

SIRT1 expression is associated with poor prognosis of lung adenocarcinoma

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Abstract: Several studies have reported that the overexpression of Sirtuin 1 (SIRT1) was associated with poor prognosis in various human cancers. However, little is known regarding the prognostic value of SIRT1 in lung adenocarcinoma. Therefore, the aim of this study is to evaluate the role of SIRT1 in the prognosis of lung adenocarcinoma patients. Using a tissue microarray, we detected SIRT1 expression by immunohistochemistry in lung adenocarcinoma tissue, as well as in corresponding noncancerous tissues (NCTs). A high expression level of SIRT1 was observed in 74.7% (56/75) of patients with lung adenocarcinoma and 6.7% (5/75) of NCTs ($P < 0.001$). SIRT1 expression was significantly associated with high pathological stage. Importantly, we found that SIRT1 expression was associated with worse overall survival in these lung adenocarcinoma patients (67.0 months vs 104.5 months; $P = 0.005$). In addition, anaplastic lymphoma kinase, epidermal growth factor receptor, vascular endothelial growth factor (VEGF), and Survivin expression were evaluated by fluorescent in situ hybridization or immunohistochemistry, respectively. We found that VEGF and Survivin were both highly expressed in the lung adenocarcinoma tissues, as compared to NCTs. Moreover, the SIRT1 and VEGF expression statuses were significantly positively correlated ($r = 0.238$, $P = 0.039$), while SIRT1 and Survivin expression status were not significantly correlated ($r = 0.220$, $P = 0.058$). Correlation analysis showed a positive correlation between VEGF and Survivin expression ($r = 0.436$, $P < 0.001$). However, we found that VEGF and Survivin expression were not associated with the prognosis of lung adenocarcinoma patients ($P = 0.334$; $P = 0.433$, respectively). Taken together, our findings suggest that SIRT1 plays a role in the progression of lung adenocarcinoma and may be a significant prognostic indicator for lung adenocarcinoma patients.

Keywords: SIRT1, VEGF, Survivin, prognosis, lung adenocarcinoma

Introduction

Silent mating-type information regulation 2 homolog 1 (SIRT1) is one of the mammalian homologs of silent information regulator 2 (Sir2), which functions as a nicotinamide adenine dinucleotide (NAD⁺)-dependent histone deacetylase.^{1,2} SIRT1 deacetylates not only histones, but also many nonhistone proteins, such as p53, p73, androgen receptor (AR), Ku70, NF- κ B, E2F1, and FOXO, which are involved in cell growth, apoptosis, cell senescence, and tumorigenesis.³⁻⁷ Upregulation of SIRT1 has been reported in various human malignancies including prostate cancer, breast cancer, lung cancer, lymphoma, colon cancer, and gastric cancer.⁸⁻¹¹ However, the role of SIRT1 in malignant tumors is controversial. On the one hand, SIRT1 might act as a tumor promoter by inhibiting tumor suppressor genes such as p53. It was reported that SIRT1 could bind and deacetylate p53, resulting in repressing p53-mediated transactivation.¹² On the other hand, SIRT1 might also act as a tumor suppressor by repressing several oncogenes or oncoproteins such as Survivin.¹³ Wang et al¹³ reported that SIRT1 negatively regulated Survivin expression, leading to reduced tumor cell

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proliferation and increased apoptosis. Thus, SIRT1 can serve as a tumor promoter or suppressor, depending on the oncogenic pathways specific to particular tumors.

Several studies reported that overexpression of SIRT1 was associated with poor prognosis in various human cancers, including hepatocellular carcinoma,¹⁴ diffuse large B-cell lymphoma,¹⁵ gastric carcinoma,^{16,17} breast carcinoma,^{18,19} soft-tissue sarcomas,²⁰ and colorectal carcinoma.²¹ However, it was also reported that overexpression of SIRT1 was associated with good prognosis in colorectal carcinoma, as well as in head and neck squamous cell carcinoma.^{22,23} However, despite the ongoing evaluation of SIRT1 as a therapeutic target, little is known regarding the prognostic value of SIRT1 in lung adenocarcinoma. Therefore, the aim of this study is to evaluate the role of SIRT1 in the prognosis of lung adenocarcinoma patients. Here, we examined the expression of SIRT1 and related proteins such as Survivin and vascular endothelial growth factor (VEGF), and their relationship to clinicopathological features and prognosis in lung adenocarcinoma patients.

Materials and methods

Clinical samples

Lung adenocarcinoma tissues and corresponding noncancerous tissue (NCT) sections containing HLug-Ade150Sur-01 (75 cancer cases and 75 NCTs) were provided by Outdo Biotech Co., Ltd. (Shanghai, People's Republic of China). None of the patients received chemotherapy or radiotherapy prior to surgery. The experiments were approved by the Ethics Committee of Jinling Hospital (Nanjing, People's Republic of China) and were conducted in compliance with the Declaration of Helsinki. Disease histology was determined in accordance with the criteria of the World Health Organization. Pathologic staging was performed in accordance with the current International Union against Cancer tumor-lymph node metastasis classification.

Immunohistochemistry

Lung adenocarcinoma tissue samples were deparaffinized in xylene. Heat-mediated antigen retrieval was applied using citrate buffer (BioGenex Laboratories, Inc., San Ramon, CA, USA). The immunostaining began with SIRT1 (rabbit monoclonal, ab32441; Abcam plc, Cambridge, UK), Survivin (rabbit monoclonal, ab134170; Abcam plc), and VEGF (mouse monoclonal, ab1316; Abcam plc) as primary antibodies for 60-minute staining, and it continued with the MaxVision™ HRP-Polymer anti-Rabbit IHC Kit (KIT-5005; Maxim) for 15 minutes, according to the manufacturers' protocol, and it

was followed by diaminobenzidine (D-5637; Sigma-Aldrich Co., St Louis, MO, USA) for visualization. All sections were counterstained with hematoxylin.

Evaluation of immunoreactivity

Every section was evaluated and scored independently by two pathologists. The H-score method was used in this trial. We multiplied the percentage score by the staining intensity score. The percentage of positively stained cells was scored as “–” (0%), “+” (1%–25%), “++” (26%–50%), or “+++” (51%–100%). Intensity was scored as “–” (negative), “+” (weak), “++” (moderate) and “+++” (strong). Immunohistochemical scoring was performed without prior knowledge of the clinical response. Immunostained sections were scanned using a microscope (Axiovert 200; Carl Zeiss Meditec AG, Jena, Germany).

Fluorescent in situ hybridization

Fluorescent in situ hybridization (FISH) was performed on 4 μm paraffin-embedded tissue sections following deparaffinization and digestion. The slides were washed in saline-sodium citrate buffer, fixed in 10% buffered formalin for 5 minutes, dehydrated in graded alcohol, and allowed to air dry. Hybridization was performed using a dual-color break-apart rearrangement probe (ZSGB-BIO, Beijing, People's Republic of China) for the *EGFR* and *ALK* gene on chromosome 7 and 2, respectively. The probes were denatured by incubation at 78°C for 5 minutes in a humidified box, after which they were hybridized overnight at 42°C. The following day, the cover glass was removed and the slides were washed in posthybridization washing-buffer (Vysis) at 72°C for 2 minutes. After drying, 4'-6-diamidino-2-phenylindole (DAPI) (Vysis) was applied and the slides were protected from light at –20°C until reading. Automated scanning, capture, and scoring of interphase FISH was analyzed by the CytoVision® System (Applied Imaging Corp., San Jose, CA, USA).

Statistical analyses

SPSS Statistics 19.0 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. Data were analyzed using one-way analysis of variance or a Student's *t*-test. Data are presented as the mean ± standard deviation of three independent experiments. The χ^2 tests were used to compare the distribution of demographic variables between the high and low SIRT1 expression groups. The log-rank test was used to assess the statistical significance of Kaplan-Meier plots. Univariate and multivariate analyses were performed using

the Cox proportional hazards regression model to identify the most significant variables for predicting overall survival (OS). For immunohistochemistry (IHC) data, the two-related samples test between lung adenocarcinoma tissues and NCTs was used, and the statistical significance of the correlation between SIRT1, Survivin, and VEGF expression level in lung adenocarcinoma tissues or in NCTs was estimated by Spearman's rank correlation analysis; statistical significance was again defined as $P < 0.05$ or $P < 0.001$.

Results

Patient characteristics

The clinicopathological features of 75 lung adenocarcinoma patients are summarized in Table 1. In all, 75 patients with a median age of 59 years (range, 20–84 years) were included in the final analyses. Among these cases, 39 (52.0%) patients were male and 36 (48.0%) patients were female. According to the Union for International Cancer Control cancer staging systems 7th edition stage grouping criteria, 46 (61.3%) cases were stage I–II and 19 (25.3%) were stage III–IV.

In addition, we detected *ALK* and *EGFR* expression of the 75 lung adenocarcinoma patients using FISH. Representative figures of *ALK*- and *EGFR*-positive or -negative expression were shown in Figure 1. Briefly, eight (10.7%) cases positively expressed *ALK*, while 67 (89.3%) cases negatively expressed *ALK*. There are 29 (38.7%) patients with *EGFR*-positive and 46 (61.3%) patients with *EGFR*-negative expression (Table 1).

The association between SIRT1 expression and clinical characteristics of lung adenocarcinoma patients

The expression status of SIRT1 was determined in 75 lung adenocarcinoma tissues and corresponding NCTs by IHC. As shown in Figure 2, the expression of SIRT1 in the tumor tissues and NCTs of patient number 9 were high, while the SIRT1 expression of patient number 34 was low. In total, a high expression level of SIRT1 was observed in 74.7% (56/75) of patients with lung adenocarcinoma and 6.7% (5/75) of NCTs ($P < 0.001$). As shown in Table 2, SIRT1 expression

Table 1 Relationship between the expression of SIRT1 and the clinicopathological features of lung cancer patients

Variables	Total (n=75)		SIRT1 high (n=56)		SIRT1 low (n=19)		P-value
	N	%	N	%	N	%	
Sex							0.318
Male	39	52.0	31	55.4	8	42.1	
Female	36	48.0	25	44.6	11	57.9	
Age							0.232
≤59 years	38	50.7	26	46.4	12	21.5	
>59 years	36	48.0	29	51.8	7	36.8	
NA*	1	1.3	1	1.8	0	0	
Histological grade							0.028*
I	13	17.3	6	10.7	7	36.8	
II	47	62.7	37	66.1	10	52.6	
III	15	20.0	13	23.2	2	10.5	
TNM stage							0.223
I–II	46	61.3	33	58.9	13	68.4	
III–IV	19	25.3	17	30.4	2	10.5	
NA	10	13.3	6	10.7	4	21.1	
ALK							1.000
Positive	8	10.7	6	10.7	2	10.5	
Negative	67	89.3	50	89.3	17	89.5	
EGFR							0.201
Positive	29	38.7	24	42.9	5	26.3	
Negative	46	61.3	32	57.1	14	73.7	
Survivin							0.057
High	49	65.3	40	71.4	9	47.4	
Low	26	34.7	16	28.6	10	52.6	
VEGF							0.039*
High	50	66.7	41	73.2	9	47.4	
Low	25	33.3	15	26.8	10	52.6	

Note: *denotes statistical significance.

Abbreviations: SIRT1, silent mating-type information regulation 2 homolog 1; n, sample number; N, total number; NA, not available; TNM, tumor–node–metastasis; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; NA, not available.

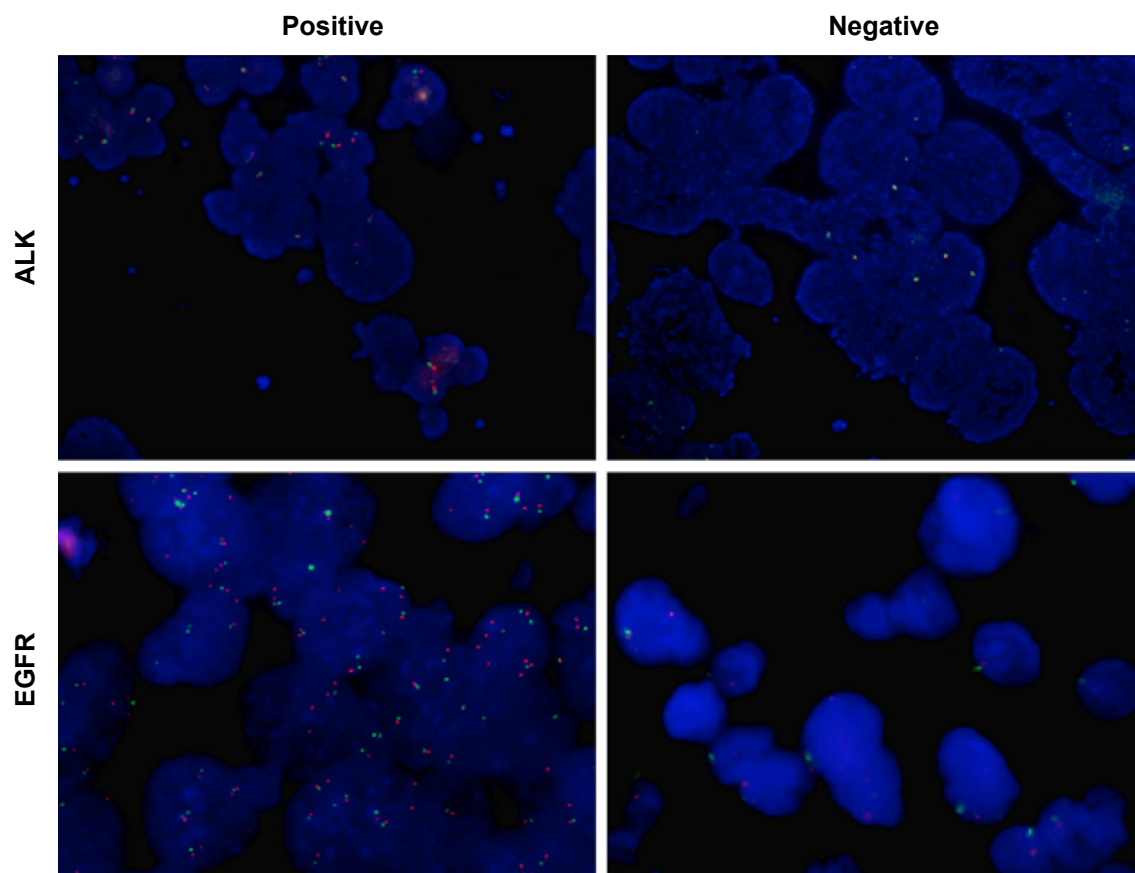


Figure 1 ALK and EGFR expression in lung adenocarcinoma tissues by fluorescent in situ hybridization.

Notes: Representative figures of ALK-positive (patient number 27), ALK-negative (patient number 9), EGFR-positive (patient number 32), and EGFR-negative (patient number 45) expression, respectively (magnification: 200 \times).

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

was significantly increased in lung adenocarcinoma tissues when compared with NCTs ($P < 0.001$). Moreover, we also assessed the association between SIRT1 expression status and the clinical characteristics of lung adenocarcinoma patients (Table 1). We found that SIRT1 expression was significantly associated with pathological stage ($P = 0.028$), but it was not related to sex, age, tumor–node–metastasis (TNM) stage, and *ALK* and *EGFR* expression status (Table 1).

SIRT1 expression predicted the prognosis of lung adenocarcinoma

The association between SIRT1 expression status and OS in lung adenocarcinoma patients was studied by log-rank test. Patients with a high expression of SIRT1 had markedly shorter OS than those with low SIRT1 expression (67.0 months vs 104.5 months, respectively; $P = 0.005$). The Kaplan–Meier survival curve is shown in Figure 3. Moreover, univariate analysis for the predefined variables showed that age, TNM stage, and SIRT1 expression were significantly associated with OS in lung adenocarcinoma patients. During

the multivariate analysis, age and TNM stage were independent adverse prognostic factors for OS (Table 3). However, multivariate analysis showed that SIRT1 expression was not an independent predictor of poor prognosis ($P = 0.087$; hazard ratio = 0.347; 95% confidence interval = 0.103–1.167). Taken together, our data suggested that the expression of SIRT1 correlated with OS, but it was not an independent predictor of poor prognosis in lung adenocarcinoma.

The association between SIRT1 and Survivin or VEGF expression in lung adenocarcinoma

This study had reported that the overexpression of Survivin and VEGF may be important in the tumorigenesis of small cell lung cancer (SCLC), and that overexpression can be used to indicate the poorer prognosis of SCLC.²⁴ Thus, we detected the expression of Survivin and VEGF in the 75 lung adenocarcinoma patients. Figure 2 showed the expression level of Survivin and VEGF in the tumor tissues and NCTs in two representative patients. As shown in Table 1,

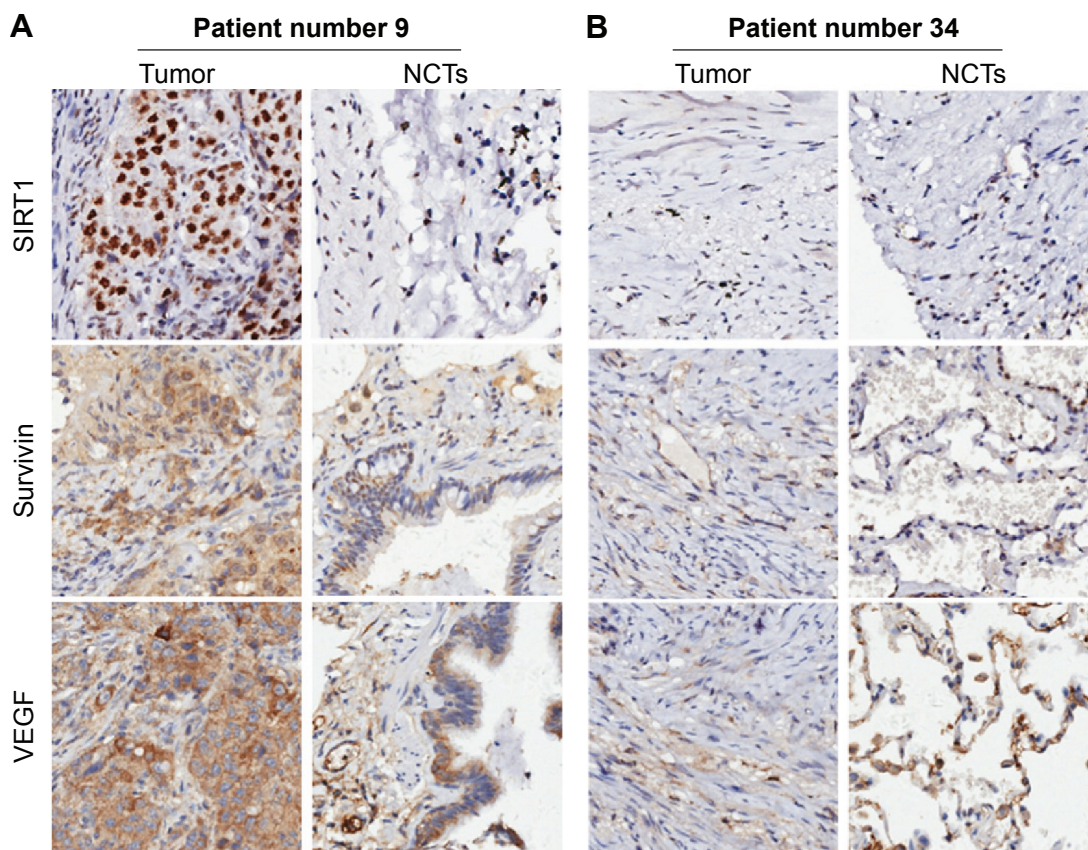


Figure 2 SIRT1, Survivin, and VEGF expression in lung adenocarcinoma tissues by immunohistochemical staining. **Notes:** SIRT1, Survivin, and VEGF expression in the tumor tissues or corresponding NCTs of (A) patient number 9 and (B) patient number 34, respectively (magnification: 200×). **Abbreviations:** NCTs, noncancerous tissues; SIRT1, silent mating-type information regulation 2 homolog 1; VEGF, vascular endothelial growth factor.

Table 2 SIRT1, VEGF, and Survivin expression in a lung cancer and NCT microarray

	Lung cancers (n=75)		NCTs (n=75)		P-value
	N	%	N	%	
SIRT1					<0.001*
0	7	9.3	50	66.7	
+	12	16.0	20	26.7	
++	40	53.3	5	6.7	
+++	16	21.3	0	0	
VEGF					<0.001*
0	10	13.3	34	45.3	
+	15	20.0	27	36.0	
++	18	24.0	10	13.3	
+++	32	42.7	4	5.3	
Survivin					<0.001*
0	9	12.0	32	42.7	
+	17	22.7	32	42.7	
++	11	14.7	9	12.0	
+++	38	50.7	2	2.7	

Note: The plus signs indicate the level of expression, and the asterisk indicates statistical significance. **Abbreviations:** SIRT1, silent mating-type information regulation 2 homolog 1; VEGF, vascular endothelial growth factor; NCT, noncancerous tissue; n, sample number; N, total number.

the χ^2 tests showed that SIRT1 expression was significantly associated with VEGF expression status ($P=0.039$), but not Survivin expression status ($P=0.057$). In addition, VEGF and Survivin expression were both significantly increased in lung adenocarcinoma tissues when compared with NCTs

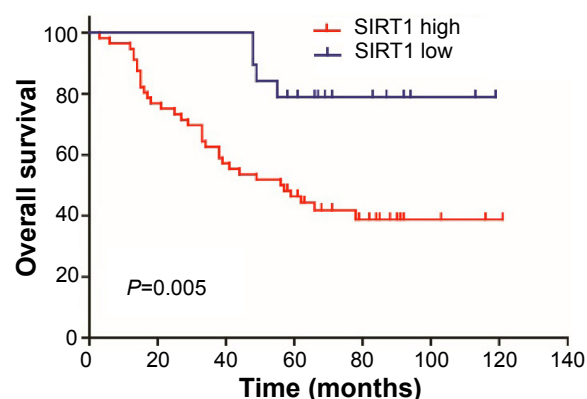


Figure 3 The association of SIRT1 with overall survival in lung adenocarcinoma. **Note:** High expression of SIRT1 was associated with worse overall survival in lung adenocarcinoma ($P=0.005$). **Abbreviation:** SIRT1, silent mating-type information regulation 2 homolog 1.

Table 3 Univariate and multivariate Cox regression analysis of overall survival in lung cancer patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (male vs female)	1.115 (0.584–2.131)	0.741		
Age	1.032 (1.002–1.063)	0.038*	1.049 (1.014–1.085)	0.006*
Histological grade (I+II vs III)	0.607 (0.286–1.288)	0.194		
TNM stage (I+II vs III+IV)	0.235 (0.115–0.479)	0.000*	0.190 (0.086–0.418)	0.000*
ALK (negative vs positive)	1.913 (0.586–6.243)	0.282		
EGFR (negative vs positive)	0.682 (0.356–1.308)	0.250		
Survivin (negative vs positive)	0.756 (0.374–1.531)	0.437		
VEGF (negative vs positive)	0.702 (0.340–1.450)	0.339		
SIRT1 (negative vs positive)	0.251 (0.089–0.709)	0.009*	0.347 (0.103–1.167)	0.087

Note: *indicates statistical significance.

Abbreviations: HR, hazard ratio; CI, confidence interval; TNM, tumor–node–metastasis; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; SIRT1, silent mating-type information regulation 2 homolog 1.

($P < 0.001$; $P < 0.001$, respectively). We then analyzed the correlation between SIRT1 and VEGF or Survivin expression at the tumor microarray (Table 4). A significant and positive correlation was found between SIRT1 and VEGF expression status using the lung adenocarcinoma tissue array ($r = 0.238$, $P = 0.039$), while SIRT1 expression status was not significantly associated with Survivin expression status ($r = 0.220$, $P = 0.058$). Moreover, correlation analysis showed a positive correlation between VEGF and Survivin expression ($r = 0.436$, $P < 0.001$; Table 5).

VEGF and Survivin expression were not associated with overall survival of lung adenocarcinoma

We then calculated the association between VEGF or Survivin expression status and OS in lung adenocarcinoma patients. As shown in Figure 4, patients with a high expression of VEGF and Survivin had shorter OS than those with low VEGF or Survivin expression (VEGF: 73.2 months vs 83.4 months; Survivin: 73.8 months vs 82.2 months,

Table 4 Correlation analysis of SIRT1 with VEGF or Survivin expression at tumor microarray

Variables	Tumor microarray (n=75)	
	SIRT1 (high)	SIRT1 (low)
VEGF (high)	41	9
VEGF (low)	15	10
<i>r</i>	0.238	
<i>P</i>	0.039*	
Survivin (high)	40	9
Survivin (low)	16	10
<i>r</i>	0.220	
<i>P</i>	0.058	

Note: The asterisk indicates statistical significance.

Abbreviations: SIRT1, silent mating-type information regulation 2 homolog 1; VEGF, vascular endothelial growth factor; n, sample number.

respectively). However, the association between VEGF or Survivin expression status and OS were not statistically significant ($P = 0.334$; $P = 0.433$, respectively).

Discussion

In the present study, it was revealed that the expression of SIRT1 correlated with OS and was a predictor of poor prognosis in lung adenocarcinoma. We found that SIRT1 expression was significantly increased in lung adenocarcinoma tissues compared with NCTs and it was significantly associated with pathological stage. Patients with high SIRT1 expression had a significantly shorter OS than those with low SIRT1 expression. Recently, several studies have shown that the overexpression of SIRT1 was associated with poor prognosis in various human cancers, such as gastric carcinoma¹⁶ and breast carcinoma.¹⁸ In contrast, SIRT1 expression was also reported to be associated with good prognosis for several human cancers, such as head and neck squamous cell carcinoma.²³ Interestingly, the role of SIRT1 expression in colorectal cancer has been controversial. Jung et al²² reported that SIRT1 overexpression is a good prognostic factor for colorectal cancer, while Chen et al²¹ showed that high levels of SIRT1 expression enhance tumorigenesis and are associated with a poor prognosis in colorectal carcinoma. The

Table 5 Correlation analysis of VEGF with Survivin expression at tumor microarray

Variables	Tumor microarray (n=75)	
	Survivin (high)	Survivin (low)
VEGF (high)	41	9
VEGF (low)	15	10
<i>r</i>	0.436	
<i>P</i>	<0.001*	

Note: The asterisk indicates statistical significance.

Abbreviations: VEGF, vascular endothelial growth factor; n, sample number.

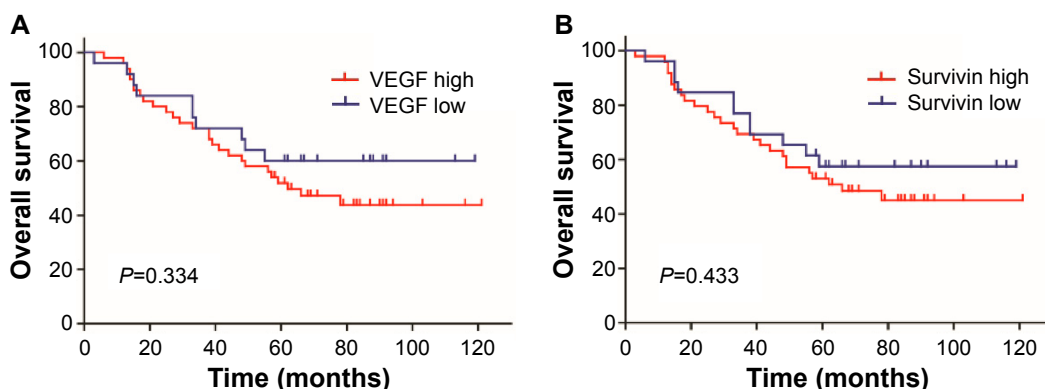


Figure 4 The association of VEGF and Survivin with overall survival in lung adenocarcinoma.

Notes: The expression of (A) VEGF and (B) Survivin was not associated with overall survival in lung adenocarcinoma ($P=0.334$; $P=0.433$, respectively).

Abbreviation: VEGF, vascular endothelial growth factor.

association between SIRT1 expression and the prognosis of lung cancer was also investigated. In non-SCLC (NSCLC), high expression of SIRT1 was significantly associated with shorter progression-free survival and OS.^{25,26} Moreover, patients with high SIRT1 expressions had a significantly higher chance of being resistant to chemotherapy than those with low SIRT1 expression.²⁵ However, little is known regarding the prognostic value of SIRT1 in lung adenocarcinoma. Here, we found that patients with high SIRT1 expression had a significantly shorter OS than those with low SIRT1 expression. These findings are consistent with previous reports indicating that SIRT1 is a tumor promoter in lung adenocarcinoma.²⁷

Survivin functions as an inhibitor of apoptosis and plays a crucial role in regulating cell proliferation, apoptosis, and angiogenesis.²⁸ Overexpression of Survivin has been implicated in tumor progression in various human cancers, including lung cancer.²⁹ Previous studies have shown that the expression of VEGF is correlated with the expression of Survivin in many cancers,³⁰ and overexpression of Survivin and VEGF were also reported to predict poor prognosis of both SCLC and NSCLC.^{24,31} In the present study, we found that VEGF and Survivin were both highly expressed in the lung adenocarcinoma tissue when compared with NCTs. Correlation analysis showed a positive correlation between VEGF and Survivin expression. However, we also found that VEGF and Survivin expression were not associated with the prognosis of lung adenocarcinoma patients. There are reports that Survivin is, independently, a poor prognostic marker in lung adenocarcinoma, and that high Survivin expression has a significantly shorter disease-free survival and shorter OS.³² However, other studies show that Survivin is a prognostic marker of advanced-stage NSCLC, but not of early-stage NSCLC.³³ In the present study, most of the

patients are early-stage lung adenocarcinoma, which could explain why Survivin is not associated with OS. Moreover, correlation analysis showed that SIRT1 and VEGF expression status were significantly and positively correlated, while SIRT1 and Survivin expression status were not significantly correlated. This was consistent with the view that SIRT1720, a well-known agonist of SIRT1, significantly increased the amount of VEGF secreted from cancer cells, and it promoted cancer cell migration and lung metastasis in breast cancer.³⁴ However, the direct effects between SIRT1 and VEGF should be validated by large-scale association clinical studies and demonstrated by further studies in vitro and in vivo.

To our knowledge, little has been reported concerning the role of SIRT1 expression on the prognosis of lung adenocarcinoma. Our results suggest that SIRT1 expression was significantly increased in lung adenocarcinoma tissues compared with NCTs, and it was significantly associated with pathological stage. Patients with high SIRT1 expression had a significantly shorter OS than those with low SIRT1 expression. In addition, we found that VEGF and Survivin were both highly expressed; we also found that SIRT1 and VEGF, but not Survivin, expression status was significantly and positively correlated in lung adenocarcinoma tissues. Taken together, our findings suggest that SIRT1 plays a critical role in the progression of lung adenocarcinoma and it may be a significant prognostic indicator for lung adenocarcinoma patients.

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Disclosure

The authors report no conflicts of interest in this work.

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