05$ was statistically significant.

Table 6
Correlation between IL-17F expression and biological markers in NSCLC tissues.

Parameters	IL-17F		r	p-value
	Positive	Negative		
CD31			−0.314	0.019*
High	15	16		
Low	19	5		
P53			−0.155	0.257
Positive	14	12		
Negative	20	9		
Ki-67			−0.191	0.162
High	16	14		
Low	18	7		
E-cadherin			0.342	0.011*
Positive	20	5		
Negative	14	16		

* $P < 0.05$ was statistically significant.

bronchial mucosa endothelial cells (47.3% *vs* 8.30%; 54.5% *vs* 16.7%; Fig. 2). No significant correlation was found between IL-17 F and P53 or Ki-67 expression in NSCLC tissues ($P > 0.05$).

Loss of E-cadherin is a hallmark of epithelial-mesenchymal transition (EMT). IHC results showed that E-cadherin was highly expressed in the membrane of normal bronchial mucosa endothelial cells while its expression obviously decreased in NSCLC cells (91.7% *vs* 45.5%; Fig. 2). There was a strong positive correlation between IL-17F and E-cadherin expression in NSCLC tissues ($r = 0.342$, $P = 0.011$; Fig. 3C-D).

4. Disscussion

IL-17A and IL-17F were both pro-inflammatory cytokines that participate in inflammatory responses [5]. The majority of studies have shown that IL-17A expression in tumor cells were positively associated with tumor metastasis and poor prognosis in NSCLC patients [10,11]. The IL-17F shares strongest homology with IL-17A, but its role in the tumorigenesis of NSCLC cells is still unclear.

It has been reported that IL-17F is produced by many types of cell lineages such as activated T cells, mast cells, basophils and vascular endothelial cells [22]. In this study, IHC staining showed that IL-17F protein was not only scattered in some immune cells and vascular endothelial cells between tumor islands, but also expressed in NSCLC cells. In addition, the positive rate and staining intensity of IL-17F in NSCLC tissues was markedly increased when compared to the normal lung tissues, indicating a close relationship between IL-17F and NSCLC development. Consistent with our findings, Huang et al. also reported an elevated expression of IL-17F in NSCLC tissues compared with normal control, but the relationships between IL-17F and clinicopathologic factors was not further explored [23].

Recent studies reported that the genetic polymorphisms of IL-17F may increase the risk of lung cancer [17,18]. Kaabachi. et al showed that patients with IL-17F 7488 G allele were more likely to be diagnosed lung cancer at advanced stage or with metastasis status in Tunisian population [17]. He et al. showed that smokers carrying homozygous variants of IL-17F (rs12203582) may increase lung cancer risk in Chinese population [18]. These studies indicate a close relationship between IL-17F and lung cancer. However, there was still lack of clinical evidences, especially from human tumor tissues to explore the relationship between IL-17F expression and the development of lung cancer.

In this study, the associations between IL-17F expression in NSCLC tissues and clinicopathologic factors were analyzed. The chi-square test showed that IL-17F expression was positively associated with tumor differentiation and negatively associated with lymph node metastasis and TNM staging, which is opposite from IL-17A function. Multivariate analysis further showed that IL-17F expression was an independent factor associated with TNM staging, suggesting that IL-17F may be a potential marker for predicting the progression of NSCLC. Consistent with our results, Tong et al. showed that IL-17F could inhibit the tumor growth in xenografted nude mice model, indicating that IL-17F may play a protective role in colon cancer progression [13]. Ding et al. showed that patients with higher tumor stage and lymph node metastasis had a significantly low ratio of serum IL-17F /VEGF, suggesting that the ratio of serum IL-17F /VEGF was negatively related to the progression of oral squamous cell carcinoma [24].

The occurrence and development of lung cancer is a complex pathological process involving multiple steps, factors and genes [25].Tumor angiogenesis, gene mutation, tumor cell proliferation and EMT were all involved in this process [26–29]. Therefore, biological markers CD31, P53, Ki-67 and E-cadherin were examined by IHC and their relationships with IL-17F were assessed.

Angiogenesis is a critical process during tumor development and regulated by a balance between pro-angiogenic and anti-angiogenic molecules [30]. IL-17A has been illustrated as a pro-angiogenic factor

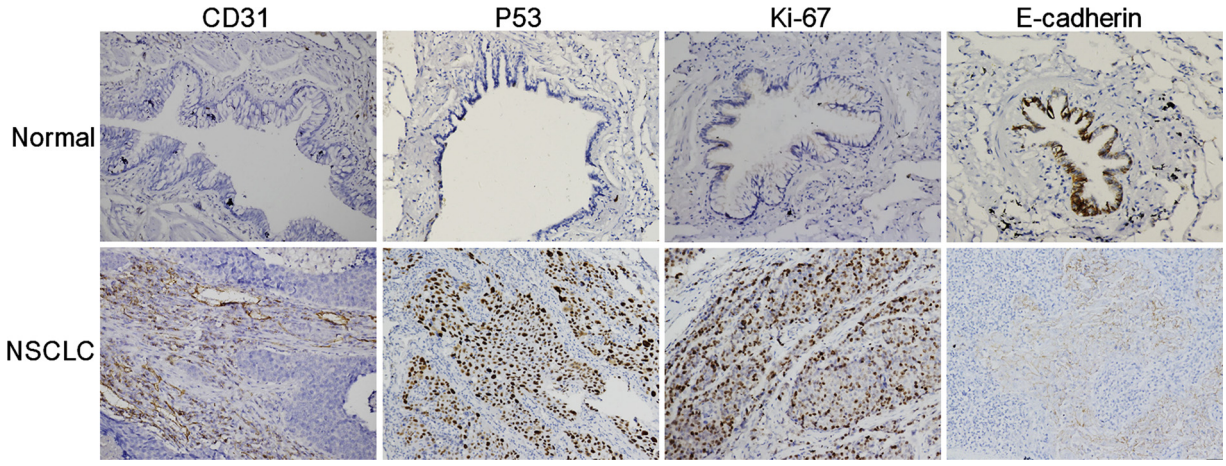

Fig. 2. IHC staining of CD31, P53, Ki-67 and E-cadherin in NSCLC and normal lung tissues. Original magnification (200 ×).

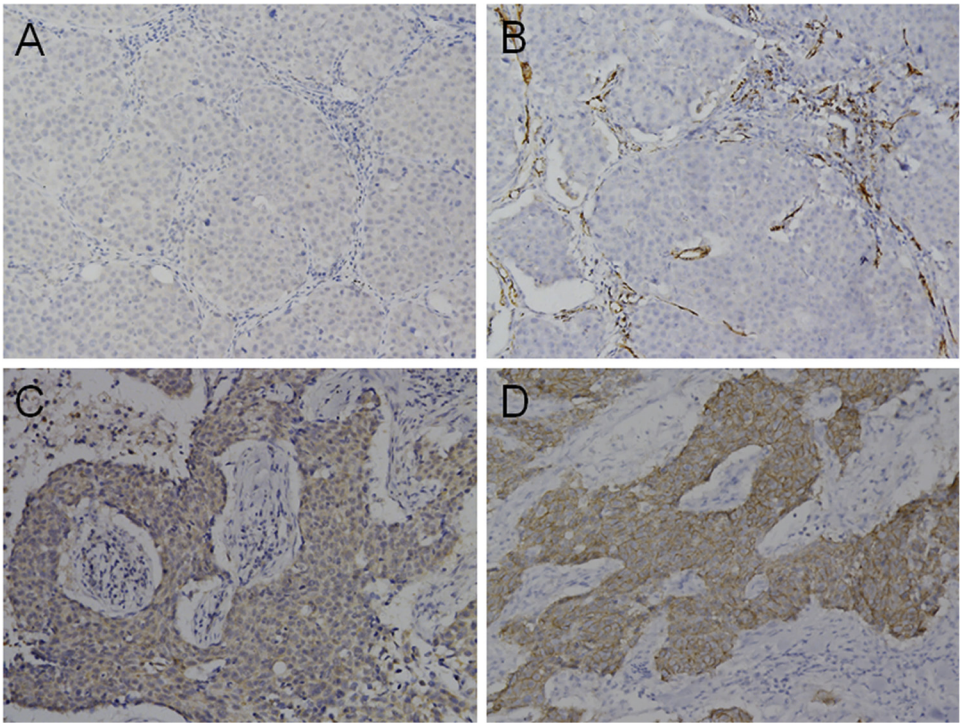

Fig. 3. Correlation between IL-17F and CD31 or E-cadherin expression in NSCLC tissues by IHC staining.
(A–B) The negative expression of IL-17F and positive expression of CD31 were simultaneously detected in NSCLC tissues; (C–D) Moderate expression levels of IL-17F and E-cadherin were simultaneously detected in NSCLC tissues. Original magnification (200 ×).

to promote lung cancer progression [11]. Conversely, IL-17F was showed to play anti-angiogenesis role in colon cancer and hepatocarcinoma [13,31]. Tong et al. found that vascular tubes and VEGF levels were increased in the colon tumor of IL-17F -deficient mice [13]. Xie et al. found that IL-17F could inhibit vascular endothelial cell growth by downregulating the expression of IL-6, IL-8 and VEGF in human hepatocarcinoma cells and decrease the MVD in nude mice model [31]. Our results showed that $CD31^+$ vascular endothelial cells were highly distributed in NSCLC tissues, and obviously increased in IL-17F negative samples compared to IL-17F positive. Statistical analysis showed a significantly negative correlation between IL-17F and MVD-CD31, suggesting that the decreased IL-17F expression in NSCLC cells may closely related to tumor angiogenesis. This finding are in agreement with the studies performed by Tong et al. and by Xie et al., and provide a clinical data to support IL-17F as an anti-angiogenic factor in NSCLC.

P53 is the most frequently mutated tumor suppressor gene in a variety of cancers [32], the mutation of P53 was detected in about 50% of lung cancer patients [33]. In this study, the mutated P53 in NSCLC tissues was about 47.3%, but the statistical analysis did not show a significant correlation between IL-17F and P53 expression. This result needs to be further confirmed in a larger cohort of patients.

The multistep process of carcinogenesis is also based on cell proliferation [34]. Ki-67 has been used as a key marker to evaluate proliferative activity and predict poor survival in NSCLC and other cancers [35,36]. In this study, Ki-67 was overexpressed in NSCLC tissues, but no significant correlation was found between IL-17F and Ki-67 expression. These data suggest that IL-17F may have no relationship with the proliferation of NSCLC cells, and this conclusion also need to be further clarified.

EMT with loss of cell adhesion is also a key event in local invasion and distant metastasis of tumor [37,38]. E-cadherin is highly expressed in epithelial cells and its absent expression results in reduced cell-cell connections and enhanced cellular mobility. Loss of E-cadherin has been considered to be a major hallmark of EMT. E-cadherin plays strong anti-invasive and anti-metastatic role, downregulation of E-cadherin has been observed in tumor cells and is related to poor prognosis in many cancers [39]. Reka et al. reported that IL-17A-treated A549 lung cancer cells diminished the expression of E-cadherin, and IL-17 A may promote the migration and invasion of A549 cells by inducing EMT [40]. In this study, E-cadherin expression was obviously decreased in NSCLC tissues, and a significantly positive correlation between IL-17F and E-cadherin, suggesting that IL-17F may play an important role in the process of EMT. It is can be inferred from the results that the lower the IL-17F expressed, the lower E-cadherin expressed, which leads to the occurrence of EMT and ultimately causes the progression of NSCLC.

Inevitably, some limitations are existed in this study. First is a small study with 55 tissues samples with NSCLC. Another limitation is the fact that the evaluation of the expression of IL-17F and other markers were done using only IHC. Therefore, more and larger studies are needed to reinforce these data and the role of IL-17F in NSCLC.

Taken together, our findings for the first time elucidated the biological role of IL-17F in NSCLC cells. IL-17F may be a potential marker for predicting the progression of NSCLC and serve as a therapeutic target for NSCLC therapy.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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