Interferon (Alpha, Beta and Omega) Receptor 2 Is a Prognostic Biomarker for Lung Cancer

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Key Words

Interferon (alpha, beta and omega) receptor 2 · Cell surface antigen · Biomarker · Lung cancer

Abstract

Objectives: It has been reported that the type I interferon receptor subunit, interferon (alpha, beta and omega) receptor 2 (IFNAR2), is overexpressed in several malignancies, primarily adenocarcinomas (ADCs); however, the biological significance of IFNAR2 in human lung cancer has not yet been studied. **Methods:** Immunohistochemical analysis of 113 surgically resected lung specimens was performed, and the results were evaluated in association with clinical variables, including survival. Serum concentrations of IFNAR2 were also determined by an enzyme-linked immunosorbent assay in 157 lung cancer patients and 164 healthy volunteers. **Results:** IFNAR2 overexpression was observed in all histological types of lung cancer examined. Furthermore, strong IFNAR2 expression was associated with shorter progression-free survival (PFS) and overall survival (OS) ($p < 0.0001$ and $p = 0.0110$, respectively) in non-small cell lung cancer patients. Multivariate analyses confirmed its independent

prognostic value for PFS and OS ($p < 0.0001$ and $p = 0.0222$, respectively). IFNAR2 serum levels were also significantly higher in lung cancer patients than in healthy volunteers ($p < 0.0001$). **Conclusions:** IFNAR2 overexpression was observed in various histological types of lung cancer, and appears to be associated with lung cancers that behave aggressively. The results of this study strongly support the potential of IFNAR2 to be a prognostic biomarker for lung cancer.

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Introduction

Lung cancer is the leading cause of cancer death in the world. Among various histological types of lung cancer, approximately 80% of the cases are non-small cell lung cancer (NSCLC), whereas small cell lung cancer (SCLC) accounts for approximately 15% [1]. Regardless of histological subtype, the 5-year survival rate of lung cancer patients is around 10–15% [2]. About 30% of NSCLC patients can undergo curative resection, and the remaining patients are mainly treated with chemotherapy alone or in combination with radiation therapy. Novel therapeutic

strategies based on the biological characteristics of tumor cells in addition to TNM staging are expected to improve survival in lung cancer patients [3, 4].

Because cell surface proteins are considered more accessible to host immune response and drug intervention, the identification of cancer-specific cell surface and/or secretory proteins is likely to be an effective approach for discovering novel diagnostic markers and developing therapeutic strategies [5]. Furthermore, if cancer-specific proteins are in patient sera, they become easily accessible molecular markers. We and other researchers have been screening for biomarkers, mainly concentrating on cell surface and/or secretory proteins that are upregulated in lung cancer. In the process, we have identified various diagnostic and/or prognostic biomarkers for lung cancer [5–9].

The type I interferons (IFNs), which have many biological functions, are mediated by the type I IFN receptor [10–13]. This cell surface receptor is composed of two functional transmembrane proteins, IFN [α , β and ω receptor 1 (IFNAR1)] and IFNAR2. IFNAR2 is the major binding receptor and IFNAR1 is necessary for tight binding. Overexpression of IFNAR2 has been reported in several types of malignancies, primarily adenocarcinomas (ADCs) [14–25], but the biological significance of IFNAR2 in human lung cancer has not yet been studied.

We hypothesized that IFNAR2 overexpression in lung cancer might be associated with malignant potential. IFNAR2 expression was examined in 113 human lung cancer tissues and the results were evaluated in association with clinical variables, including survival. IFNAR2 serum levels were determined in samples from 157 lung cancer patients and 164 healthy volunteers, and the results were also evaluated in association with clinical variables.

Material and Methods

Clinical Tissue Samples

In this study, lung cancer tissue samples were obtained from 113 patients with NSCLC who underwent curative surgery at Hiroshima University (Hiroshima, Japan) between 2000 and 2008. Patient inclusion criteria were similar to those described in previous studies [7–9]. In brief, they were as follows: (1) age ≥ 20 years, (2) newly diagnosed, untreated NSCLC, (3) patients undergoing curative surgery, (4) no significant abnormalities in liver or kidney function and (5) absence of hepatitis C virus infection. The final diagnosis of NSCLC was made histologically on surgically excised tissues using WHO criteria [26]. Postsurgical pathologic TNM staging was performed according to the guidelines of the

American Joint Committee on Cancer [27]. For postoperative adjuvant chemotherapy, oral administration of tegafur and uracil was chosen for patients with pathologic stage IB ADC, and platinum-based chemotherapy was chosen for patients with histologically confirmed lymph node metastases. Written informed patient consent and approval by the research ethics committees from participating hospitals were obtained for this study.

Serum Samples and Patient Characteristics

Serum samples from 157 lung cancer patients and 164 healthy volunteers admitted to Hiroshima University Hospital and its affiliated hospitals between 2000 and 2008 were obtained at the time of diagnosis and stored at -80°C . Disease staging in all 157 cases included computed tomography scans of the chest and abdomen, bone scintigraphy, or ^{18}F fluorodeoxyglucose positron emission tomography and magnetic resonance imaging of the head. The healthy volunteers had no abnormalities in routine laboratory tests and examinations, which included complete blood cell counts, C-reactive protein level, erythrocyte sedimentation rate, liver function tests, renal function tests, urinalysis, fecal examination, chest X-rays and an electrocardiogram.

Immunohistochemistry

Immunohistochemical analysis of IFNAR2 expression was performed on tissue sections from paraffin blocks of primary lung tumors and normal human tissues as previously described [28–32]. Antigens were retrieved by heating the sections in Target Retrieval Solution, Citrate pH 6 (DAKO Japan, Tokyo, Japan). ENVISION+ kits/horseradish peroxidase (DAKO Japan) were used for immunostaining according to the manufacturer's instructions. Mouse monoclonal anti-IFNAR2 antibodies (kindly provided by Otsuka Pharmaceuticals, Tokushima, Japan) or mouse isotype control (Zymed Laboratories, San Francisco, Calif., USA) were added to each slide after endogenous peroxidase and proteins had been blocked. The sections were then incubated with HRP-labeled anti-mouse IgG (DAKO Japan) followed by the reaction with a DAB substrate-chromogen solution (DAKO Japan) for 10 min, and were counterstained with hematoxylin. Three independent investigators assessed IFNAR2 staining patterns without prior knowledge of the clinicopathological data. The expression of IFNAR2 in cancer cells was certified when the staining of cytoplasm and/or plasma membrane was observed. When less than 10% of the cancer cells were stained, the expression of IFNAR2 was considered to be absent (score 0). When 10–75% and more than 75% of cancer cells were stained, the expression of IFNAR2 was recognized as weakly positive (score 1+) and strongly positive (score 2+), respectively. The unmatched or equivocal cases were reexamined, and the consensus category was decided by the three investigators.

ELISA

Serum levels of IFNAR2 were measured by a sandwich ELISA from a kit kindly provided by Otsuka Pharmaceuticals [24, 25, 33].

Statistical Analysis

The data were analyzed using a statistical software package (SPSS for Windows version 15.0, SPSS Inc., Chicago, Ill., USA). Contingency tables were used to analyze the relationship between IFNAR2 expression levels and clinicopathological variables. Progression-free survival (PFS) was defined as the interval starting from the date of the operation or the blood sampling and ending

at the date of documented disease progression, death from any cause or the last follow-up. Overall survival (OS) was defined as the interval starting from the date of the operation or the blood sampling and ending at the date of death from any cause or the last follow-up. Survival data were analyzed, 95% confidence intervals (CIs) were estimated by the Kaplan-Meier method and differences between groups were compared by a log-rank test. Risk factors associated with patient prognosis were evaluated using the Cox proportional hazards regression model with a stepdown procedure. Univariate and multivariate analyses were performed with the Cox proportional hazards regression model to determine associations between clinicopathological variables and cancer-related mortality. First, the associations between death and possible prognostic factors, including age, gender, histological type, pT and pN classification, were analyzed, taking into consideration one factor at a time. Second, multivariate Cox analysis was applied in backward stepwise procedures that forced IFNAR2 expression into the model, along with any and all variables that satisfied an entry level of $p < 0.05$. As factors were added to the model, independent factors did not exceed an exit level of $p < 0.05$.

Results

IFNAR2 Expression in Lung Cancer Tissues and Its Association with Clinical Characteristics

To determine whether IFNAR2 is overexpressed in NSCLC tissues and whether IFNAR2 expression is associated with clinical characteristics in NSCLC patients, an immunohistochemical analysis of IFNAR2 expression was performed on surgically resected tissues from 113 NSCLC cases. As shown in figure 1a, the strong staining in the cytoplasm and the weak staining in the plasma membrane were observed in cancer cells. In addition, a weak expression of IFNAR2 was also detected in both the lymphocytes and stromal cells around the cancer tissue (fig. 1b). There were 21 (18.6%), 40 (35.4%) and 52 (46.0%) cases scored as 0, 1 and 2, respectively (table 1). Positive staining (scored as 1 and 2) was observed in 74.7% (62 of 83) of ADC cases examined, 100% (21 of 21) of squamous cell carcinomas (SCCs), 100% (1 of 1) of large-cell carcinomas and 100% (9 of 9) of adenosquamous cell carcinomas, while no staining was observed in any of the normal epithelial portions of the same tissues. The association between IFNAR2 status and clinicopathological variables was evaluated. Histological type (other histology vs. ADC; $p = 0.0027$ by the Fisher exact test) and pT classification (pT1 vs. pT2 + 3; $p = 0.0245$) were significantly associated with IFNAR2 status.

Association of Strong IFNAR2 Expression with Poor Clinical Outcomes for Patients with NSCLC

The PFS and OS of patients with strong IFNAR2 expression were significantly poorer than seen in the

Table 1. Association between characteristics and IFNAR2 positivity in patients with surgically resected NSCLC

	Patients (total) n = 113	IFNAR strongly positive n = 52	IFNAR weakly positive n = 40	IFNAR absent n = 21	p value (strong vs. weak/absent)
Gender					
Male	74	37	27	10	0.3211
Female	39	15	13	11	
Age					
<65 years	49	22	18	9	0.8513
≥65 years	64	30	22	12	
Histological type					
ADC	83	31	31	21	0.0027 ^{a, *}
SCC	20	13	7	0	
Others	10	8	2	0	
pT factor					
T1	61	22	22	17	0.0245*
T2 + 3	52	30	18	4	
pN factor					
N0 + 1	102	46	37	19	0.7518
N2	11	6	3	2	
Smoking history					
Never	38	16	13	9	0.6898 ^b
Former	34	16	11	7	
Current	41	20	16	5	

* $p < 0.05$ (by Fisher exact test). Others = Large-cell carcinoma plus adenosquamous cell carcinoma; NS = no significance.

^a ADC versus other histology.

^b Never versus others.

cases with absent/weak IFNAR2 expression ($p < 0.0001$ and $p = 0.0110$, respectively, by a log-rank test) (fig. 2a, b). Therefore, in order to determine the prognostic importance of the clinical characteristics and IFNAR2 expression status, a Cox proportional hazards regression analysis of the parameters listed in tables 2 and 3 was performed. Univariate analyses revealed that strong IFNAR2 expression (odds ratio 3.933, 95% CI 1.937–7.986, $p = 0.0002$), histological type (odds ratio 1.434, 95% CI 1.028–2.000, $p = 0.0339$), pT stage (odds ratio 2.271, 95% CI 1.166–4.421, $p = 0.0158$) and pN stage (odds ratio 9.140, 95% CI 4.111–20.319, $p < 0.0001$) were significant prognostic factors for PFS. Strong IFNAR2 expression (odds ratio 3.286, 95% CI 1.244–8.679, $p = 0.0164$), histological type (odds ratio 1.589, 95% CI 1.007–2.509, $p = 0.0466$) and pN stage (odds ratio 11.743, 95% CI 3.963–34.791, $p < 0.0001$) were significant prognostic factors for OS (table 4). A multivariate analysis for PFS in NSCLC patients

Fig. 1. a Representative examples of IFNAR2 staining patterns for strong, weak or absent IFNAR2 expression in lung cancer tissues and negative control staining are shown (×200 and ×400). **b** Weak expression of IFNAR2 was detected in lymphocytes (arrows) and stromal cells (arrowheads) around cancer tissue.

demonstrated that strong IFNAR2 expression (odds ratio 4.659, 95% CI 2.208–9.830, $p < 0.0001$) and pN stage (odds ratio 11.800, 95% CI 4.701–29.623, $p < 0.0001$) were independent prognostic factors. Another multivariate analysis revealed that strong IFNAR2 expression (odds ratio 3.143, 95% CI 1.178–8.387, $p = 0.0222$) and pN stage (odds ratio 12.357, 95% CI 4.134–36.933, $p < 0.0001$) were independent prognostic factors for OS in these patients.

To further evaluate the prognostic value of IFNAR2 expression in cancer tissue, we conducted subgroup analyses based on tumor stage and histological type. As shown in figure 2c and d, strong IFNAR2 expression was found to associate with shorter PFS than absent/weak

IFNAR2 expression regardless of the tumor stage (stage IA $p = 0.003$, stage IB–IIIA $p = 0.017$, respectively). Strong IFNAR2 expression was also associated with shorter PFS than absent/weak IFNAR2 expression in the patients with ADC ($p < 0.0001$) but not in the patients with non-ADC (fig. 2e, f).

Serum Levels of IFNAR2 in Patients with Lung Cancer

Whether or not IFNAR2 was secreted into the sera of patients with lung cancer was examined by IFNAR2 ELISAs of samples from 157 patients and 164 healthy volunteers (fig. 3a); the mean serum level of IFNAR2 in the

Fig. 2. Association between IFNAR2 expression in cancer tissue and prognosis in surgically resected NSCLC patients. PFS (a) and OS (b) in the 113 NSCLC patients, and PFS analyzed in the subgroup restricted to the patients with stage IA (c), stage IB-III A (d), ADC (e), or non-ADC (f) are shown. Differences between the 2 groups were evaluated using a log-rank test. Number at risk is the number of patients whose follow-up continued at each time point.

Table 2. Cox proportional hazards model analysis of PFS in patients with surgically resected NSCLC

Variables	Hazard ratio	95% CI	Unfavorable/favorable	p value
Univariate analysis				
IFNAR2	3.933	1.937–7.986	strong/weak or absent	0.0002*
Age (years)	0.986	0.514–1.890	≥65/<65	0.9652
Gender	1.095	0.776–1.545	male/female	0.6069
Histological type	1.434	1.028–2.000	others/ADC	0.0339*
pT factor	2.271	1.166–4.421	pT2 + 3/T1	0.0158*
pN factor	9.140	4.111–20.319	pN2/N0 + 1	<0.0001*
Smoking history	1.060	0.751–1.495	smoker/never-smoker	0.7418
Multivariate analysis				
IFNAR2	4.659	2.208–9.830	strong/weak or absent	<0.0001*
Histological type	1.045	0.741–1.473	others/ADC	0.8025
pT factor	1.360	0.660–2.804	pT2 + 3/T1	0.4051
pN factor	11.800	4.701–29.623	pN2/N0 + 1	<0.0001*

* p < 0.05.

Table 3. Cox proportional hazards model analysis of OS in patients with surgically resected NSCLC

Variables	Hazard ratio	95% CI	Unfavorable/favorable	p value
Univariate analysis				
IFNAR2	3.286	1.244–8.679	strong/weak or absent	0.0164*
Age (years)	1.473	0.579–3.747	≥65/<65	0.4165
Gender	1.173	0.722–1.905	male/female	0.5194
Histological type	1.589	1.007–2.509	others/ADC	0.0466*
pT factor	1.891	0.757–4.722	pT2 + 3/T1	0.1723
pN factor	11.743	3.963–34.791	pN2/N0 + 1	<0.0001*
Smoking history	1.125	0.693–1.826	smoker/never-smoker	0.6348
Multivariate analysis				
IFNAR2	3.143	1.178–8.387	strong/weak or absent	0.0222*
Histological type	1.366	0.861–2.168	others/ADC	0.1854
pN factor	12.357	4.134–36.933	pN2/N0 + 1	<0.0001*

* p < 0.05.

patients was 1.55 ± 0.72 ng/ml (mean $\pm$ SD) and in healthy volunteers 1.09 ± 0.44 ng/ml ($p < 0.0001$, by the Mann-Whitney U test). When classified according to histological type, the serum levels of IFNAR2 were 1.54 ± 0.70 ng/ml in ADC patients, 1.54 ± 0.79 ng/ml in SCC patients and 1.59 ± 0.71 ng/ml in SCLC patients (fig. 3a). Differences were significant between ADC patients and healthy volunteers ($p < 0.0001$, Mann-Whitney U test), between SCC patients and healthy volunteers ($p = 0.0025$), and between SCLC patients and volunteers ($p = 0.0009$).

Receiver-operating characteristic curve analysis of the IFNAR2 data from these 157 lung cancer patients and 164

healthy volunteers was performed to determine the ELISA cutoff level that provided optimal diagnostic accuracy and likelihood ratios (minimal false-negative and false-positive results). A value of 1.81 ng/ml had a sensitivity of 25.4% (40 of 157 lung cancer patients) and a specificity of 93.3% (11 of 164 healthy volunteers). To evaluate the potential of serum IFNAR2 as a cancer-specific biomarker, the relationships between serum IFNAR2 positivity and patient characteristics were examined. As shown in table 4, serum IFNAR2 positivity was significantly associated with age and distant organ metastases in lung cancer patients ($p = 0.0296$ and $p = 0.0107$, respectively, by the Fisher exact test).

Fig. 3. a Serum levels of IFNAR2 were determined by ELISA in lung cancer patients and in healthy volunteers (normal). Distribution of IFNAR2 in sera from patients with lung ADC, SCC and SCLC. Averaged serum levels are shown as black lines. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (vs. normal volunteers, Mann-Whitney U test). **b** Comparison between the serum IFNAR2 level (ng/ml) and the expression of IFNAR2 in the tumor tissues from patients with ADC and adenosquamous cell carcinoma (ASC).

To determine whether there was a relationship between the serum and expression levels of IFNAR2 in a tumor, the two levels were compared in 8 NSCLC patients whose sera had been collected before surgery (4 patients with IFNAR2-positive tumors and 4 with IFNAR2-neg-

ative tumors). Although the analysis was performed in a limited number of patients, the serum levels of IFNAR2 showed a trend of correlating with the expression levels of IFNAR2 in the tumors (fig. 3b).

Table 4. Association between serum IFNAR2 levels and clinical characteristics in patients with NSCLC

Variables	Patients (total) n = 157	Circulating IFNAR2, pg/ml		p value
		high level (≥1.81 ng/ml) n = 41	low level (<1.81 ng/ml) n = 116	
Age				0.0296*
<65 years	69	12	57	
≥65 years	88	29	59	
Gender				0.8456
Male	107	29	78	
Female	50	12	38	
Histological type				0.2683 ^a
ADC	93	21	72	
SCC	35	9	26	
SCLC	29	11	18	
pT factor				0.3627
T1 + 2	84	19	65	
T3 + 4	73	22	51	
pN factor				0.9999
N0 + 1	63	16	47	
N2 + 3	94	25	69	
pM factor				0.0107*
M0	85	15	70	
M1	72	26	46	
Smoking history				0.4200 ^b
Never	43	9	34	
Former	28	8	20	
Current	86	24	34	

* p < 0.05 (by Fisher exact test).
^a ADC versus others.
^b Never versus others.

Discussion

In this study, we found that IFNAR2 was detectable by immunohistochemistry in all histological types of lung cancer specimens. Strong IFNAR2 expression in lung cancer tissue was shown to correlate with poor prognosis. In addition, serum levels of IFNAR2 were significantly higher in patients with lung cancer than in healthy volunteers. These results support the hypothesis that IFNAR2 can serve as a prognostic biomarker in lung cancer.

IFNAR2 is a type I membrane protein that forms one of the two chains of the receptor for alpha and beta interferons. When IFN binds to the receptors, IFNAR-associated JAK tyrosine kinases are activated, followed by the phosphorylation of signal transducer and activation of

transcription factors (STATs) 1, 2 and 3. Recent studies have revealed that mutant epidermal growth factor receptor proteins selectively activate Akt and STAT pathways, which are important in NSCLC cell survival [34]. Furthermore, it was recently reported that nearly 50% of early-stage NSCLCs exhibit phosphorylated STAT3 expression, which approximates the percentage of patients experiencing clinical benefit from epidermal growth factor receptor tyrosine kinase inhibitors [35]. Considered along with these results, JAK-STAT pathways that are activated via IFNAR2 may play an important role in the pathogenesis of lung cancer.

Expression of IFNAR2 has been studied in cancers including hepatocellular and renal cell carcinoma, chronic myelogenous leukemia, and pancreatic cancer [14–25]; however, the significance of IFNAR2 expression in the clinical outcomes of these cancers was variable. In addition, the association between the IFNAR2 expression levels and the response to IFN therapy is still controversial [18–21, 24, 33]. In this study, immunohistochemical analysis demonstrated that IFNAR2 expression was higher in all histological types of lung cancer compared with normal tissues. With regard to the localization of IFNAR2 in cancer cells, strong staining in the cytoplasm and weak staining in the plasma membrane were observed. This observation is consistent with the result of a previous study that demonstrated the localization of IFNAR2 in the hepatocytes of chronic hepatitis C patients which utilized the same monoclonal antibody as our study [13]. Furthermore, strong IFNAR2 expression in NSCLC tissues was found to correlate with shorter cancer-specific survival than seen in patients with tumors with weak or absent IFNAR2 expression. Even when the survival analysis was restricted to those NSCLC patients with stage IA, strong IFNAR2 expression was found to correlate with shorter PFS than absent/weak IFNAR2 expression. This result suggests that IFNAR2 expression levels in NSCLC tissues may indicate the aggressiveness of disease and be useful for selecting patients who should receive adjuvant chemotherapy. In addition, strong IFNAR2 expression was associated with shorter PFS than absent/weak IFNAR2 expression in the patients with ADC but not in the patients with non-ADC. Taking all these observations into consideration, an association between IFNAR2 expression and disease progression in lung cancer, particularly in patients with ADC, is suggested. To our best knowledge, this is the first report indicating that high IFNAR2 expression in human lung cancer has a prognostic value.

Increased serum levels of IFNAR2 have been reported in many malignancies and chronic viral infections, al-

though the biological significance of IFNAR2 in these diseases remains unclear [22–25, 33]. In this study, the serum levels of IFNAR2 in patients with lung cancer were significantly higher than in the healthy volunteers. Although the analysis was performed in a limited number of patients, the IFNAR2 serum levels showed a trend of correlating with the expression levels in the tumor tissues. Furthermore, the serum levels of IFNAR2 in patients with distant organ metastases (stage IV) were significantly higher than in patients with stage I–III disease. These results suggest that IFNAR2 may accelerate metastasis development in patients with lung cancer. However, the sensitivity of IFNAR2 for the detection of lung cancer was lower than that of conventional serum biomarkers, such as carcinoembryonic antigen and the cytokeratin 19 fragment (data not shown). It is possible that the significant difference between lung cancer patients and healthy volunteers was observed because of the extremely high serum levels of IFNAR2 in some of the patients. Furthermore, serum levels of IFNAR2 reflect the presence of inflammation and/or comorbidities. These results suggest that serum IFNAR2 may not be valuable as a diagnostic biomarker in lung cancer.

Inflammation plays an important role in various types of carcinogenesis [36]. IFNs are important inflammatory cytokines and can stimulate the proliferation, migration and differentiation or apoptosis of various cancer cells [37]. In this study, we found that IFNAR2 was also weakly expressed in both lymphocytes and stromal cells around cancer tissue. A similar observation was reported in a previous publication [14] that studied the expression of IFNAR2 in a large series of liver tissues obtained from patients with chronic hepatitis C. These results suggest that IFNAR2 expression might be upregulated at the site of inflammation. Additional studies investigating the

signaling pathways in cancer cells mediated by IFNAR2 should provide important information on the association between inflammation and carcinogenesis.

Although promising results were obtained, we are aware that this study has a number of limitations. First, we could not evaluate the association between IFNAR2 expression and inflammatory markers such as high-sensitivity C-reactive protein. Second, only Asian patients were studied. Considering that ethnicity has an effect on lung cancer treatment efficacy, we should carefully interpret the results when this monitoring system is applied to non-Asian lung cancer patients. Third, the association between IFNAR2 and JAK-STAT pathway (including pAkt or pSTAT) expression status was not evaluated. To confirm the linkage of IFNAR2 expression to this signal transduction pathway in cancer cells, another immunohistochemical study would be required. In addition, large validation studies investigating the association between IFNAR2 expression patterns in tumors and circulating IFNAR2 levels are also needed to confirm the usefulness of IFNAR2 as a prognostic biomarker.

In conclusion, we observed an elevated expression of IFNAR2 in lung cancer compared with normal tissues, and our results indicated that this was associated with aggressive lung cancer characteristics. The data reported here strongly support the potential of IFNAR2 to be a diagnostic and prognostic marker for lung cancer.

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