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Research Article

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Clinical Significance and Potential Function of S100a10 in Lung Adenocarcinoma

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Abstract

Objective To investigate the clinical significance and potential function of S100A10 in lung adenocarcinoma.

Methods: *The RNAseq data of lung adenocarcinoma tissues and normal lung tissues in The Cancer Genome Atlas (TCGA) database and Genotype-Tissue Expression (GTEx) project were obtained from the UCSC Xena. The correlation between S100A10 expression and clinic pathological features in patients with lung adenocarcinoma was analyzed. The Metascape database was used for Gene Ontology (GO) enrichment analysis of S100A10-related genes. Another 32 pairs of lung adenocarcinoma and matched lung tissues were selected to verify the expression of S100A10 protein by immunohistochemistry.*

Results: *The expression of S100A10 in lung adenocarcinoma tissues was significantly higher than that in normal lung tissues on RNA ($P<0.001$) and protein ($P=0.009$) levels, and the RNA expression level in lung adenocarcinoma tissues was significantly correlated with tumor stage ($P=0.004$), lymph node metastasis ($P=0.0002$), overall survival ($P=0.002$) and disease-free survival ($P=0.011$). GO enrichment analysis showed that S100A10 related genes were significantly enriched in terms of cell adhesion, suggesting that S100A10 may be mainly involved in the process of cell adhesion in lung adenocarcinoma. Conclusion S100A10 is highly expressed in lung adenocarcinoma and is significantly correlated with some clinic pathological features, overall survival (OS) and disease-free survival (DFS) by Kaplan–Meier (K–M) analysis, indicating a potential biomarker for diagnosis and prognosis for lung adenocarcinoma.*

Keywords: S100A10, lung adenocarcinoma, TCGA, metastasis, diagnosis.

Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide, with a 15.6% 5-year survival rate, which is classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC,85% cases) [1-2]. While lung adenocarcinoma, a subtype of NSCLC, accounts for about 40% of lung cancer, with a rapid increasing rate in recent years [3]. Compared to other subtypes, lung adenocarcinoma tends to have both low early diagnosis rates and high death rates. Although advances in treatment methods have been made available in recent years, like minimally invasive surgical approaches, chemotherapies, and targeted therapies, however, the prognosis of lung.

Adenocarcinoma is far from satisfaction. At present, the commonly used serological markers for NSCLC are mainly CEA, Cyfra21-1, CA125, CA153, TPA, and SCC-Ag, but they cannot be used as markers for lung adenocarcinoma screening due to low specificity. Therefore, identifying novel diagnostic and prognostic biomarkers is urgently demanded.

S100A10, also known as Annexing light chain, is a member of the S100 protein family. S100A10 is unique among S100 proteins in that it is locked in a permanently open conformation, similar to the Ca2+-bound configuration of the other S100 proteins, and cannot bind to Ca2+[4].

S100A10 is widely expressed in different cell types and plays a vital role in fibrinolysis, wound healing, angiogenesis, and im-

mune regulation. Several studies indicated that S100A10 has high expression and is associated with the prognosis of patients with breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, and lung squamous cell carcinoma [5-9]. In the present study, database research and bioinformatics analysis were performed to explore the correlation between S100A10 and clinic pathological features and determine its prognostic value in lung adenocarcinoma. And a small surgical sample was selected to validation the expression of S100A10 protein in lung adenocarcinoma and normal tissue.

Methods

RNA Expression and Analysis

Data Preprocessing from TCGA and GTEx

TCGA and GTEx data were downloaded using the UCSC Xena browser (https://xenabrowser.net/). 526 LUAD cases and 59 normal tissue samples from TCGA were included, with a data type of log2(x+1) converted FPKM value. The GTEx data contained the RNA sequencing data of 288 normal lung tissues, with a data type of log2(x+0.001) converted FPKM value. The GTEx data were converted to log2 (FPKM+1) and merged with the TCGA data to obtain an expression matrix comprising the sequencing data of 347 cases of normal lung tissue and 526 cases of LUAD tissue. In addition, another 515 LUAD patients' RNA-seq data with complete prognosis information from the TCGA database were involved for further survival analysis. Patient datasets included met the following criteria: (1) patients with primary LUAD confirmed by cytological or pathological examination following imaging examination; (2) complete sequencing data of the primary site of LUAD. Exclusion criteria: (1) patients with missing clinical data; (2)

Combined with other tumors or benign diseases.

GO Enrichment Analysis

The biological function of S100A10 was determined by Gene Ontology (GO) (http://www.geneontology.org) database, which described from three categories: biological process (BP), cellular component (CC), and molecular function (MF) [10]. GO enrichment analysis of highly- related genes was performed using the Metascape database http://metascape.org/ with the enrichment threshold of P<0.01[11].

Protein Expression and Analysis

Case Selection

Paired lung adenocarcinoma and corresponding normal lung tissues were collected from 32 stage I - II patients undergoing LUAD surgery at National Center/Cancer Hospital, Chinese Academy of Medical Sciences of Peking Union Medical College (Beijing, China) from 2007 to 2010. All pathological slides were reviewed by an experienced pathologist. No patients received chemotherapy or radiotherapy before surgical operation.

Immunohistochemistry Detection

Preprocessing procedures of specimens were as follows: The FFPE sections were first deparaffinized in xylene and rehydrated, followed by antigen retrieval using 0.01 M Tris-EDTA buffer (pH 9.0). Then the sections were incubated with 3% H2O2 for 5 minutes. The sections were then incubated with rabbit anti-human S100A10 monoclonal primary antibody (1:100, [EPR3317] (ab76472); Abcam, USA) overnight at 4°C. After PBS washing, the sections were incubated with Dako secondary antibody system (Dako, Glostrup, Denmark) for 20 minutes at 37°C. PBS was washed three times for three minutes each time. Finally, the slide was developed with 3,3′- diaminobenzidene (DAB) and then counterstained with hematoxylin. Staining for S100A10 was leveled as absent (<5% positive), weak (5~25%), moderate (25~50%), and strong (>50%). For subsequent analysis, absent was categorized as negative, while weak, moderate and strong were
Positive.

Statistical Analysis

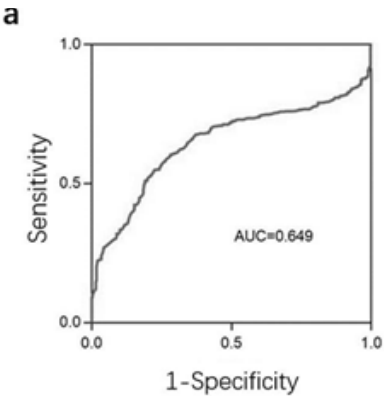
Calculate the correlation of gene expression by Spearman rank correlation in R software, and those genes with a Spearman's correlation coefficient greater than 0.4 were defined as highly related genes of S100A10. Statistical analysis was analyzed using SPSS 23.0 software package and

GraphPad Prism 7.0. The Mann-Whitney U test was used to compare the difference in S100A10 expression between cancer and normal tissues at the RNA level. The relationship between S100A10 and clinic pathological features was evaluated by $\chi 2$ test. Kaplan–Meier (K–M) survival curves were generated to graphically demonstrate the overall survival (OS) and disease-free survival (DFS) of the high expression and low expression groups, and the difference between survivals curves were evaluated by Log-rank test. Univariate Cox regression method was used to investigate whether S100A10 expression and other clinical factors can be correlated with prognosis. Factors with statistical significance in univariate analysis were further analyzed using multivariate Cox regression to determine their role as independent prognostic factors. $P < 0.05$ means statistically significant.

Results

1. S100A10 Expression Is Elevated in Lung Adenocarcinoma Tissues On Transcription And Protein Levels

Using TCGA RNA-seq data, we first analyzed S100A10 mRNA expression in LUAD and normal tissues. Results showed significantly elevated S100A10 expression in LUAD (n = 526) tissues compared with the normal counterparts (n = 347, $P < 0.0001$). The ROC curve of S100A10 for the diagnosis of LUAD is shown in Figure 1a. The area under the curve (AUC) is 0.649, indicating that the expression of S100A10 was of a certain diagnostic value for LUAD patients.



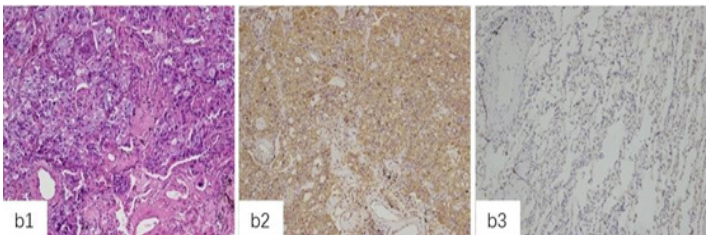


Figure 1: S100A10 was upregulated in LUAD tissues based on the TCGA database.

(a) ROC curve of S100A10 in the diagnosis of lung adenocarcinoma. (b) Representative IHC images of S100A10 in clinical LUAD tissues and normal lung tissues, b1, H&E staining for lung adenocarcinoma(x20); b2, Immunohistochemical staining of S100A10 protein exhibited in cytoplasm of tumor cells (x20); b3, Negative immunostaining of S100A10 protein in normal lung tissues(x10).

Subsequently, we performed immunohistochemistry (IHC) assays to detect the protein expression of S100A10 in 32 pairs of surgical specimens from the Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, as mentioned above. As shown in Figure 1b, S100A10 protein was mainly located in the cytoplasm and membranes. Almost no S100A10 staining or very weak staining was observed in normal lung epithelium. Conversely, a ubiquitous positive staining was observed in most malignant cells. The S100A10 protein expression in lung adenocarcinoma tissues were significantly higher than that in normal pulmonary parenchyma (P=0.009), consistent with the mRNA expression.

2. S100A10 Expression Correlated with Pathological Characteristics of Lung

Adenocarcinoma

According to the relative expression level of S100A10 at the maximum value of Youden Index (8.388) in ROC curve, LUAD samples from the TCGA database were divided into high expression group (n = 314) and low expression group (n = 212). The $\chi 2$ test was used to analyze the relationship between the expression level of S100A10 and clinic pathological characteristics. As shown in Table 1, tumor stage (P=0.004) and lymph node metastasis (P=0.0002) were significantly correlated with S100A10 expression in LUAD tissues, while gender and age were not (P>0.05).

Table 1: Correlation between S100A10 transcription level and clinicopathological characteristics of lung adenocarcinoma from TCGA.

Group	S100A10		χ^2 value	P-value
	Low expression (n=212)	High expression (n=314)		
Gender			2.382	0.123
Male	107	137		
Female	105	177		
Agea			2.534	0.111
≤65	91	157		
>65	113	146		
Clinical stagea			8.077	0.004
I+II	176	232		
III+IV	31	79		
T classificationa			1.228	0.268
T1-T2	189	267		
T3-T4	23	44		
N classificationa			13.860	0.0002
N0	156	185		
N1-N3	49	122		
M classificationa			1.771	0.183
M0	147	207		
M1	7	18		

a: Some samples with incomplete clinicopathological information.

Kaplan- Meier survival analysis was performed to estimate the prognostic significance of S100A10 expression in LUAD patients with follow-up data from TCGA. The median OS of the low expression group was 5.96 years, while the high expression group was only 3.38 years. Moreover, the median DFS time of the low and high expression group was 3.54 years and 2.13 years, respectively. The results showed that patients with high S100A10 expression had a shorter OS (P = 0.002, Figure 2a) and DFS (P = 0.011, Figure 2b). In addition, as shown in Table 2 and Table 3, the univariate Cox regression analysis revealed the same result, while multivariate Cox regression method showing that S100A10 could not be an independent prognostic factor for lung adenocarcinoma.

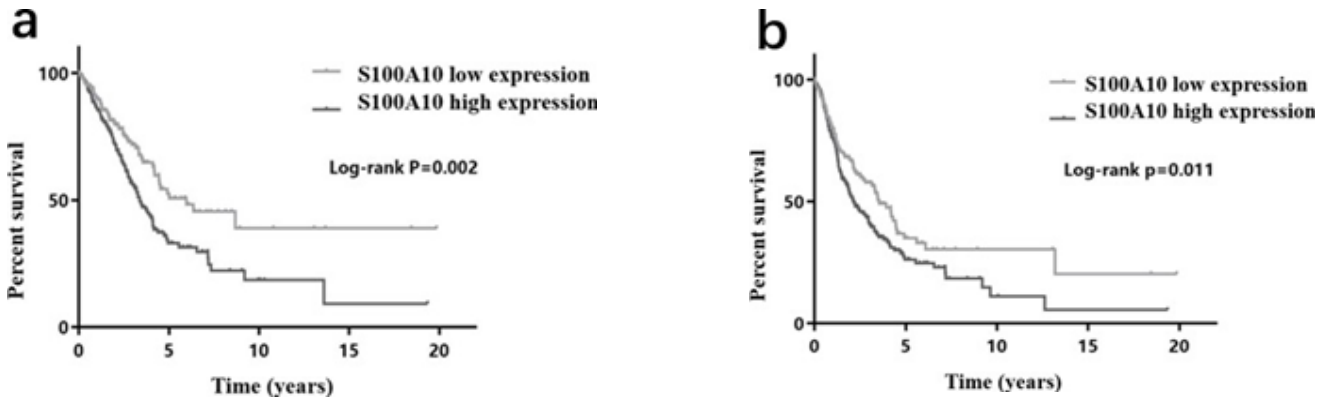


Figure 2: The correlation between S100A10 transcription level and the prognosis of patients with lung adenocarcinoma. Kaplan–Meier curves for overall survival (a) and disease-free survival (b) in LUAD patients from TCGA dataset.

Table 2: Cox regression analysis of the relationship between various factors and overall survival

Parameters	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age	1.008	0.993-1.023	0.312			
Gender	1.056	0.791-1.409	0.711			
Smoking	1.028	0.894-1.182	0.702			
history						
T classification	0.560	1.299-1.874	<0.001	1.342	1.083-1.664	0.007
N classification	1.714	1.448-2.030	<0.001	1.612	1.316-1.976	<0.001
M classification	2.128	1.243-3.642	0.006	1.603	0.893-2.877	0.114
S100A10	1.282	1.094-1.503	0.002	1.034	0.876-1.221	0.690

Table 3: Cox regression analysis of the relationship between various factors and disease-free survival time

Parameters	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age	1.012	0.999-1.025	0.072			
Gender	1.079	0.839-1.388	0.554			
Smoking	1.047	0.927-1.182	0.461			
history						
T classification	1.622	1.380-1.906	<0.001	1.427	1.168-1.743	0.001
N classification	1.466	1.259-1.708	<0.001	1.346	1.107-1.636	0.003
M classification	2.146	1.327-3.472	0.002	1.484	0.863-2.550	0.153
S100A10	1.169	1.020-1.339	0.025	0.963	0.831-1.115	0.613

A total of 161 genes highly-related to S100A10 expression were obtained from 55187 genes in LUAD tissue sequencing data. To further study the signaling pathways that S100A10 might be involved in, highly-related genes were enriched and analyzed by GO enrichment analyses using the Metascape database, finding a total of 212 significantly enriched items. Among the first 20 significantly enriched items (Table 4), the biological process items included response to injury, cell connection organization, establishment or maintenance of cytoskeleton polarity, actin cytoskeleton organization, thyroid hormone response, cell adhesion regulation, neuronal maturation regulation, skin development, cell differentiation-related morphogenesis, regulation of cell morphogenesis, positive regulation of apoptosis process, regulation of Wnt signaling pathway, chemotaxis, innervation, molting cycle and gonadal hormone response. Additionally, CC analysis showed that highly-related genes were associated with collagen-containing extracellular matrix and adhesion junctions, and molecular function items included cell adhesion molecule binding and cytoskeleton structure. Results suggested that S100A10 is involved in many aspects of the development of lung adenocarcinoma.

Table 4: GO enrichment analysis of S100A10 highly related genes.

Categories	Items	Description	Gene	-lgP
Biological	GO:0009611	response to injury	17	6.07
Process	GO:0034330	cell connection organization	11	5.78
	GO:0030952	establishment or maintenance of cytoskeleton polarity	4	5.66
	GO:0030036	actin cytoskeleton organization	16	5.53
	GO:0097066	thyroid hormone response	4	4.76
	GO:0030155	cell adhesion regulation	15	4.68
	GO:0014041	neuronal maturation regulation	3	4.60
	GO:0043588	skin development	11	4.30
	GO:0000904	Cell differentiation-related morphogenesis	14	3.75
	GO:0022604	regulation of cell morphogenesis	11	3.74
	GO:0043065	positive regulation of apoptosis process	13	3.64
	GO:0030111	regulation of Wnt signaling pathway	9	3.40
	GO:0006935	chemotaxis	12	3.25
	GO:0060384	innervation	3	3.25
	GO:0042303	molting cycle	5	3.22
	GO:0034698	gonadal hormone response	3	3.20
Cellular Component	GO:0062023	collagen-containing extracellular matrix	14	6.72
	GO:0005912	adhesion junction	15	5.90
Molecular	GO:0050839	cell adhesion molecule binding	14	5.66
Function	GO:0005200	cytoskeleton structure	5	3.41

Discussion

The long-term survival rate of lung adenocarcinoma patients still remains extremely low due to prone to recurrence and metastasis. Therefore, searching for potential prognostic markers is essential for lung adenocarcinoma patients to formulate treatment strategies in time. Our current study aims to investigate relation between S100A10 and clinicopathological characteristics and prognostic significance, as well as to analyze the functional role of S100A10 in lung adenocarcinoma using genome-wide RNA sequencing (RNA-seq) dataset, immunochemistry and bioinformatics analysis tools. In the transcription level, expression of S100A10 in lung adenocarcinoma tissues was significantly higher than that in normal lung tissues, and significantly correlated with OS and DFS. Meanwhile, S100A10 protein was found higher expressed in lung adenocarcinoma tissues than that in normal lung tissues, which indicating a significant biomarker for both diagnosis and prognosis for lung adenocarcinoma.

S100A10 was reported as one member of S100 family, which included other members as S100A4, S100A11 and S100A16, etc. Rachel L et al. identified that S100A4 is preferentially elevated in lung adenocarcinoma tissues, where it promotes lymphatic vascular infiltration and predicts poor prognosis. Silencing S100A4 by shRNA can inhibit NF-κB activity and decrease TNFα-induced MMP9 expression [12]. S100A11 levels were significantly higher in adenocarcinomas with KRAS mutations, strong proliferating

activity and poorly differentiated tumors. Furthermore, higher levels of S100A11 were associated with shorter disease-free survival [13]. Chen et al. showed increased S100A16 expression might be modulated by its DNA hypo methylation and serves as an independent prognostic indicator of unfavorable OS and RFS in LUAD [14]. S100A10 usually interacts with ANXA2 to form a heterotetramer, which enhances the conversion of plasminogen to plasmin.

Plasmin can activate metalloproteinase (MMPs) and promote the degradation of extracellular matrix (ECM), processes which all contribute to tumor development and metastasis [15]. Shang et al. have shown that upregulation of S100A10 is correlated with poorly differentiated histology and more aggressive behavior in colorectal cancer [6]. Li et al. have found that S100A10 is also overexpressed in gastric cancer tissue and is related to mTOR pathway [7]. These findings suggest the potential relationship between S100A10 and cancer metastasis and prognosis. Lung adenocarcinoma is prone to early metastasis, but detailed analysis on S100A10 in lung adenocarcinoma has not been reported, and still needs further exploration.

Katono K et al. used to study the expression of S100A10 in lung tissues by immunohistochemical methods, and they found S100A10 was not detected in normal alveolar epithelial cells, while 65 of 202 lung adenocarcinomas were positively expressed. Positive patients had poorer tumor differentiation, a higher pathological stage, more severe vascular invasion, and poorer prognosis, but S100A10 was not an independent predictor of survival [16]. Based on a large amount of sequencing data in the database and clinical data immunohistochemistry results, our present work further verified the results of Katono K. Although there are relatively few clinical cases of immunohistochemistry, the RNA and protein level of S100A10 in lung adenocarcinoma was higher than that in normal lung tissue, which has a specific diagnostic value. Survival analysis showed that the expression level of S100A10 was markedly correlated to the prognosis of patients with lung adenocarcinoma.

Shang J et al. demonstrated that knockdown of S100A10 by siRNA significantly reduced the proliferation, migration, and invasion capacity of HCT-116 and DLD-1colorectal cancer cell lines [6]. Myrvang et al. found that S100A10 on the cell surface mediates the adhesion of breast cancer cells and microvascular endothelial cells in in vitro experiments [17]. There are numerous studies on the mechanism of S100A10 in cancer, but its role in lung adenocarcinoma is still unknown. We therefore calculated the correlation coefficients of 55187 genes in lung adenocarcinoma tissue sequencing data with S100A10, and performed GO enrichment analysis on S100A10 expression highly related genes to infer its potential function. Among the first 20 significantly enriched items of GO enrichment analysis, items related to cell adhesion were significantly enriched in the three functional categories of biological processes, cell components, and molecular functions, suggesting that S100A10 is maybe mainly involved in the cell adhesion process. In addition, cell differentiation, apoptosis and other related items involved in the occurrence and development of tumors are also significantly enriched.

In conclusion, we found in this study that S100A10 was highly expressed in lungadenocarcinomas both in RNA and protein levels, and was significantly correlated with some clinicopathological features and survival, indicating a potential biomarker for diagnosis and prognosis for lung adenocarcinoma.

Conflicts of Interest

All authors have declared that there are no financial conflicts of interest with regard to this work.

Ethics Approval and Consent

Ethical clearance was obtained from the institutional review office of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. The study used existing information of patients' histories, so no informed consent was required. All the patients' data obtained from records followed the Declaration of Helsinki.

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