Clinical significance of fascin-1 and laminin-5 in non-small cell lung cancer

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ABSTRACT. Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women worldwide. Fascin-1 and laminin-5 were associated with the invasiveness and prognoses of several cancers. The expression and the serum levels of fascin-1 and laminin-5 in patients with non-small cell lung cancer (NSCLC) were analyzed in this study. The expression of fascin-1 and laminin-5 were examined in 378 patients and their serum level was measured in 154 patients. The health of all patients was followed post-surgery. The expression of fascin-1 (P = 0.000) and lanminin-5 (P = 0.001) and the serum levels of fascin-1 (P = 0.015) and laminin-5 (P = 0.046) were related to the relapse of patients with NSCLC. Both serum levels and expression of fascin-1 and laminin-5 can be used to effectively evaluate the prognoses of patients with NSCLC.

Key words: NSCLC; Fascin-1; Laminin-5

INTRODUCTION

Lung cancer was rare before the twentieth century (Page et al., 2000), but now it is the leading cause of death due to cancer in both men and women (Fitzmaurice et al., 2015). It is estimated that 1.8 million new lung cancer cases and 1.6 million lung cancer deaths (accounting for 19% of all cancer deaths) occurred in 2012 worldwide (Ferlay et al., 2013; Siegel et al., 2014; Torre et al., 2016). Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are main subtypes of lung cancer, and NSCLC accounts for approximately 80% of all lung cancer cases (Page et al., 2000). The most effective treatment of early stage NSCLC is surgery; however, most patients suffer from recurrence (Wu et al., 2015). Poor prognosis has been attributed to tumor invasion, metastasis, and recurrence. Therefore, determination of biomarkers that are relevant to the prognosis of patients with NSCLC is urgently required.

Fascin-1 is a member of the 55 kDa globular fascin family of proteins that contain four tandem fascin domains, each of which corresponds structurally to a β-trefoil fold (Machesky and Li, 2010). Fascin-1 generally localizes to protrusions underneath the plasma membrane and plays an important role in the organization of several types of actin-based structures such as filopodia, spikes, lamellipodial ribs, dendrites, and microvilli (Kureishy et al., 2002; Hashimoto et al., 2011). The overexpression of fascin-1 can decrease cell-to-cell adhesion and increase epithelial cell motility (Kureishy et al., 2002; Hashimoto et al., 2011).

Laminin-5 is an extracellular matrix (ECM) protein with a cruciform structure composed of a long arm and three short arms. The laminin-5 molecule consists of α3, β3, and γ2 chains, the latter two being unique to this isoform (Niessen et al., 1994). Laminin-5 can promote cell migration and scattering (Kikkawa et al., 1994; Zhang and Kramer, 1996). Since laminin-5 contains Epidermal Growth Factor (EGF)-like repeats in the short arms, it may interact with one of its many potential ligands to mediate diverse cellular functions, including activation of EGFR signaling, similar to integrins (Engel, 1996). Being an extracellular matrix protein, laminin-5 plays an important role in cell migration (Fukai et al., 2005) and may be relevant for disease progression from adenocarcinoma *in situ* (AIS) to lepidic predominant adenocarcinoma (LPA) of the lung (Naito et al., 2016).

Previous studies have showed that both the expression of fascin-1 and laminin-5 were associated with the invasiveness and prognoses of several cancers, including colorectal (Adams, 2015; Fukazawa et al., 2015), gastric (Saito et al., 2010; Tu et al., 2016), pancreatic (Tsai et al., 2013; Chen et al., 2015) cancers and breast adenocarcinomas (D'Alfonso et al., 2015; Wang et al., 2016). Recently, some authors reported that the expression of fascin-1 and laminin-5 were associated with clinico-pathological characteristics of non-small cell lung cancer (Moriya et al., 2001; Niki et al., 2002; Pelosi et al., 2003; Choi et al., 2006; An et al., 2012; Ling et al., 2015; Luo et al., 2015; Zhao et al., 2015; Liu et al., 2016). However, reports regarding the clinical significance of both the expression and serum levels of fascin-1 and laminin-5 in non-small cell lung cancer are scarce.

In this study, we analyzed the expression and the serum levels of fascin-1 and laminin-5 in patients with non-small cell lung cancer and evaluated their clinical significance.

MATERIAL AND METHODS

Patients

This study was approved by the review board of the Beijing Chest Hospital of Capital

Medical University and all patients gave written informed consent. The specimens were anonymized and handled according to accepted ethical and legal standards.

The patients were divided into two groups; group 1 (Table 1) contained 224 patients with stage I and II NSCLC who were being surgically treated at the Beijing Chest Hospital of the Capital Medical University during January 2011-June 2013, whereas group 2 (Table 2) contained 154 patients with stage I and II NSCLC who were surgically treated at the same hospital from July 2013 to December 2014. The hematoxylin and eosin (H&E)-stained slides of all the patients were reviewed in each case to confirm the original diagnosis that was based on the criteria accepted by the World Health Organization. The disease stage was determined based on the 7th tumor, node, and metastasis (TNM) classification of The International Association for the Study of Lung Cancer's (IASLC) staging manual. No preoperative chemotherapy or radiotherapy had been performed in any of these cases. Standard lobectomy and lymph node dissections were performed in every case. The postoperative treatments were performed according to the National Comprehensive Cancer Network's (NCCN) guideline. Cases with any other malignancies that occurred before or after the occurrence of the primary lung cancer were excluded from our study.

Table 1. Patients of group 1.

Group 1	No. of cases (N = 224)
Male	122
Female	102
Stage I	95
Stage II	129
Relapsed	76
No relapsed	148

Table 2. Patients of group 2.

Group2	No. of cases (N = 154)
Male	89
Female	65
Stage I	53
Stage II	101
Relapsed	18
No relapsed	136

We determined the expression of fascin-1 and laminin-5 in all patients and measured their levels in the serum of the group 2 patients before the surgery. All patients were followed up after the surgery. The serum levels of fascin-1 and laminin-5 in 150 normal individuals were measured to determine the threshold levels.

Immunohistochemistry

Formalin-fixed and paraffin-embedded tissue samples obtained during surgery were cut into 4-micrometer-thick sections and investigated. The primary antibodies used in the study were mouse monoclonal antibody directed against fascin-1 (Cloud-Clone Corp, Houston, Texas, USA) and laminin-5 (Cloud-Clone Corp, USA). Immunohistochemical staining methods were employed according to the manufacturer's instructions. Paraffin sections were washed with an ethanol series (100, 100, 95, 90, 80, 70% ethanol) and double

distilled water according to standard protocols. Heat-induced antigen retrieval was performed in citrate buffer and boiled for 10 min. After antigen retrieval, sections were treated with 3% hydrogen peroxide and 1% bovine serum albumin to block the endogenous peroxidase activity and non-specific binding. The sections were incubated with fascin-1 and laminin-5 antibodies overnight at 48°C. After washing with phosphate buffered saline, the tissue sections were incubated with the biotinylated secondary antibody and streptavidin-horseradish peroxidase complex, each for 30 min at room temperature. Diaminobenzidine was used as the chromogen, and tissue sections were counterstained with hematoxylin and viewed under a bright-field microscope.

The cells were divided into the following categories according to staining intensity: 0 points for no staining, 1 point for pale yellow staining, 2 points for yellowish-brown staining, and 3 points for brown staining. The percentage of positive-staining cells was counted as following: <10% = 0; 11-30% = 1; 31-60% = 2; >60% = 3. The final score was determined by the combined staining score and proportion score (intensity score x proportion score). For statistical analysis, final staining scores of 0, 1-4, and > 4 were considered to be negative, moderate, and positive, respectively (Figures 1 and 2).
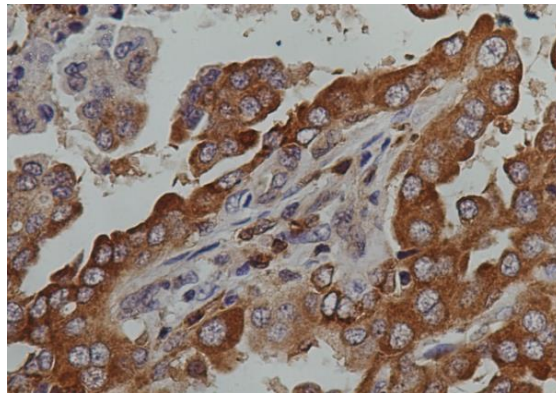

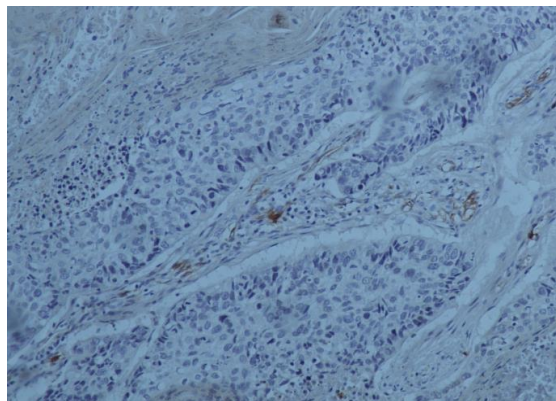**Figure 1.** Positive expression of fascin-1 in NSCLC tissues.

Figure 2. Negative expression of fascin-1 in NSCLC tissues.

Measurements of serum fascin-1 and laminin-5 levels

Serum samples were obtained from the patients at the time of diagnosis; those who had received preoperative adjuvant therapy such as radiotherapy or chemotherapy at enrollment were excluded from the study. Normal volunteers recruited from among individuals undergoing annual physical examination showed no evidence of malignancy. In brief, clotted serum samples were separated by centrifugation at 3,000 rpm for 15 min at room temperature and stored in aliquots at -80°C until use.

The fascin-1 and laminin-5 levels were measured using enzyme-linked immunosorbent assay (ELISA) commercial kits (Cloud-Clone Corp, Houston, Texas, USA) according to the manufacturer's instructions.

Statistical analysis

Statistical evaluations between different groups were performed using the chi-square test of the SPSS 16.0 software. P values less than 0.05 were considered to be statistically significant.

RESULTS

The threshold values

The threshold values were determined as the mean value plus two-folds of standard deviation. The threshold values of fascin-1 and laminin-5 were 4.351 ng/mL and 152 ng/mL, respectively.

Association between fascin-1 expression and relapse of NSCLC

The expression of fascin-1 and laminin-5 in the patients of the current series were divided into three grades: negative, moderate, and positive. There were 80 positive, 164 moderate, and 134 negative cases. Following were the percentages in the three grades for patients with relapse of the disease during the follow-up: 44 (55%) negative, 36 (21.9%) moderate, and 14 (10.4%) positive (P = 0.000) (Table 3). This indicated that the expression of fascin-1 was related to the relapse of NSCLC in these patients.

Table 3. Association between the expression of fascin-1 and relapse of patients with NSCLC.

Expression of fascin-1		Relapse	No relapse	
Positive	80	44	36	χ = 54.537
Moderate	164	36	128	P = 0.000
Negative	134	14	120	

Association between laminin-5 expression and the relapse of NSCLC

The expression of laminin-5 in patients of the current series was divided into three grades: negative, moderate, and positive. There were 124 positive, 176 moderate, and 78 negative cases. The percentage of patients with relapse during the follow-up were 48 (38.7%) negative, 38 (21.6%) moderate, and 8 (10.3%) positive, respectively (P = 0.002) (Table 4).

This indicated that the expression of laminin-5 was related to the relapse of NSCLC in these patients.

Table 4. Association between the expression of fascin-1 and the relapse of NSCLC.

Expression of laminin-5		Relapse	No relapse	
Positive	124	48	76	χ = 16.323
Moderate	176	38	138	P = 0.001
Negative	78	8	70	

The expression of fascin-1 and laminin-5 in patients with NSCLC

The expression of both fascin-1 and laminin-5 were positive or moderate in 226 patients, among which 66 (29.2%) patients showed symptoms of relapse during the follow-up. Among the 152 patients with negative expression of either fascin-1 or laminin-5, 28 (18.4%) patients showed signs of relapse during the follow-up. The rates of relapse in the two groups were statistically different (P = 0.017) (Table 5).

Table 5. Expression of fascin-1 and laminin-5 in patients with NSCLC.

Expression of fascin-1 and laminin-5	Relapse	No relapse	
All positive or moderate	66	160	χ = 5.655
Atleast one negative	28	124	P = 0.017

Serum level and expression of fascin-1 in patients with NSCLC

Among 154 patients, the serum fascin-1 levels of 48 patients were positive and 106 were negative. The number of patients with relapse in the positive and negative groups were 10 (20.83%) and 8 (7.55%), respectively, and the rates of relapse of the two groups were statistically different (P = 0.015) (Table 6).

Table 6. Serum levels of fascin-1 in patients with NSCLC.

Fascin-1 level	Relapse	No relapse	
Positive	10	38	χ = 5.868
Negative	8	98	P = 0.015

There were 40 patients with positive serum levels of fascin-1 and positive or moderate expression of fascin-1 (Table 7). Among them, 9 patients (22.5%) relapsed during the follow-up, and the rate of relapse was higher than those of other patients (P = 0.046).

Table 7. Serum level and expression of fascin-1 in patients with NSCLC.

Serum level and expression of fascin-1	Relapse	No relapse	
Fascin-1 level and positive or moderate expression of Fascin-1	9	31	χ = 5.258
At least one negative	9	105	P = 0.046

Serum level and expression of laminin-5 in patients with NSCLC

Among 154 patients, the serum levels of laminin-5 of 39 patients were positive and

115 were negative. The number of patients with relapse in the positive and negative groups were 9 (23.07%) and 9 (7.83%) respectively, and the rates of relapse of the two groups were statistically different (P = 0.043) (Table 8).

Table 8. Serum levels of laminin-5 in patients with NSCLC.

Laminin-5 level	Relapse	No relapse	
Positive	9	30	$\chi = 4.114$
Negative	9	106	P = 0.043

The serum levels of laminin-5 were positive and the expression of laminin-5 was positive or moderate in 30 patients (Table 9). Among them, 5 patients (20%) relapsed during the follow-up, and the rates of relapse were not statistically different from those of other patients (P = 0.046).

Table 9. Serum level and expression of laminin-5 in patients with NSCLC.

Serum level and expression of laminin-5	Relapse	No relapse	
Laminin-5 level positive and positive or moderate expression of laminin-5	5	25	$\chi = 0.895$
At least one negative	13	111	P = 0.344

DISCUSSION

Fascin actin-binding protein 1 (Fascin-1) is a 55-kDa conserved actin bundling protein, which is important for the maintenance and stability of parallel bundles of filamentous actin in different cell types (Adams, 2004; Hashimoto et al., 2011). The phosphorylation of protein kinase C can adjust the binding activity of fascin and actin (De Arcangelis et al., 2004). Consequently, specific assembly and disintegration of the actin filament changes the mobility of cells by reducing intra and intercellular adhesion as well as adhesion between cells and the matrix (Yamashiro, 2012). Therefore, the overexpression of fascin-1 can decrease cell-to-cell adhesion and increase epithelial cell motility and may be associated with the invasiveness and metastatic ability of tumor cells (Kureishy et al., 2002; Hashimoto et al., 2011). In fact, studies in mouse tumor models showed that the fascin-1 levels were elevated and the invasive and metastatic abilities of tumor cells were strengthened (Ma et al., 2013). Laminin-5, composed of α3, β3, and γ2 chains, is an epithelial basement membrane-specific variant (Rousselle and Beck, 2013). The main role of laminin-5 in normal tissues is the maintenance of epithelial-mesenchymal cohesion in tissues exposed to external forces, including the skin and stratified squamous mucosa (Rousselle et al., 1991; Rousselle et al., 1997). During tissue injury, laminin-5 induces migration of keratinocytes and promotes cell migration and wound closure (Verrando et al., 1994). Reports show that laminin-5 in culture promotes cell migration and scattering (Zhang and Kramer, 1996). In addition, laminin-5 is secreted by several squamous cell carcinoma lines, and is involved in tumor metastasis and invasion (Miyazaki, 2006).

Recent studies highlighted the association between the expression of fascin-1 and laminin-5 and the prognoses of NSCLC. Pelosi et al. (2003) and Choi et al. (2006) indicated the value of fascin-1 immunoreactivity for predicting lymph node metastases. Several other groups showed that the fascin-1 expression is significantly associated with the prognoses of NSCLC and may be a useful prognostic indicator (Ling et al., 2015; Luo et al., 2015; Zhao et al., 2015). Niki et al. (2002) showed laminin-5 expression at the invasive front of lung adenocarcinomas,

and Moriya et al. (2001) and An et al. (2012) showed that overexpression of laminin-5 may be a useful prognostic factor in patients with NSCLC. Our result showed that the expression of fascin-1 and laminin-5 were related to the relapse of NSCLC in patients, which corroborates previous findings. We evaluated the co-expression of fascin-1 and laminin-5 and found that the rates of relapse of the two groups (patients showing positive/moderate expression of fascin-1 and laminin-5 or expressing only one of the two proteins) were statistically different (P = 0.017). To our knowledge, this is the first report that shows that fascin-1 and laminin-5 co-expression can be used as a prognostic marker for relapse of NSCLC.

Recently, reports regarding serum levels of fascin-1 and laminin-5 in patients with NSCLC have been published. Teng and his colleagues indicated that the serum levels of fascin-1 and laminin-5 were associated with poor prognosis in NSCLC (Teng et al., 2013; Teng et al., 2016). We measured the serum levels of fascin-1 and laminin-5 in 154 patients with NSCLC prior to surgery. Among the 154 patients, the rate of relapse in patients with fascin-1 positivity and negativity were 20.83 and 7.55% respectively. Among these patients, the serum laminin-5 levels of 39 patients were positive and 115 were negative. The number of patients with relapse in the positive and negative groups were 9 (23.07%) and 9 (7.83%), respectively. The rates of relapse of the two groups were statistically significant.

Theoretically, simultaneous use of the serum levels and expressions of fascin-1 and laminin-5 may improve the evaluation of NSCLC prognoses. Our results showed that 40 patients had positive serum levels of fascin-1 and positive/moderate expression of fascin-1. Among them, 9 patients (22.5%) showed signs of relapse during the follow-up, and the rate of relapse was higher than those in other patients (P = 0.046). However, similar correlation was not identified for laminin-5, the reason for which is not clear at present. We speculate that the small sample size could be one of the reasons. Further investigations are required to understand the involvement of laminin-5 in NSCLC prognosis.

CONCLUSIONS

Our results indicated that both serum levels and expression of fascin-1 and laminin-5 could be prognostic factors for patients with NSCLC. Simultaneous use of these factors may lead to more effective evaluation of the disease prognoses.

Conflict of interests

The authors declare no conflict of interest.

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