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Original Article

Decreased *SARI* expression predicts poor prognosis of Chinese patients with non-small cell lung cancer

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Abstract: *SARI* is associated with the risk for several cancers, and loss of *SARI* expression is frequently found in aggressive and metastatic cancer. Limited evidence shows that *SARI* is a tumor suppressor gene, but the role of *SARI* in non-small cell lung cancer (*NSCLC*) has not been previously reported. This study was to investigate the *SARI* expression profile in surgically resected lung cancer tissues of Chinese patients by immunohistochemistry and evaluate the relationship between *SARI* expression and prognosis of lung cancer patients. Furthermore, *SARI* gene was transfected into lung cancer cells (*A549*), and the growth curve and cell healing of lung cancer cells were determined, aiming to investigate the influence of *SARI* on the growth and migration of lung cancer cells in vitro. Results showed that 103 of 195 (52.82%) tissues were positive for *SARI*. When compared with normal tissues, *SARI* expression significantly reduced in 50.26% of *NSCLC* tissues. Patients with negative or reduced *SARI* expression were more likely to have advanced lung cancer and lymph node metastasis. In squamous carcinoma and adenocarcinoma patients, the *SARI* expression had no relation with the survival time; However in one-on-one analysis *SARI* expression in tumor cells and adjacent tissues, patients which tumor cells *SARI* express reduced than adjacent tissues, survival time was significantly shorter than those without reduction in *SARI* expression (Log Rank test, $p = 0.001$). After transfection by *SARI* gene, the proliferation and migration of *A549* cells were obviously inhibited ($p < 0.001$). These results demonstrate that decreased *SARI* expression may predict a poor prognosis in *NSCLC* patients, and *SARI* may serve as a prognostic biomarker and potential therapeutic target for lung cancer.

Keywords: *SARI*, non-small cell lung cancer, prognosis, surgically resected cancer

Introduction

Lung cancer is one of the malignant tumors with the highest incidence and mortality [1], and it has been the most common cancer worldwide for several decades. The prognosis of non-small cell lung cancer *(NSCLC*) is currently unacceptable because the 5-year survival rate is only around 50%, even in patients who undergo radical surgical resection [2]. Therefore, prevention and treatment of lung cancer are a focus of intensive current research.

SARI is a leucine zipper as the basic structure of interferon (*IFN*) can induce early reaction protein, and belongs to the *AP-1* family of transcription factors [3]. However, *SARI* is different from the traditional proteins in *AP-1* family: traditional proteins including *JUN* (i.e., *AP-1*), *FOS, MAF* and so on, often form dimmers accompanied by activation of transcription factor (*ATF*); this kind of proteins have the basic leucine zipper structure domain (*bZIP*) and transcription activation area (*AD*); *SARI* protein has no *AD* structure although *it* contains *bZIP* structure domain [4-6]. *SARI* is widely expressed in a variety of normal tissues/cells, but its expression reduces in most tumors [3]. To date, few studies have been conducted to investigate *SARI* and the signal pathways related to *SARI* are still

Table 1. *SARI* expression and Characteristic Variable

Characteristic/Variable, n (%)	Positive expression (n = 103)	Negative expression (n = 92)	Entire Sample (n = 195)	*Chi-square value*	*P* Value
Histology					
SCC	51 (51%)	49	100	0.273	0.352
ADC	52 (54.7%)	43	95		
Gender					
Male	76 (51.7%)	71	147	0.301	0.352
Female	27 (56.3%)	21	48		
Age (yr)					
≥ 60	74 (55.6%)	59	133	1.101	0.186
< 60	29 (46.8%)	33	62		
Tumor Grade					
I	14 (87.5%)	2	16	I vs. II 7.23	0.006
II	57 (51.8%)	53	110	I vs. III 8.846	0.003
III	32 (46.4%)	37	69	II vs. III 0.502	0.290
Tumor Stage					
I	56 (76.7%)	17	73	I vs. II 8.671	0.003
II	32 (52.5%)	29	61	I vs. III 32.363	0.001
III	14 (25.9%)	40	54	II vs. III 8.402	0.003
IV	1 (14.3%)	6	7		
Lymph node metastasis					
Yes	26	57	83	27.076	0.001
No	76	34	110		

unclear. Studies have shown that a variety of normal cell lines have stable *SARI mRNA* expression. The *SARI mRNA* expression is the highest in the pancreas and spleen, moderate in the colon, heart, kidney, liver, lung and prostate tissues, and low in the placenta and stomach. However, in their corresponding cancer cells, the *SARI mRNA* expression is undetectable or declined. This suggests that *SARI* may inhibit the cancer cell growth. This study aimed to detect the *SARI* protein expression in surgically resected *NSCLC* tissues of Chinese patients by immunohistochemistry and evaluate the relationship between *SARI* expression and prognosis of *NSCLC* patients with. In addition, *SARI* gene was transfected into lung cancer cells and the growth curve and wound healing of lung cancer cells (scratch healing test) were determined aiming to explore the, influence of *SARI* on the growth and migration of lung cancer cells in vitro.

Patients and methods

Patients and tissue microarray (TMA)

While 45 paired NSCLC and adjacent normal tissues were collected from 45 patients from January to December in 2010, of whom 20 were diagnosed with lung adenocarcinoma and 25 with lung squamous carcinoma. These patients received surgical intervention and cancers were staged according to the International System of Staging for Lung Cancer (6*th* edition) [7]. Tissues were formalin-fixed, paraffin-embedded (*FFPE*) sectioned for observation. The demographics and clinicopathological characteristics (age, gender, stage, tumor grade, lymph node metastasis) at baseline were collected after reviewing medical record. The overall survival was determined from the date of surgery for lung cancer to the time of death. Censored data were defined at the time

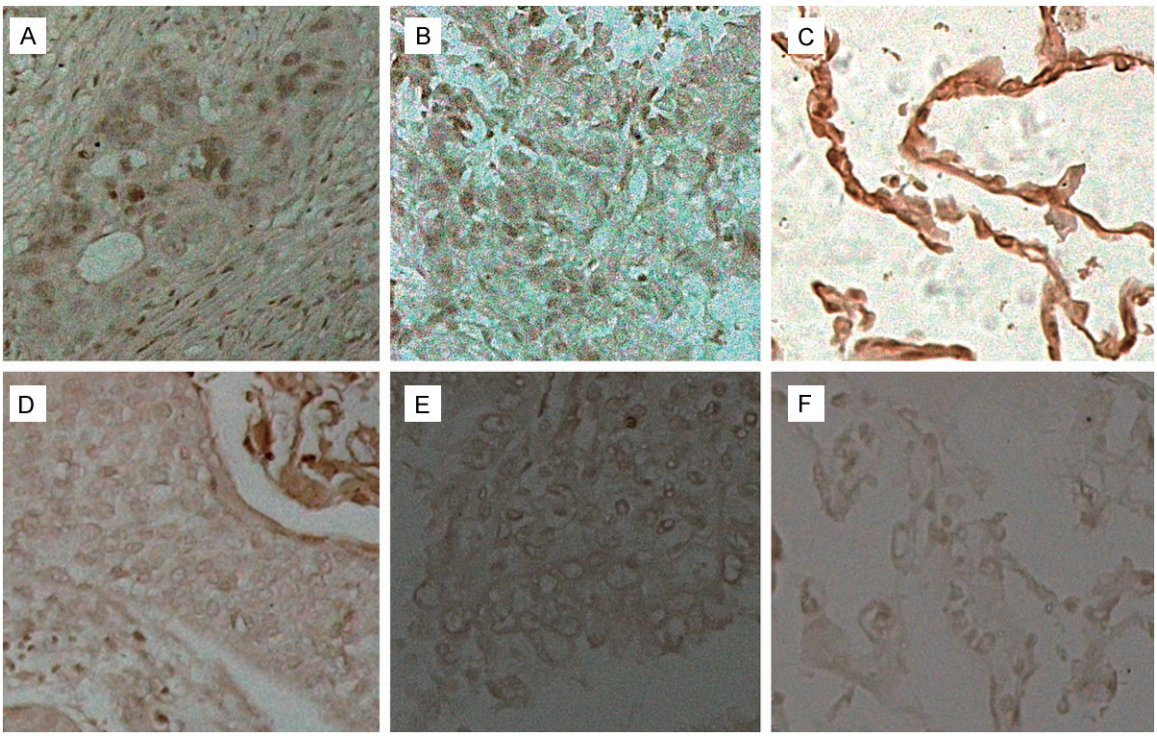


Figure 1. Figure 1 Immunohistochemistry analysis. A: SCC *SARI* (+); B: ADC *SARI* (+); C: Adjacent Tissue *SARI* (+); D: SCC *SARI* (-); E: ADC *SARI* (-); F: Adjacent Tissue *SARI* (-).

of the last follow up when the date of death was unclear, patients were alive or patients had recurrence. This study was approved by the Ethics Committee of Xinqiao Hospital.

The tissue microarray (diameter, 1.5 mm; depth, 4 μm) was prepared by *Outdo Biotech* (Shanghai, China) using standard techniques [8]. Additional *TMAs* were purchased from Shanghai Outdo Biotech.

Cells and cell culture

Lung cancer cell line (*A549* cells) was obtained from the Committee of Type Culture Collection of Chinese Academy of Sciences (Shanghai, China). Cells were cultured in *RPMI* 1640 supplemented with 10% (*v/v*) fetal bovine serum (*FBS*) and antibiotics (50 μg/ml each of penicillin, streptomycin and gentamicin) at 37°C in a humidified environment with 5% CO_2.

Immunohistochemistry

All tissue sections were routinely deparaffinized, rehydrated, and prepared for immunohistochemistry. Sodium citrate buffer (*pH* 6) was used as an antigen retrieval solution. Sections were blocked with 5% *BSA*, and incubated with 1:50 polyclonal anti-*SARI* antibody (SANTA CRUZ BIOTECHNOLOGY INC. USA) overnight and then with secondary antibodies and *DAB* reagent (Boshida, Wuhan, China). After dehydration, visualization was done with 3.3-diaminobenzidine (Gene Tech, Shanghai, China). For *SARI* is mainly expressed in the nucleus, we did not counterstain the nucleus with hematoxylin.

Scoring: The *SARI* expression was scored by evaluating the staining intensity of positive cells. Positive cells had brown granules, and scoring was done as follows: negative (-), no staining; weak positive (+), positive cells was < 50% and staining intensity was low; strong positive (+ +), positive cells were more than 50% or staining intensity was high. The *kit* had provided positive controls, and *TBS* was used in the negative control group.

Construction and infection of SARI expression adenovirus vector

T-293 cells (Molecular Genetic Research Third Military Medical University) were maintained, and total *RNA* was extracted and underwent

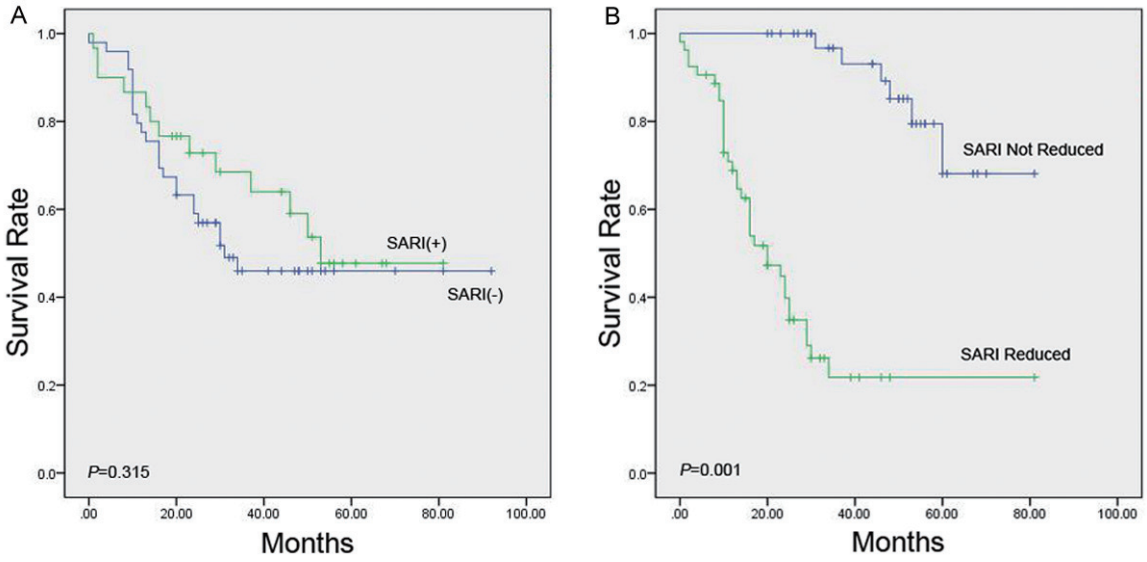


Figure 2. SCC patients' survival rate. The overall survival rate of patients with SCC estimated according to the SARI expression level in SCC tissue samples (*Log Rank* test) with immunohistochemical staining.

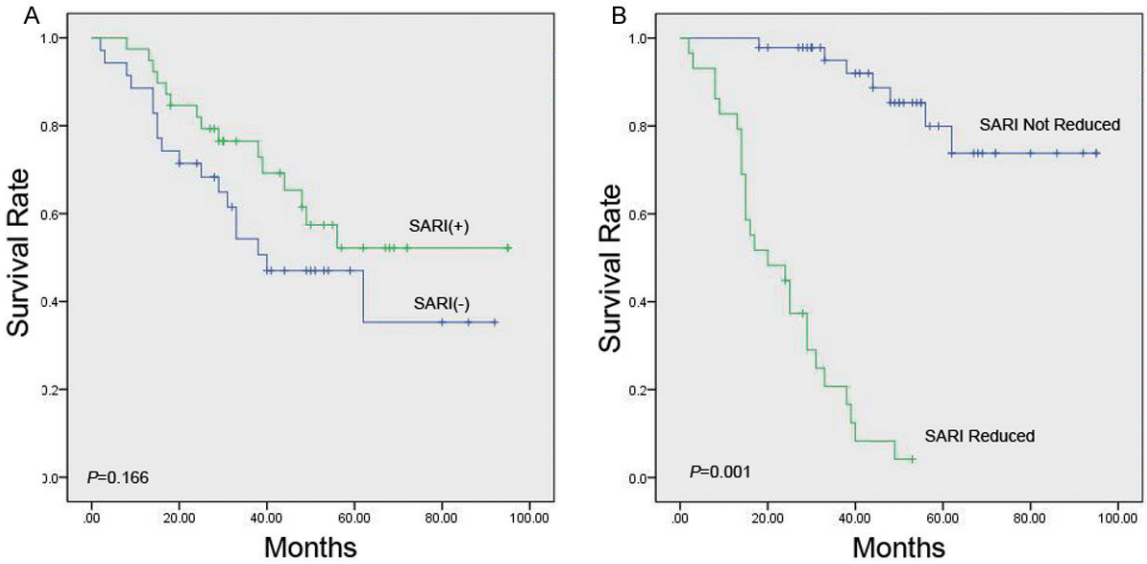


Figure 3. ADC patients' survival rate. The overall survival rate of patients with ADC estimated according to the *SARI* expression level in ADC tissue samples (*Log Rank* test) with immunohistochemical staining.

reverse transcription into *cDNA* which was used for *PCR* amplification of *bATF* gene. The primers were as follows: *bATF*: 5'-GCCTAAGCC-ATGCACCTCTGT-3', (forward) *bATF*: 5'-GCTCCG-AAGACCAGGTTAGAAGT-3' (reverse), and the expected size was 849 *bp*. By using common agarose gel *DNA* recovery *kit* (Beijing day root company) recovery of *DNA* fragments, *PCR* product through the *T4 DNA* ligase connection *PTA2* carrier, transformation competent Escherichia coli *DH5 α*, with ampicillin *LB* medium plate screening, incubation overnight, pick take positive clone colony, shake bacteria after alkali cracking method extracted plasmid, after the sequencing results right plasmid named *PTA2-BATF*; then *BATF* target gene connection adenovirus skeleton carrier *Adtrack*, get *Adtrack-BATF* recombinant plasmid, *NotI* and *HindIII* were used to digest cells aiming to confirm whether transfection was successful.

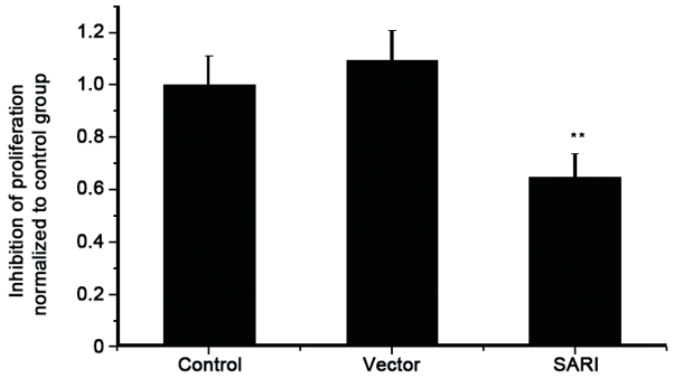


Figure 4. Ratio of inhibition of proliferation after *SARI* gene transfer. Proliferation in *SARI* over expression group was significantly lower than control group and vector group ($p < 0.001$).

There were *BATF* transfected *A549* cells, negative control group (empty virus vector infected *A549* cells) and blank control group (*PBS* infected *A549* cells).

MTT assay

MTT assay was done to determine the cell proliferation. In brief, *A549* cells (2×10^4) were plated in 96-well plates (Boshida; Wuhan, China) and then transfected with control or *SARI*-adenovirus vector. After incubation for 48 *h*, cells were stained with *Cell Stain* (Chemicon; Tokyo, Japan) and quantified by measuring the optical density (OD) at 560 nm (OD_{560}).

Scratch wound healing assay

The scratch wound healing assay was employed to investigate the cell migration. *A549* cells (2×10^5) were plated in 6-well plates (Boshida; Wuhan, China) and then transfected with control or *SARI*-adenovirus vector. After incubation for 48 *h*, a sterilized 200-*μl* pipet tip was used to scratch the monolayer cells across the center of the well with the long-axial of the tip always being perpendicular to the bottom of the well. Cells were washed with *PBS*, followed by incubation for 0 *h* and 24 *h*. Cells were observed under a light microscope (× 40) and the gap distance was quantitatively evaluated using software. Experiment was done 3 times, and the average was obtained.

Statistical analysis

The *SPSS version 18.0* (SPSS Inc., Chicago, IL) was used for statistical analysis. A value of $P < 0.05$ was considered statistically significant.

Results

Clinicopathologic characteristics

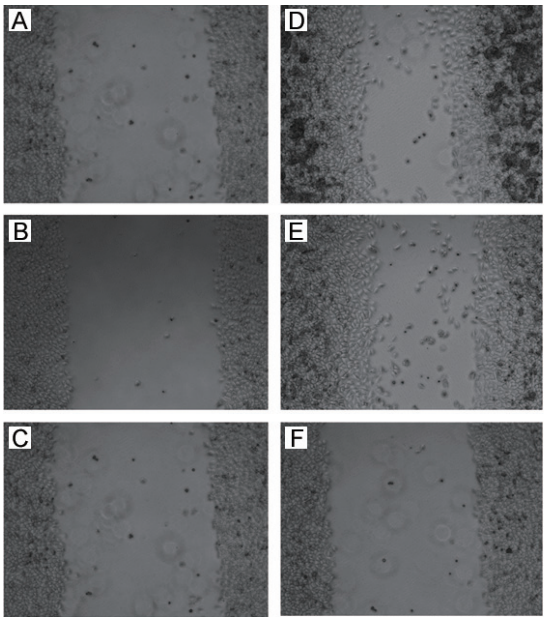
A total of 195 *NSCLC* patients were recruited into this study. The mean age was 62.61 years (range: 37-84 years) and 75.90% of patients were males. All patients received surgical intervention and pathological examination. Squamous cell carcinoma (*SCC*) was found in 100 patients (51.28%) and adenocarcinoma *ADC* in 95 (48.72%). In addition, 84 (43.08%) patients had lymph node metastasis and 111 (56.92%) had no lymph node metastasis. Moreover, 159 patients were randomly selected to receive follow up. The median duration of follow up was 37.99 months (range: 6-95 months) in survived patients, and a total of 73 (45.91%) patients died during the study. The median survival time was 21.38 months (range: 0-62 months).

Association of SARI expression with lung cancer pathology and clinical stage

Results showed *SARI* is mainly expressed in the nuclei (**Table 1**, **Figure 1**). About 52.82% of cancer cells expressed *SARI* and almost 88.72% of normal cells in the adjacent tissues expressed *SARI*. In addition, in 98 cases, *SARI* expression in the cancer was lower than that in adjacent tissues. There were no relationships of *SARI* expression in *NSCLC* with the types of lung cancer, age and sex, but correlation was found with the pathological classification and clinical stage of lung cancer: the higher the differentiation, the higher the rate of *SARI* expression was (I *vs.* II, $p = 0.006$; I *vs.* III $p = 0.003$); the higher rate of the *SARI* expression and the more advanced the lung cancer, *SARI* positive expression rate is lower (I *vs.* II, $p = 0.003$; I *vs.* III $p = 0.001$; II *vs.* III $p = 0.003$); the *SARI* expression rate in patients with lymph node metastasis was significantly lower than that in patients without lymph node metastasis ($p = 0.001$).

Association between SARI expression and patients' survival

The estimated survival time was calculated with *Kaplan-Meier* method. In squamous carcinoma patients and adenocarcinoma patients, *SARI* expression had no significant relationship



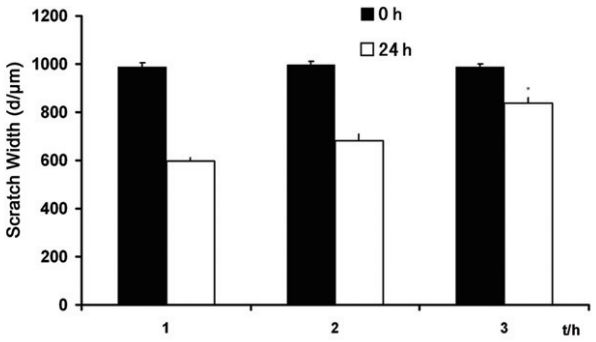


Figure 5. Effects of *SARI* over expression on migration ability of lung cancer *A549* cells Scratch test of each group: A: Control group 0 h (× 40); B: Vector group 0 h (× 40); C: *SARI* over expression group 0 h (× 40); D: Control group 24 h (× 40); E: Vector group 24 h (× 40); F: *SARI* over expression group 24 h (× 40). The migration width of *SARI* over expression group (837 ± 24 *μm*) was significantly higher than control group and vector group (597.7 ± 13.9 *μm*, 680.5 ± 30.5 *μm*; $p < 0.001$), which prompted that *SARI* over expression could significantly inhibit *A549* cells migration.

with survival time. However, in a specific patients whose tumor cells had reduced *SARI* expression as compared to adjacent tissues, survival time was significantly shorter than that of patients without reduced SARI expression in cancer cells (*Log Rank* test, $p < 0.01$; **Figures 2** and **3**).

Proliferation of A549 cells after SARI gene transfection

The *A549* cells were transfected with *Adtrack-BATF* recombinant plasmid for 48 *h* and *MTT* assay was done to detect the proliferation of *A549* cells. Results showed that the proliferation of transfected cells was significantly inhibited as compared to normal control group and blank control group ($p < 0.05$, **Figure 4**).

3.5 Scratch wound healing of A549 cells after SARI gene transfection: The A549 cells were transfected with *Adtrack-BATF* recombinant plasmid for 24 *h*, and Scratch wound healing assay was performed to detect the migration ability of *A549* cells. Results showed that the migration ability of *SARI* transfected cells was obviously suppressed when compared with normal control group and blank control group ($p < 0.05$, **Figure 5**).

Discussion

Lung cancer is one of the malignant tumors with the highest incidence and mortality, and it has a poor prognosis despite its diagnosis and therapy has been improved. One of the most promising strategies for lung cancer treatment is targeted therapy in which some key genes or pathways are regulated to inhibit the tumor growth. Therefore, it is imperative to identify specific molecular biomarkers of lung cancer.

SARI, (also known as *mda-D-74*) is an important gene and the melanoma differentiation associated gene (*mda*), which can make the human melanoma cells irreversible growth inhibition and terminal differentiation *in vitro* [9]. To date, a series of *mda* genes have been identified, including *mda-5* [10] , *mda-7* [11], *mda-9* [12] and so on. These genes are closely related to the immunity, tumor suppressor and tumor metabolism [13-15].

SARI is a 274 amino acid protein containing one *bZIP* domain, and has similarity with *BATF* and *BATF3*, which belong to the *AP-1/ATF* superfamily of transcription factors, suggesting that *SARI* may be involved in the transcriptional regulation. However, *SARI* gene has its specific structural place, *AP-1* transcription factors family *(p65, p50, p52, RelB* and *Rel*) and its members are composed of two polymers possessing transcriptional activity [16]. A lot of *AP-1* protein contains *bZIP* and *AD* domain. However, three *BATF* proteins have been found to belong to *AP-1* protein family and only contain *bZIP* domain (no *AD* domain). After binding to *AP-1* transcription factor, *BATF* can inhibit *AP-1* tran-

scription activity. *SARI* is one of above three *BATF* protein, and can form dimmers in the *JUN* subunit of *AP-1*. Through the basic leucine zipper domain, the *AP-1* transcription factor's dimer subunit combination inhibits the *AP-1* transcription activity [17]. Recently, Su *et al* [3] found that over-expression of *SARI* induced profound growth inhibition and apoptosis in malignant glioma, melanoma and prostate cancer cell lines with no effect on the survival of corresponding normal cells. However, no studies have been conducted to investigate the role of *SARI* in lung cancer.

In the present study, the *SARI* expression was detected in cancer tissues and adjacent normal tissues of *NSCLC* patients. Results showed *SARI* protein was mainly expressed in the nucleus, and normal tissues had moderate *SARI* expression. In the cancer tissues (squamous carcinoma and adenocarcinoma), the *SARI* expression significantly reduced; in patients with advanced *NSCLC,* the *SARI* expression was significantly lower than that in patients with lung cancer at early stage (I *vs.* II, $p = 0.003$; I *vs.* III $p = 0.001$; II *vs.* III $p = 0.003$). In addition, the *SARI* expression in patients with lymph node metastasis was significantly lower than that in patients without lymph node metastasis ($p = 0.001$). In addition, the *SARI* expression and survival time were compared between patients with squamous carcinoma and adenocarcinoma. Results indicated that the *SARI* expression in cancer tissues had no relation with survival time of patients in both groups. However, in a specific patient, the survival time in patients with reduced *SARI* expression as compared to adjacent normal tissues was significantly shorter than that in patients without reduced *SARI* expression (*Log Rank* test, $p < 0.01$). Therefore, lower *SARI* expression predicts a poor prognosis of the lung cancer patients which was consistent with the results in the study of Ma, *et al* [18] on liver cancer.

One of characteristics of cancer cell growth is out of control and abnormal proliferation [3]. In order to further confirm the relationship between *SARI* expression and lung cancer cell growth and migration, *SARI* gene was transfected into *A549* cells, which were negative for *SARI*, and the detection of cell growth and scratch wound healing assay were performed. Results showed that the proliferation and migration of *A549* cells were significantly inhibited ($p < 0.05$) after transfection of by *SARI* gene. This indicates that the *SARI* expression can inhibit the proliferation and migration of lung cancer cells, which was consistent with the fact that patients with lung cancer positive for *SARI* had low grade cancer, were less likely to develop lymph node metastasis and had longer survival time. Thus, we speculated that *SARI* as an *AP-1* inhibitory protein can selectively inhibit cancer growth via the interaction with *c-Jun*, thus indirectly interfering with the function of transcription factor *AP-1* complex, which finally results in the inhibited proliferation and survival of cancer cells [19].

Taken together, our findings showed that decreased *SARI* expression in Chinese patients with *NSCLC* had a poor prognosis, and overexpression of SARI in *A549* cells by transfection could inhibit the growth and migration of these cells. Thus, we postulate that *SARI* may serve as a marker for the diagnosis and prognosis of *NSCLC* and as a target for future treatment of *NSCLC*.

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Disclosure of conflict of interest

None.

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