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Prognostic significance of IFITM1 expression and correlation with microvessel density and epithelial–mesenchymal transition signature in lung adenocarcinoma

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ABSTRACT

We evaluated the relationship between interferon-induced transmembrane protein 1 (IFITM1) expression, epithelial–mesenchymal transition (EMT) signature and angiogenesis in lung adenocarcinoma. Additionally, we examined prognostic significance of IFITM1 according to pTNM stage to confirm that IFITM1 can serve as a complement to the pTNM stage. A total of 141 lung adenocarcinoma specimens were evaluated retrospectively by immunohistochemical staining for IFITM1, EMT markers (e-cadherin, β-catenin, and vimentin), and CD31 to measure microvessel density. IFITM1was expressed in 46.8% of the specimens. IFITM1 expression was significantly correlated with increased microvessel density ($P = 0.048$). However, IFITM1 expression was not associated with three EMT markers. In a multivariate analysis, IFITM1 was an independent prognostic factor for overall survival in a multivariate analysis (hazard ratio: 2.59, $P = 0.01$). Online database with data from 720 lung adenocarcinoma patients also revealed a negative prognostic significance of IFITM1 ($P < 0.001$). Furthermore, high IFITM1 expression was significantly correlated with decreased OS rates in each pTNM stage. IFITM1 is significantly correlated with angiogenesis and it may be used as a useful additional prognostic marker to aid pTNM classification.

1. Introduction

Non-small cell lung cancer (NSCLC) is a common cause of cancer-related deaths globally. Recently, surgery was performed on NSCLC of the stage I-IIIA, but 5-year survival rate was 41% in IIIA group and 56% in IIB group [1]. Adjuvant chemotherapy after surgical resection of localized NSCLC improved the survival rate at 5 years by approximately 5% [2]. However, despite receiving adjuvant chemotherapy, the risk of relapse is still relatively high [3]. If we find patients who are at a high risk of recurrence in NSCLC, these patients have the greatest benefit from adjuvant therapy, including chemotherapy, radiotherapy or personalized treatment based on molecular classification. Therefore, early detection of patients at high risk for recurrence after surgery is important in designing a personalized management strategy to reduce lung cancer mortality.

Interferon-induced transmembrane protein 1 (IFITM1) is a member of the interferon-inducible transmembrane protein family and was initially known as a leukocyte antigen, a part of the membrane complex involved in the transduction of antiproliferative and homotypic adhesion signals in lymphocytes [4–6]. Recently, IFITM1 plays an important role in tumorigenesis. IFITM1 has been shown to be highly expressed in a variety of cancers including breast [7], cervical [8], esophageal [9], ovarian [10], brain [11], and colorectal cancers [12]. Several studies reported a negative prognostic significance of IFITM1 in colorectal [12,13] and breast cancers [14]. Sari et al. reported that IFITM1 is essential for the migration of colorectal cancer cells and is involved in the maintenance of epithelial-mesenchymal transition (EMT) signature through Caveolin-1 [15]. Expression of IFITM1 promotes breast cancer cell proliferation and is associated with increased blood vessel density [14].

Our previous study revealed that IFITM1 enhanced migration and invasion of lung adenocarcinoma cells and IFITM1 expression was

Abbreviations: EMT, Epithelial-mesenchymal transition; IFITM1, interferon-induced transmembrane protein 1; MVD, microvessel density; NSCLC, non-small cell lung cancer; OS, overall survival

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associated with poor prognosis [16]. Although previous studies reported that IFITM1 induced cancer progression via induction of EMT signature and angiogenesis [14,15], no studies have evaluated the relationship between IFITM1 expression, EMT signature and angiogenesis. This retrospective study evaluated the relationship between IFITM1 expression, EMT signature and angiogenesis in lung adenocarcinoma. Additionally, we examined prognostic significance of IFITM1 in lung adenocarcinoma patients according to pTNM stage to confirm that IFITM1 can serve as a complement to the pTNM stage.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the Institutional Review Board of Ajou University School of Medicine. Inform consent was granted a waiver due to the retrospective nature of this study. All analyses were performed in accordance with ethical guidelines for clinical research at the respective institution. A total of 141 patients confirmed to have adenocarcinoma after surgical resection between January 2009 and December 2013 were consecutively collected. The case was excluded if there was no residual cancer tissue or no follow-up data. Smoking history was collected when the patient was hospitalized. Regardless of whether patients quit smoking now, if patients have smoked before, these patients were considered to be positive smoking history.

The demographic data of the patients included in this study are provided in Table 1. Patient age ranged from 35 to 86 years (median, 64 years). There were 72 (51.1%), 22 (15.6%), and 45 (31.9%) stage I, II, and III patients, respectively. Fifty-six patients experienced relapse, disease progression, or death (42 died). The median OS was 79.2 months. The estimated 5-year OS was 66.6%. The median follow-up time was 40.1 months (range: 0.5–83.9 months).

2.2. Histopathological analysis and immunohistochemistry

Histological subclassification was performed by two pathologists (YWK and JHH) according to the 2015 World Health Organization Classification of Lung Tumors [17]. The TNM stage based on the 8th edition of the AJCC Cancer Staging Manual [18]. We used tissue microarrays for immunohistochemical analysis. A representative paraffin block of a tumor section (a donor block) was prepared for each case, from which two 2-mm-diameter tumor cores were obtained using a trephine apparatus. Tissue microarrays samples were arranged in a Benchmark XT automatic immunohistochemical staining device (Ventana Medical Systems, Tucson, AZ, USA). Samples were incubated with antibody to IFITM1 (dilution 1:100, polyclonal, Genetex), e-cadhein (dilution 1:120, monoclonal, 36B5, Novocastra), vimentin (dilution 1:100, monoclonal, V9, Novocastra), β-catenin (dilution 1:50, monoclonal, β-catenin1, DAKO), and CD31 (dilution 1:50, monoclonal, JC70, Cell marque). IFITM1 intensity was evaluated on a four-point intensity scale (0, none; 1, faint; 2, moderate; 3, strong). The proportion of membranous and/or cytoplasmic expression of IFITM1 was also evaluated. The percentage of tumor cells expressing IFITMl was investigated by increasing by 10% to define the cutoff (10%, 20%, 30%, 40% …). The percentage of tumor cells expressing IFITM1 that showed the most significant difference with respect to OS was selected as the cutoff value for defining high- and low-IFITM1 groups. The cutoff that showed the most significant difference for OS was 30%. A sample was considered IFITM1 high if > 30% of definitive tumor cells showed moderate or strong immunohistochemical reactivity with the anti-IFITM1 antibody in Ref. [18] For E-cadherin, negative expression is defined as a reduction of E-cadherin membrane-stained cells to less than 50%. For vimentin, a 50% cutoff was also used to define the staining pattern. When at least 50% of tumor cells exhibited vimentin cytoplasmic staining, the tumor was considered as vimentin positive. For β-catenin, a 50% cutoff was used to define the staining pattern. When less than 50% of tumor cells exhibited β-catenin membranous staining, the tumor was considered as β-catenin negative. For microvessel counting, regions with the highest angiogenesis were selected at low magnification (×40). Counting was performed at high magnification (×400). Three fields have been examined per case. The final microvessel density (MVD) for each case was presented as the mean value of the three fields examined. Microvessel with clearly defined lumens or well-defined linear vessel shapes were selected by counting. Branching vessel structures were considered as a single vessel. If IFITM1 or EMT marker expressions differ in the two tissue microarray cores, we have chosen the average of the two tissue microarray cores.

Table 1
Demographic and clinical characteristics.

Variable	Number (%)
Age, median (range), years	62 (35–86)
Male sex	79 (56%)
Smoking history	66 (51.6%)
Operation	
Pneumonectomy	4 (2.8%)
Lobectomy	121 (85.8%)
Sublobar resection	16 (11.3%)
pT stage	
T1/T2	14 (9.9%)/117 (83%)
T3/T4	9 (6.4%)/1 (0.7%)
pN stage	
Nx/N0/N1	2 (1.4%)/87 (61.7%)/12 (8.5%)
N2/N3	38 (27%)/2 (1.4%)
pTNM 8th edition	
Stage I	72 (51.1%)
Stage II	22 (15.6%)
Stage III	45 (31.9%)
EGFR mutation	18 (51.4%)
Adjuvant chemotherapy	48 (34%)
Adjuvant radiotherapy	48 (34%)

Smoking history is collected in 128 patients. pTNM is collected in 139 patients. EGFR mutation is collected in 35 patients.

2.3. Web-based mRNA profiling

The online Kaplan–Meier plotter tool was used to assess the effect of particular gene on survival in lung cancer [19]. The online Kaplan–Meier plotter tool used mRNA expression profiling and overall survival (OS) information from GEO datasets. To analyze the prognostic information of a specific gene, patient samples were divided into two groups according to the median value of mRNA expression, and compared using the Kaplan–Meier survival plot.

2.4. Statistical analyses

OS was analyzed by Kaplan–Meier curve, which was compared by the log-rank test. Multivariate prognostic analysis of OS was performed using the Cox proportional hazards regression model. The predictors with a p value of 0.05 in univariate analysis, together with clinically important variables, were included in the final multivariate analysis. The enter method was employed to determine the final Cox model for multivariate analysis. Categorical variables were compared using the chi-squared test, and continuous variables were compared using an independent-sample t-test. All of the statistical analyses were performed using the SPSS statistical software (version 25.0; SPSS; Chicago, IL, USA), and a p value less than 0.05 was considered statistically significant.

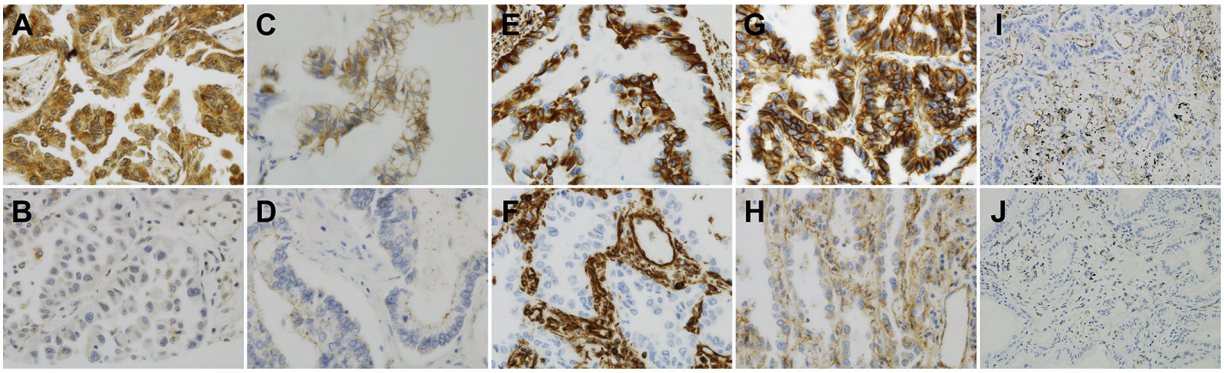

Fig. 1. IFITM1, e-cadherin, vimentin, β-catenin and CD31 expression in lung adenocarcinoma. (A) Positive IFITM1 cytoplasmic expression on tumor cells. (B) Negative IFITM1 cytoplasmic expression on tumor cells. (C) Positive e-cadherin membranous expression on tumor cells. (D) Negative e-cadherin membranous expression on tumor cells. (E) Positive vimentin cytoplasmic expression on tumor cells. (F) Negative vimentin cytoplasmic expression on tumor cells. (G) Positive β-catenin membranous expression on tumor cells. (H) Negative β-catenin membranous expression on tumor cells. (I) High microvessel density with CD31 expression on tumor. (J) Low microvessel density with CD31 expression on tumor.

3. Results

3.1. IFITM1, EMT markers, and microvessel density in adenocarcinoma tissues

Sixty-six (46.8%) patients showed cytoplasmic and membranous positivity for IFITM1 (Fig. 1A and B). Thirty-two (22.6%) patients showed negative membranous expression for e-cadherin (Fig. 1C and D). Seventeen (12%) patients showed positive cytoplasmic expression for vimentin (Fig. 1E and F). Six (4.2%) patients showed negative membranous expression for β-catenin (Fig. 1G and H). The mean MVD of all cases was 12.02 ± standard deviation (SD) 5.53 (range, 3–26) (Fig. 1I and J). 94.3% (133/141) of adenocarcinoma cells were positive for IFITM1 in endothelial cells.

3.2. Correlation among IFITM1, EMT markers, and microvessel density

The mean MVD of tumors with high IFITM1 was significantly higher than that of tumors with low IFITM1 (13 ± 5.74 vs. 11.14 ± 5.21, $P = 0.048$; Fig. 2). However, IFITM1 expression was not significantly associated with e-cadherin expression ($P = 0.546$), β-catenin expression ($P = 0.419$) and vimentin expression ($P = 0.067$) (Table 2). IFITM1 positivity was not correlated with other clinicopathologic variables including histologic subtype, pathologic stage, lymphovascular invasion, spread through air spaces, EGFR mutation and smoking history (Table 2).

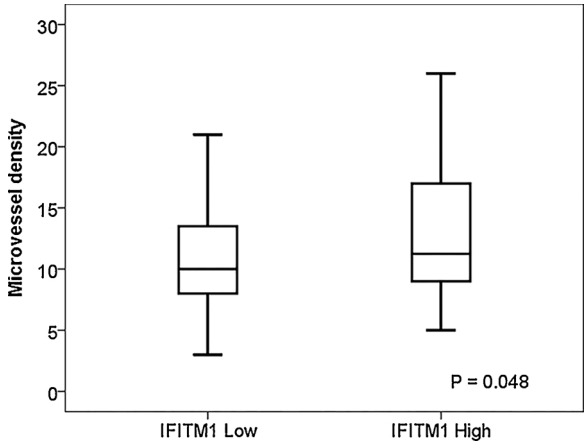

Fig. 2. Correlation between IFITM1 and microvessel density in adenocarcinoma patients.

Table 2
Correlation of IFITM1 expression with pathologic characteristics, e-cadherin, vimentin, and β-catenin expression.

Characteristic	IFITM1 expression		p
	Negative ($n = 75$)	Positive ($n = 66$)	
Predominant histologic subtype			0.119[a]
Acinar	36 (48%)	35 (53%)	
Lepidic	5 (6.7%)	0 (0%)	
Papillary	11 (14.7%)	14 (21.2%)	
Micropapillary	2 (2.7%)	3 (4.5%)	
Solid	15 (20%)	13 (19.7%)	
Mucinous	6 (8%)	1 (1.5%)	
Lymphovascular invasion			0.065[b]
Negative	47 (62.7%)	31 (47%)	
Positive	28 (37.3%)	35 (53%)	
Spread through air spaces			> 0.999[b]
Negative	47 (62.7%)	41 (62.1%)	
Positive	28 (37.3%)	25 (37.9%)	
pTNM 8th edition			0.447[b]
Stage I	42 (56.8 %)	30 (46.2%)	
Stage II	10 (13.5%)	12 (18.5%)	
Stage III	22 (29.7%)	23 (35.4%)	
Smoking history			0.382[b]
Negative	35 (52.2 %)	27 (44.3%)	
Positive	32 (47.8 %)	34 (55.7%)	
EGFR mutation			0.499[b]
Wild type	6 (40 %)	11 (55%)	
Mutation	9 (60%)	9 (45%)	
E-cadherin expression			0.546[b]
Negative	19 (25.3 %)	13 (19.7%)	
Positive	56 (74.7%)	53 (80.3%)	
β-catenin expression			0.419[b]
Negative	2 (2.7 %)	4 (6.1%)	
Positive	73 (97.3%)	62 (93.9%)	
Vimentin expression			0.067[b]
Positive	13 (17.3 %)	4 (6.1%)	
Negative	62 (82.7%)	62 (93.9%)	

[a] Chi-squared test by two-sided Fisher's exact test.
[b] Chi-square test by two-sided Pearson's exact test.

3.3. Prognostic significance of IFITM1 expression

High IFITM1 patients with adenocarcinoma had a lower 5-year overall survival (OS) rate than low IFITM1 patients (52% vs. 78%, $p < 0.001$; Fig. 3A). We further assessed the prognostic value of IFITM1 expression in adenocarcinoma using the online tool kmplot.com [19]. In concordance with our findings, Kaplan–Meier survival analysis of data for 720 lung adenocarcinoma patients revealed decreased OS

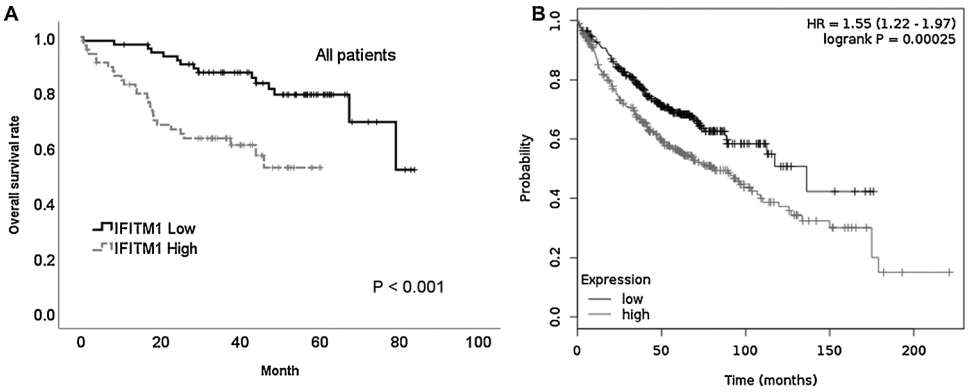

Fig. 3. Comparison of survival rates according to IFITM1 expression (A) adenocarcinoma patients in our study. (B) adenocarcinoma patients using the online tool kmplot.com.

Table 3
Multivariate analyses of overall survival in patients with adenocarcinoma.

	Overall survival		
Variables	HR	95% CI	*p*
Age (< 65 vs. ≥65)	1.152	0.577–2.300	0.688
Sex (female vs. male)	2.921	0.886–9.623	0.078
Smoking history (− vs. +)	1.015	0.331–3.118	0.979
Pathologic stage			
II (vs. I)	2.332	0.924–5.883	0.073
III (vs. I)	3.141	1.463–6.743	0.003
IFITM1 expression (− vs. +)	2.590	1.250–5.364	0.01

CI: confidence interval, HR: hazard ratio.

rates for patients with high expression levels of IFITM1 compared with patients with low expression levels of IFITM1 expression ($P < 0.001$; Fig. 3B). Univariate analysis of IFITM1 patients revealed that OS was associated with age, sex, smoking history and pathologic stage. In multivariate analysis, IFITM1 expression was an independent prognostic marker for OS in adenocarcinoma (hazard ratio = 2.59, $P = 0.01$; Table 3).

Nextly, we performed subgroup analysis according to pTNM stage to confirm that IFITM1 can serve as a complement to the pTNM stage. In stage I and II, high IFITM1 expression was significantly correlated with decreased OS rates ($P = 0.029$; Fig. 4A and $P = 0.031$; Fig. 4B). Although high IFITM1 expression was correlated with decreased OS rates in stage III, statistical significance was not achieved ($P = 0.052$; Fig. 4C). When we perform subgroup analyses according to substage (IA, IB, IIA …), IFITM1 was associated with inferior overall survival rate in stage IB ($P = 0.015$). However, IFITM1 was not associated with overall survival rate in other substage.

4. Discussion

Our study provides several novel findings. First, it shows the correlation between IFITM1 expression and MVD, characterized by CD31 expression in lung adenocarcinoma patients. Secondly, IFITM1 expression was able to distinguish patients with poor prognosis in each pTNM stage. These results suggest that IFITM1 expression may promote tumor progression through enhancing tumor angiogenesis in lung adenocarcinoma and it may be used as a useful adjunct marker to help pTNM classification.

Other studies have also found an important role for IFITM1 in tumor angiogenesis. Previous study reported that blood vessel endothelial cells in several adult organs express IFITM1 [20] and IFITM1 may be a potential pan-endothelial marker [21]. Popson et al. reported that IFITM1 is essential for blood vessel formation and stabilizes endothelial cell interactions during endothelial lumen formation by regulating junctional stability [22]. Lui et al. reported that loss of IFITM1 significantly reduced angiogenesis in xenograft models of human breast cancer in mice, as demonstrated by CD31 staining [14]. Zoledronate, a potent inhibitor of angiogenesis, restrains IFITM1 expression in endothelial cells [23]. In our study, most adenocarcinoma showed IFITM1 positivity on endothelial cells. Furthermore, our study revealed that IFITM1 expression on tumor cells was correlated with high MVD. Although it is not known as to which pathway the expression of IFITM1 in tumor cells affects angiogenesis, our results suggest that inhibition of IFITM1 can be a new therapy to block angiogenesis.

Several studies have reported a negative effect of IFITM1 on cancer prognosis. The patients with higher IFITM1 expression had worse overall survival outcomes than those with lower IFITM1 expression in colorectal cancer [12,13]. IFITM1 expression was positively correlated with lymph node and distance metastasis and advanced clinical stage in colorectal cancer [12]. In breast cancer, IFITM1 expression correlated with increased clinical stage and increased risk of recurrence during endocrine therapy [14]. However other studies have shown that IFITM1

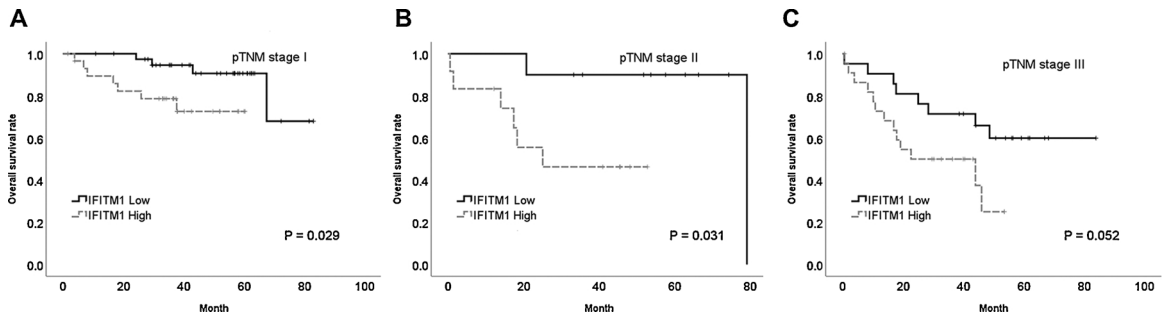

Fig. 4. Comparison of survival rates according to IFITM1 expression and pTNM stage (A) adenocarcinoma patients in stage I. (B) adenocarcinoma patients in stage II. (C) adenocarcinoma patients in stage III.

expression has a rather beneficial prognosis. In gastric cancer, IFITM1 expression had a positive impact on time to recurrence [24]. IFITM1 expression was significantly elevated in patients without distant metastases [24]. IFITM1 expression correlated with improved survival in chronic myeloid leukemia patients [25]. In lung adenocarcinoma, our study and online database with 720 lung adenocarcinoma patients revealed a negative prognostic impact of IFITM1. IFITM1 has been rarely studied in malignant tumor including lung adenocarcinoma yet, so other studies need to validate the prognostic impact of IFITM1 expression in cancer.

Although IFITM1 expression is associated with the progression of several types of aggressive cancer, the mechanism by which IFITM1 promotes tumor progression is unclear. IFITM1 has been linked to proliferation, migration and invasion of cancer cell. IFITM1 promoted the migration and invasion capacity of colorectal or breast cancer cells [7,12,14,15]. IFITM1 has a role in DNA damage resistance that contributes to the failure of treatment of cancer. IFITM1 was constitutively overexpressed in aromatase inhibitor-resistant breast cancer cells [26]. The expression of IFITM1 was increased in oral cancer cell lines when dose and radiation time were increased [27].

In colorectal cancer, IFITM1 was required for the expression of EMT signature, which plays an important role in cell invasion [15]. However, in our study, there was no correlation between IFITM1 expression and EMT markers. In our study, the rate of β-catenin negative expression is 4% and the rate of vimentin positive expression is 12%. EMT phenotype positive ratio is very low, so it is not easy to obtain statistically significant results. Therefore, a further large-scale study will be needed to evaluate the roles of IFITM1 in EMT phenotype.

The limitations of this study include its retrospective design and relatively small sample size. Because of the heterogeneous distribution of immunohistochemical staining, tissue microarray design is difficult to reflect the entire tumor section.

In conclusion, IFITM1 expression is an independent negative prognostic factor for OS in lung adenocarcinoma. IFITM1 may be used as a useful additional prognostic marker to aid pTNM classification because IFITM1 expression could further distinguish patients with poor prognosis at each pTNM stage. Furthermore, IFITM1 expression is correlated with increased microvessel density. The IFITM1-angiogenesis pathway may provide further insight into tumor progression in lung adenocarcinoma.

Competing interests

The authors declare that they have no competing interests.

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