RESEARCH ARTICLE

Clinicopathological Significance of S100A10 Expression in Lung Adenocarcinomas

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Abstract

Background: S100A10, of the S100 protein family, is reported to be involved in cancer cell invasion and metastasis. The aims of the present study were to immunohistochemically examine S100A10 expression in surgically resected lung adenocarcinomas, and evaluate any relationships with clinicopathological parameters and prognosis of patients. Materials and Methods: S100A10 expression was immunohistochemically studied in 202 consecutive resected lung adenocarcinomas, and its associations with clinicopathological parameters were evaluated. Kaplan-Meier survival analysis and Cox proportional hazards models were used to estimate the effect of S100A10 expression on survival. Results: S100A10 expression was detected in 65 of the 202 (32.2%) lung adenocarcinomas, being significantly correlated with poorer differentiation (P =0.015), a higher pathological TNM stage (stages II and III) (P=0.004), more frequent and severe intratumoral vascular invasion (P=0.001), and a poorer prognosis (P=0.030). However, S100A10 expression was not an independent predictor of survival after controlling for clinicopathological factors. Conclusions: The present study reveals that S100A10 is expressed in a subset of lung adenocarcinomas, and this is related to some clinicopathological parameters, although further studies are required to confirm the correlation between S100A10 expression and prognosis of lung adenocarcinoma patients.

Keywords: S100A10 - plasminogen receptor - lung adenocarcinoma - prognosis

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Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide, and lung adenocarcinoma accounts for about a half of NSCLCs (Parkin, 2001; Alberg et al., 2013). Despite advances in surgical techniques, the 5-year survival rates of patients with surgically resectable NSCLC has only slightly improved over the last few decades (Yoshino et al., 2012). Furthermore, molecular targeted therapies such as epidermal growth factor receptor (EGFR) -tyrosine kinase inhibitors demonstrated high-level efficacy in patients with lung adenocarcinoma harboring EGFR mutations, although acquired resistance develops an average of 12 months after the initiation of therapy (Kobayashi et al., 2005). Thus, further understanding of the tumorigenesis and tumor biology of lung adenocarcinoma is crucial in order to develop novel therapeutic strategies to improve patients' prognoses.

The S100 protein family comprises calcium-binding protein of the EF-hand type which consists of at least 25 distinct members, and plays roles including intra- and extracellular functions involved in the cell cycle, growth, migration, and protein phosphorylation (Donato, 2001). Recently, the S100 protein family has been thought to play key roles during different steps of the tumorigenic processes and tumor progression (Chen et al., 2014). Moreover, expression of the S100 protein family is detected in many human cancers and has been related to a poorer prognosis. In lung cancer, S100A2, S100A4, and S100A9 expressions were related to a poorer prognosis and suggested to be prognostic markers (Wang et al., 2005; Tsuna et al., 2009; Kawai et al., 2011).

S100A10 is also a member of the S100 protein family, and it forms a heterotetramer with annexinA2, which functions as a plasminogen receptor on the cell surface (Godier and Hunt, 2013). Plasminogen converts plasmin through binding to its receptors including the S100A10-annexinA2 heterotetramer, and plasmin catalyzes the degradiation of proteins of the basement membrane and extracellular matrix (ECM) (Hedhli et al., 2012; Liu et al., 2015). Increasing plasmin production has been shown to enhance the capability of cancer cells to degrade proteins of the basement membrane and ECM, which facilitated the infiltration of tumor cells into surrounding tissues (Godier and Hunt, 2013; Madureira

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et al., 2012). The overexpression of S100A10 is observed in renal cell carcinoma and anaplastic thyroid carcinoma (Domoto et al., 2007; Ito et al., 2007). Furthermore, the overexpression of S100A10 is related to poorer prognoses in gallbladder and colorectal cancer patients (Tan et al., 2011; Shang et al., 2013). However, to our knowledge, no report is available concerning the significance of S100A10 expression in the clinicopathological features and prognoses in a large series of lung adenocarcinoma patients. The present study examined S100A10 expression in resected lung adenocarcinomas and analyzed the correlation with clinicopathological parameters and its prognostic significance.

Materials and Methods

Patients and tissue specimens

A total of 202 consecutive lung adenocarcinoma patients who underwent complete resection from January 2002 to December 2005 at Kitasato University Hospital were included in this retrospective cohort study. Those who received preoperative chemotherapy and/or radiotherapy were excluded. Ten percent formalin-fixed and paraffin-embedded tissues were processed into 3-μm-thick sections and stained with hematoxylin and eosin. The histological diagnosis was based on the criteria of the World Health Organization/International Association for the Study of Lung Cancer (Travis et al., 1999). Each case was reassessed according to the 7th edition of the TNM classification (Goldstraw et al., 2007). The clinical and pathologic parameters retrospectively reviewed included the age at surgical resection, sex, smoking habit, tumor differentiation, nodal status, intratumoral vascular invasion, intratumoral lymphatic invasion, pleural invasion, pathological TNM (p-TNM) and stage, receiving adjuvant chemotherapy, viability status, and survival time after surgery. The viability status was determined based on whether or not lung cancer-related death occurred, and the survival time was defined as the duration from the date of surgery to that of death or the end of follow-up. Cases of death from other causes or those lost to follow-up were treated as censored cases. The study was approved by the Ethics Committee of Kitasato University School of Medicine (KMEO B15-21). Appropriate informed consent was obtained from all patients.

Immunohistochemical Staining of S100A10

After deparaffinizing in xylene, 3-μm-thick sections were rehydrated in a descending ethanol series and tap water, and then treated with 3% hydrogen peroxide for 10 min. Tissue sections were antigen-retrieved by autoclaving for 10 min in 0.01 M citrate buffer (pH 6.0) with 0.1% Tween 20. After blocking with 0.5% casein for 10 min, the sections were reacted with 1,000-times-diluted anti-S100A10 polyclonal antibody (Abcam, Cambridge, UK) for 2 hr at room temperature (RT). The sections were rinsed in Tris-buffered saline three times for 5 min each, and then allowed to react with ChemMate ENVISION (DAKO; Glostrup, Denmark) for 30 min at room temperature. The sections were subsequently visualized with Stable DAB solution (Invitrogen; Carlsbad, CA, USA) and counterstained with Mayer's hematoxylin. Negative controls were prepared by substituting phosphate-buffered saline for the anti-S100A10 antibody.

Evaluation of Immunohistochemical Staining

Only staining on the cytoplasmic membrane of the tumor cells was considered to be a positive result for S100A10. Vascular endothelial cells were used as an internal positive control (Figure 1A). The staining intensity was categorized into four groups by comparing the staining intensity of tumor cells with the positive control: 0=negative; 1 (weak)=weaker than the positive control; 2 (moderate)=the same as the positive control; 3 (strong)=stronger than the positive control. Tumor with a staining score of 2 or 3 as well as positive staining in more than 5% of its total tumor cells were judged as positive. All of the immunostained sections were reviewed by two investigators (K.K. and S.Y.) without knowledge of the clinical data. Discordant cases were reviewed and discussed until a consensus was reached.

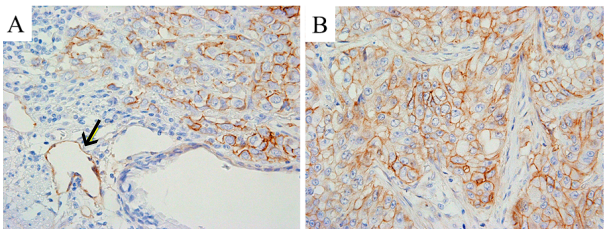

Figure 1. S100A10 Expression in Lung Adenocarcinomas. A) The normal vascular endothelial cells in the tumor stroma were used as an internal control for S100A10 expression (arrows). B) The vast majority of the tumor cells showed S100A10 expression at the membrane in lung adenocarcinoma. (original magnification: A ×200 B ×400)

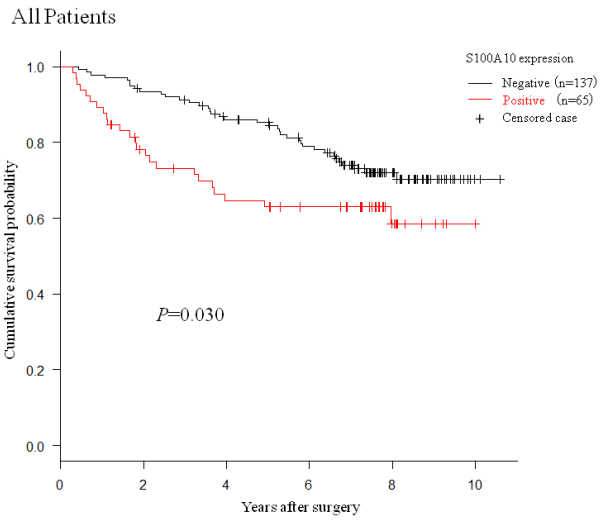

Figure 2. Cumulative Survival of Patients with Lung Adenocarcinoma According to S100A10 Expression Estimated by the Kaplan-Meier Method, Treating All Other Causes of Death and those Lost to Follow-up as Censored cases. S100A10 expression was significantly correlated with poorer survival in patients with lung adenocarcinoma

Statistical analysis

Continuous variables are presented as the median (range), while numerical variables are given as N (%). The relationships between S100A10 expression and clinicopathological parameters were assessed with Fisher's exact test. The cumulative survival of patients was estimated using the Kaplan-Meier method, and the significance of the survival differences between S100A10-positive and -negative groups was tested using the log-rank test. The 5-year cumulative survival probability was estimated using the life table method with the interval length set at 1 month. Multivariable analysis was performed by employing the Cox proportional hazards regression model to examine the interaction between S100A10 expression and other clinicopathological variables, and estimate the independent prognostic effect of S100A10 on survival by adjusting for confounding factors. The conventional P-value of 0.05 or less was used to determine the level of significance. All reported P-values are two-sided. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

S100A10 Expression in Lung Adenocarcinoma

Although S100A10 staining was observed simultaneously on the cytoplasmic membrane and in the cytoplasm of some tumor cells, the membraneous staining was much stronger and the majority of tumor cells showed only membraneous staining. (Figure 1B). Of the 202 surgically resected lung adenocarcinomas, 65 cases (32.2%) were judged as positive for S100A10. S100A10 expression was also observed in vascular endothelial cells and fibroblasts in the tumor stroma. S100A10 was not detected in normal alveolar epithelial cells. No expression was observed in the negative controls.

Clinicopathological Characteristics of Patients

The clinicopathological characteristics of the 202 lung adenocarcinomas are summarized in Table 1. The overall follow-up durations ranged from 4 to 129 months (median, 88 months). A total of 118 patients were alive at the end of the follow-up, 61 patients died of lung cancer, 8 patients died from other causes, and 15 patients were lost to follow-up. The causes of the 8 non-lung cancer deaths were pneumonia (n=4), cholangiocellular carcinoma (n=2), gastric cancer (n=1), and leukemia (n=1). None of these 8 patients died due to a surgery-related reason. Loss to follow-up of the 15 was due to discontinuing hospital attendance, and the durations of these patients' follow-up ranged from 15 to 87 months (median, 61 months).

Relationship between S100A10 Expression and Clinicopathological Characteristics

The relationships between S100A10 expression and clinicopathological characteristics are summarized in Table 2. S100A10 expression was significantly correlated related with poorer tumor differentiation (P=0.015), higher stages of the disease (stages II and III) (P=0.004), and more frequent intratumoral vascular invasion (P=0.001). There was no significant correlation between S100A10 expression and the age, sex, smoking habit, tumor size, nodal status, or frequency of intratumoral lymphatic invasion or pleural invasion.

Kaplan-Meier Estimate of Survival in S100A10-Positive and -Negative Patients

All 202 patients with lung adenocarcinoma were included in the survival analysis. The overall follow-up periods ranged from 4 to 129 months (median, 87 months), and the 5 -year cumulative survival probability was 75% for all patients. Because a cumulative survival probability of 50% had not yet been reached, the overall median survival time was not determined. The 5 -year cumulative survival probability was 62% for the S100A10-positive group and 88% for the S100A10-negative group. While the median survival time was not available, the survival rate of the S100A10-positive group was significantly poorer (P=0.030) (Figure. 2).

Effect of S100A10 expression on patient's survival with uni- and multivariable analyses

Univariable analysis was performed according to the Cox proportional hazard model to evaluate the effect of S100A10 expression and other clinicopathological factors on survival. The p-TNM stage (HR, 6.99; 95% CI, 3.98-12.27; P<0.001), adjuvant chemotherapy (HR, 4.02; 95% CI, 2.33-6.94; P<0.001), tumor differentiation

Table 1. Clinicopathological Characteristics of the Patients

Characteristics	Number of Patients (%) (N=202)
Age (years)	
Median age (range)	63 (37-82)
<65	111 (55.0)
≥65	91 (45.0)
Sex	
Male	108 (53.4)
Female	94 (46.6)
Smoking habit	
Never smoker	96 (47.5)
Smoker	106 (52.5)
Tumor differentiation	
Well	113 (55.9)
Moderately/Poorly	89 (44.1)
p-TNM stage	
StageI	131 (64.9)
StageII	35 (17.3)
StageIII	36 (17.8)
Receiving adjuvant chemotherapy	
Yes	30 (14.9)
No	172 (85.1)
Vital status	
Alive	118 (58.4)
Lung cancer-related death	61 (30.2)
Other cause of death	8 (4.0)
Unknown	15 (7.4)

Table 2. Relationships between S100A10 Expression and Clinicopathological Parameters

Clinicopathological Parameters	S100A10 Expression		Total	P-Value
	Positive (N = 65)	Negative (N = 137)		
Age, y; N (%)				0.88
< 65	35 (31.5)	76 (68.5)	111	
≥ 65	30 (33.0)	61 (67.0)	91	
Sex; N (%)				0.132
Male	40 (37.0)	68 (63.0)	108	
Female	25 (27.0)	69 (73.0)	94	
Smoking habit; N (%)				0.097
Never smoker	25 (26.0)	71 (74.0)	96	
Smoker	40 (37.7)	66 (62.3)	106	
Tumor differentiation; N (%)				0.015
Well	28 (24.8)	85 (75.2)	113	
Moderately/Poorly	37 (41.6)	52 (58.4)	89	
p-TNM stage; N (%)				0.004
Stage I	33 (25.2)	98 (74.8)	131	
Stage II/III	32 (45.0)	39 (55.0)	71	
Tumor size; N (%)				0.113
≤5 cm	56 (30.4)	128 (69.6)	184	
>5 cm	9 (50.0)	9 (50.0)	18	
Nodal status; N (%)				0.054
N0	43 (28.3)	109 (71.7)	152	
N1/N2/N3	22 (44.0)	28 (56.0)	50	
Vascular invasion; N (%)				0.001
Yes	33 (45.2)	40 (54.0)	73	
No	23 (21.7)	83 (78.3)	106	
Lymphatic invasion; N (%)				0.05
Yes	24 (41.4)	34 (58.6)	58	
No	26 (25.5)	76 (74.5)	102	
Pleural invasion; N (%)				0.337
Yes	24 (36.9)	41 (63.1)	65	
No	41 (29.9)	96 (70.1)	137	

Table 3. Univariable and Multivariable Analyses of the Effect of S100A10 Expression on Survival

Factors	univariate analysis			multivariate analysis		
	HR	95% CI	P-Value	HR	95% CI	P-Value
S100A10 expression						
Positive vs Negative	1.75	1.05-2.93	0.03	1.12	0.61-2.31	0.60
Age						
≥ 65 vs <65	1.26	0.76-2.09	0.36	n/d	n/d	n/d
Sex						
Male vs Female	0.83	0.50-1.38	0.48	n/d	n/d	n/d
Smoking habit						
Smoker vs Never Smoker	1.13	0.68-1.86	0.64	n/d	n/d	n/d
p-TMN stage						
Stage II/III vs Stage I	6.99	3.98-12.27	<0.001	3.42	1.66-7.05	<0.001
Adjuvant chemotherapy						
No vs Yes	4.02	2.33-6.94	<0.001	3.45	1.68-7.05	<0.001
Tumor differentiation						
Moderately/Poorly vs Well	3.08	1.82-5.23	<0.001	1.57	0.76-3.24	0.22
Vascular invasion						
Yes vs No	5.48	3.00-9.99	<0.001	2.06	0.82-5.16	0.12
Lymphatic invasion						
Yes vs No	4.43	2.48-7.92	<0.001	1.04	0.47-2.31	0.91
Pleural invasion						
Yes vs No	3.35	2.02-5.56	<0.001	1.86	0.9-3.53	0.06

(HR, 3.08; 95% CI, 1.82-5.23; P<0.001), vascular invasion (HR, 5.48; 95% CI, 3.00-9.99; P<0.001), lymphatic invasion (HR, 4.43; 95% CI, 2.48-7.92; P<0.001), pleural invasion (HR, 3.35; 95% CI, 2.02-5.56; P<0.001), and S100A10 expression (HR, 1.75; 95% CI, 1.05-2.93; P=0.03) were significant predictors of cancer-specific

survival. However, when S100A10 expression and other clinicopathlogical variables including the p-TNM stage, adjuvant chemotherapy, tumor differentiation, vascular invasion, lymphatic invasion, and pleural invasion were included in multivariable analysis using the Cox proportional hazards regression model, S100A10 expression was not an independent predictor of a poorer survival (HR, 1.12; 95%CI, 0.61-2.31; P=0.60). On the other hand, the p-TNM stage (HR, 3.42; 95%CI, 1.66-7.05; P <0.001) and adjuvant chemotherapy (HR, 3.45; 95%CI, 1.68-7.05; P <0.001) were independent predictors of a poorer survival (Table 3).

Discussion

In the present study, S100A10 was expressed in a subset of lung adenocarcinomas, and its expression was related to poorer tumor differentiation, a higher stage of disease, more frequent intratumoral vascular invasion, and a poorer prognosis, in keeping with the findings of Shang et al. in colorectal cancer (Shang et al., 2013).

S100A10 forms a heterotetramer with annexin A2 at the cell surface, which functions as a plasminogen receptor and facilitates the conversion of plasminogen to plasmin. Plasmin catalyzes the degradation of proteins of the basement membrane and ECM (Godier and Hunt, 2013). Therefore, S100A10 might contribute to the invasiveness of tumor cells by increasing plasmin production with consequent basement membrane and ECM degradation. Choi et al. reported that the HT1080 fibrosarcoma cell line, which has lost S100A10 expression, showed a marked decrease in invasiveness and the metastatic potential (Choi et al., 2003). Additionally, Zhang et al. (2004) reported similar findings in a CCL-222 colorectal cancer cell line, when S100A10 expression was down-regulated (Zhang et al., 2004). These results argue for the contributions of S100A10 to cancer cell invasiveness. In the present study, S100A10 expression was significantly correlated with more frequent intratumoral vascular invasion, and there was also a clear tendency toward more frequent intratumoral lymphatic invasion, supporting the previously reported relationship between S100A10 and cancer cell invasiveness. S100A10 was also shown to contribute to cell spreading/migration, required for invasion of the local microenvironment. Sayeed et al. reported that the depletion of S100A10 using two different siRNAs induced the suppression of cell spreading in HeLa and MDA-MB 231 cell lines. Furthermore, they suggested that S100A10 could activate Rac1, which is essential for the promotion of cell spreading (Sayeed et al., 2013). Hence, the correlation of S100A10 expression and intratumoral lymphovascular invasion found in the present study might reflect the enhancement of cell spreading/migration caused by S100A10.

S100A10 staining was detected in both the membrane and cytoplasm of some tumor cells, although the membraneous staining was much stronger and the majority of positive cells showed only staining on the cell membrane, suggesting the important function of S100A10 as a plasminogen receptor at the tumor cell surface.

There are also some reports of S100A10 being related to other processes of tumor metastasis and progression, including the migration of tumor-promoting macrophages into tumor sites, suppression of apoptosis in cancer cells, and regulation of angiogenesis (Hsu et al., 1997; Phipps et al., 2011; Surette et al., 2011). Further studies are needed to elucidate the multiple functions of S100A10 in various tumors.

In conclusion, we report for the first time that S100A10 is expressed in a subset of lung adenocarcinoma, and its expression is related to a poorer tumor differentiation, higher stage of the disease, more frequent intratumoral vascular invasion, and a poorer prognosis. Further studies are needed to elucidate the biological functions of S100A10 in lung adenocarcinoma in more detail, which might lead to the development of novel therapeutic strategies against lung adenocarcinoma.

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