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High kinesin family member 18A expression correlates with poor prognosis in primary lung adenocarcinoma

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Keywords
Bioinformatics; kinesin family member 18A (KIF18A); lung adenocarcinoma (LUAD); prognosis.

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Abstract

Background: Lung adenocarcinoma (LUAD) is the most prevalent pathological subtype of lung cancer. Kinesin family member 18A (KIF18A) plays an important role in tumorigenesis. Its roles in breast cancer, colorectal cancer, and other tumors have been demonstrated; however, studies of KIF18A in LUAD are limited. This study aimed to determine the role of KIF18A in LUAD progression and prognostic prediction.

Methods: KIF18A expression was examined in LUAD cells and tissues by immunohistochemistry and Western blotting. Cell proliferation assay was performed to study the role of KIF18A in LUAD cells. Correlations between KIF18A expression and clinicopathological features were analyzed. The role of KIF18A in LUAD prognosis was evaluated using data from The Cancer Genome Atlas (TCGA).

Results: KIF18A expression was increased in tumor cells and tissues. Downregulation of KIF18A expression resulted in the suppression of cancer cell proliferation in in vitro assays, and was particularly related to poor tumor differentiation, big tumor size, lymph node metastasis, and more advanced tumor stage. In the TCGA dataset, high KIF18A messenger RNA expression was associated with poor disease-free and overall survival in patients with LUAD. In addition, multivariate analysis indicated that KIF18A is an independent prognostic factor of disease-free and overall survival in LUAD.

Conclusions: Collectively, our results demonstrate that KIFl8A is highly expressed in LUAD. KIFl8A plays an important role in LUAD cell proliferation, but is a poor prognostic factor.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, accounting for one million deaths per year.[1] Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer, with two main histological subtypes: adenocarcinoma and squamous cell carcinoma. As a common histological subtype of NSCLC, most clinical treatments of lung adenocarcinoma are decided based on the Union for International Cancer Control and American Joint Committee on Cancer (UICC/AJCC) staging system. Despite advanced and successful therapies for NSCLC, five-year survival currently varies from 4% to 17%, depending on the stage and regional differences.[2,3] Therefore, it is important to determine biomarkers that can predict the risk of high recurrence and metastasis.

During tumor progression, cellular division is unregulated, and aberrant mechanisms drive chromosome congregation.[4] To date, human kinesin superfamily proteins (KIFs) have been identified and classified into 14 families (1–14) according to the standardized nomenclature for kinesins.[5] A number of KIFs are known to be involved in diseases, especially tumorigenesis and carcinogenesis. Abnormally expressed kinesins and motor proteins are key

proteins that regulate mitotic events and are the potential targets of human cancers.[5–7] Taniwaki *et al.* reported approximately five-fold upregulation of KIF4A, most often in cases of small-cell lung cancer.[8] In approximately 40% of NSCLC cases, the treatment of NSCLC cells with specific small interfering RNAs (siRNAs) to knockdown KIF4A expression resulted in the suppression of cancer cell growth. Kinesin family member 18A (KIF18A) is a member of the kinesin-8 family, which consists of molecular motor proteins that use adenosine triphosphate hydrolysis to produce force and movement along microtubules.[9] It plays key roles in the regulation of chromosome congression during prometaphase and in the maintenance of chromosome alignment during metaphase.[6] Previous studies have revealed that KIF18A function is essential for the accurate architecture of the mitotic spindle and the proper alignment of chromosomes in mammalian cells.[10,11] KIF18A expression is unregulated in breast cancer,[12] colorectal cancer[4] and hepatocellular carcinoma[13] however, knowledge of its expression and roles in LUAD is limited.

In this study, we hypothesized that KIF18A plays a significant role in LUAD progression and demonstrated the potential role of KIF18A in LUAD prognosis with bioinformatics analyses.

Methods

Cell lines and cell culture

Human lung adenocarcinoma cell lines, A549, H1975, and PC9 were used in this study; all lines were preserved in our laboratory. Cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (Gibco, Grand Island, NY, USA) at 37°C in a humidified incubator with 5% CO_2.

Patients and tissue samples

Primary LUAD and paired normal tissue samples were obtained from the surgical specimens of 82 patients who underwent radical surgery at the Tianjin Medical University General Hospital (Tianjin, China) from January to December 2017. Normal tissue was collected from at least 1 cm away from the primary adenocarcinoma site and was histopathologically identified as normal and nonpolypoid by a pathologist. Written informed consent was obtained from all patients. None of the patients were administered chemotherapy, radiotherapy, immunotherapy, or other antitumor treatments prior to surgery. The postsurgical pathological stage of each tumor tissue was classified according to the international tumor node metastasis (TNM) classification. All demographic and pathological data, including age, gender, smoking history, primary tumor size, lymph node metastasis, and degree of differentiation, were obtained from clinical and pathology records.

Immunohistochemistry and scoring

Immunohistochemistry of KIF18A was performed using the streptavidin-peroxidase method. Briefly, after dewaxing and hydration, endogenous peroxide activity was blocked in 3% hydrogen peroxide. Sections (5 μm) from paraffin-embedded tumor tissue were subjected to high pressure-induced epitope retrieval in 0.01 M citrate buffer (pH 6.0). After washing three times with phosphate buffered saline (PBS), the sections were incubated overnight with rabbit anti-human anti-KIF18A antibody (sc-390600, 1:500, Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA) at 4°C in a humidified chamber. After rinsing with PBS, the slides were incubated for 30 minutes with secondary anti-rabbit antibody (PV-6000, working solution; ZSGB Biotech, Beijing, China). The slides were then exposed to 3-3-diaminobenzidine (DAB) for color development and hematoxylin was used for counterstaining. Negative control slides were similarly processed without the primary antibody.

Two pathologists blinded to patient details independently scored the tissue sections using a semiquantitative scoring system. KIF18A expression levels were assessed semiquantitatively by combining scores of the proportion of positive-staining cells and staining intensity. Positive-staining cells were scored as follows: 0, no cytoplasm expression or < 5% positive staining; 1, 5–25% positive staining; 2, 26–50% positive staining; 3, 51–100% staining. Intensity was scored as 1, 2, and 3 for weak, moderate, and strong staining, respectively. The sum of two parameters represented the expression levels: 0–2, low expression; 3–6, high expression.

Knockdown of KIF18A by transfecting plasmid

KIF18A knockdown was achieved by the transfection of a plasmid containing KIF18A siRNA, designed using siDirect software; cells transfected with the empty plasmid were used as the control. The A549 cells were transfected with KIF18A siRNA or negative control siRNA using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Transfected cells were used in subsequent assays.

Cell proliferation assay

The A549 cells transfected with KIF18A siRNA and scrambled siRNA were seeded at a density of 1.0×10^4 cells/well in a 96-well plate for 24, 48, and 72 hours. Cell Counting Kit-8 (CCK-8) solution (10 μL, B34302, Selleck Chemicals,

Houston, TX, USA) was added to each well prior to the endpoint of incubation. The absorbance, which represents the cell count, was determined with a microculture plate reader at 450 nm.

Colony formation

The cells were seeded at a density of 6×10^2 cells/well in six-well culture dishes with 10% fetal bovine serum and incubated for three days. The cells were then washed with PBS and fixed with 4% paraformaldehyde at room temperature for 10 minutes. After washing again with PBS, the cells were stained with 0.1% crystal violet, and the colonies were counted with naked eyes. The average numbers of colonies in both the control and experimental groups were calculated. All experiments were repeated three times.

Western blotting

Protein samples were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes (Merck Millipore, Billerica, MA, USA). Membranes were blocked with fat-free milk combined with tris-buffered saline plus tween 20 for one hour at room temperature and then incubated with the appropriate primary antibody and horseradish peroxidase-conjugated secondary antibodies. Imager was used to visualize the blots. The primary antibodies used in this study are as follows: anti-KIF18A (sc-390600, 1:500) and GAPDH (sc-47724, 1:5000, Santa Cruz); and anti-PCNA (ab92552, 1:1000) and anti-Ki67 (ab16667, 1:1000, Abcam, Cambridge, MA, USA).

Bioinformatics analysis

KIF18A messenger RNA (mRNA) expression was classified as low (n = 347) or high (n = 483) in The Cancer Genome Atlas (TCGA) and

Genotype-Tissue Expression (GTEx) datasets, with median KIF18A mRNA expression as the cutoff point. Disease-free survival (DFS) and overall survival (OS) were analyzed from TCGA public dataset, including 477 LUAD patients (http://www.cbioportal.org/study?id=luad_tcga).

Statistical analysis

Statistical analysis was performed using SPSS version 22.0. The chi-square test was used to identify associations between KIF18A and clinicopathological factors. Associations between the KIF18A expression level and DFS and OS were analyzed using the Kaplan–Meier method. Two-sided values of $P < 0.05$ were considered significant.

Results

KIF18A expression in lung adenocarcinoma (LUAD) cells and tissues

To examine the expression of KIF18A in LUAD, we first detected the mRNA level on the Gene Expression Profiling Interactive Analysis (GEPIA) website based on TCGA and GTEx datasets (http://gepia.cancer-pku.cn/). As shown in Figure 1a, the expression of KIF18A in LUAD tissues was 1.74 times higher compared to normal lung tissues ($P < 0.05$). We further confirmed the results in the cell lines and tissues. To identify the proliferative function of KIF18A in LUAD cells, KIF18A expression in the A549, H1975, and PC9 cell lines was analyzed by Western blot. As shown in Figure 2b, KIF18A expression was higher in A549 cells than in other cell lines. Therefore, we chose the A549 cell line for subsequent experiments.

Immunohistochemistry was performed to determine KIF18A expression in 82 paraffin-embedded primary LUAD tissues and adjacent normal tissues. Positive-staining for KIF18A expression was observed in the cytoplasm and nucleus of cancer cells; in normal lung tissue, it was either not expressed or only weakly expressed. Of all specimens examined, the protein level of KIF18A was higher in primary LUAD than in the adjacent normal lung tissues in 54 of 82 cases ($P < 0.05$) (Table 1). Representative KIF18A staining of the tumor and its adjacent normal tissues is shown in Figure 1c.

KIF18A influences cell proliferation in A549 cells

To identify the proliferative function of KIF18A in LUAD, we knocked down KIF18A expression by RNA interference. Compared to the scrambled siRNA group, A549 cells transfected with KIF18A siRNA exhibited significant down-regulation, which was confirmed by Western blotting (Fig 2a).

Colony formation and CCK-8 assays were used to investigate the effect of KIF18A on the proliferation of A549 cells. KIF18A knockdown significantly inhibited A549 cell proliferation ($P < 0.05$) (Fig 2c,d). Western blot analysis further demonstrated that low KIF18A expression significantly reduced the expression of Ki67 and PCNA, which represented cell proliferation (Fig 2b).

Clinicopathological significance of KIF18A expression in LUAD tissues

The clinicopathological characteristics analyzed in relation to KIF18A expression in lung cancer tissue are shown in Table 2. There were significant associations between KIF18A expression and tumor differentiation (P = 0.005),

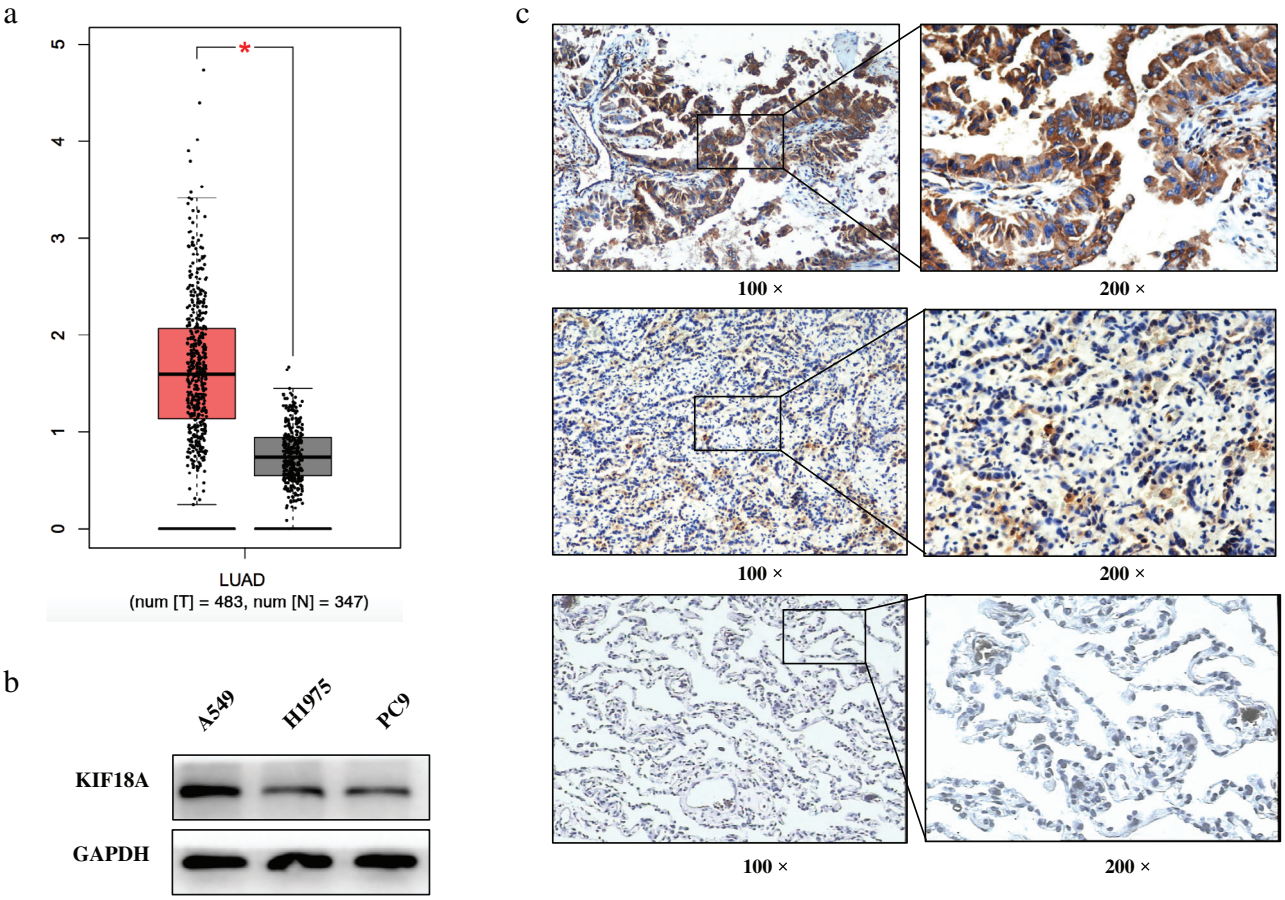

Figure 1 Expression level of kinesin family member (18A KIF18A) in lung adenocarcinoma (LUAD). (**a**) KIF18A messenger RNA expression was higher in LUAD tissues than in normal lung tissues, (The Cancer Genome Atlas and Genotype-Tissue Expression databases). (**b**) KIF18A expression in different LUAD cells. (**c**) Immunostaining of KIF18A in LUAD and adjacent normal lung tissues showed different expression levels. Magnification 100 × (left) and 200 × (right). GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

tumor size (P = 0.003), lymph node metastasis (P = 0.03), and tumor stage (P = 0.026). Conversely, no significant differences were observed with regard to age, gender, or smoking history.

Association between KIF18A expression and poor prognosis.

Kaplan–Meier analysis was used to evaluate the survival of LUAD patients using data from TCGA (n = 477). KIF18A mRNA expression was classified as low (n = 347 in TCGA and GTEx) or high (n = 483 in TCGA and GTEx) in relation to median KIF18A mRNA expression as the cutoff point. LUAD patients with high KIF18A expression were likely to have significantly shorter DFS (P = 0.004) (Fig 3a) and OS (P < 0.0001) (Fig 3b).

We conducted univariate and multivariate Cox proportional hazards regression to verify the clinical prognostic value of KIF18A in LUAD datasets (Table 3). Univariate analysis showed that KIF18A (DFS: hazard ratio [HR] 1.535, 95% confidence interval [CI] 1.146–2.056, P = 0.004; OS: HR 1.688, 95% CI 1.255–2.270, P = 0.004), tumor size (DFS: HR 1.573, 95% CI 1.299–1.904, P < 0.001; OS: HR 1.555, 95% CI 1.294–1.870, P < 0.001), lymph node metastasis (DFS: HR 1.420, 95% CI 1.183–1.704, P < 0.001; OS: HR 1.711, 95% CI 1.442–2.028, P < 0.001), and tumor stage (DFS: HR 1.439, 95% CI 1.234–1.677, P < 0.001; OS: HR 1.683, 95% CI 1.465–1.933, P < 0.001) were significant predictors related to DFS and OS in LUAD. Furthermore, the variable factors were analyzed in multivariate Cox proportional hazards models for both DFS and OS. Results indicated that tumor stage (OS: HR 1.537, 95% CI 1.124–2.087; P = 0.007) only influenced OS in LUAD patients, while KIF18A (DFS: HR 1.518, 95% CI 1.120–2.058, P = 0.007; OS: HR 1.537, 95% CI 1.124–2.087, P = 0.007) and tumor size (DFS: HR 1.518, 95% CI 1.120–2.058, P = 0.007; OS: HR 1.537,

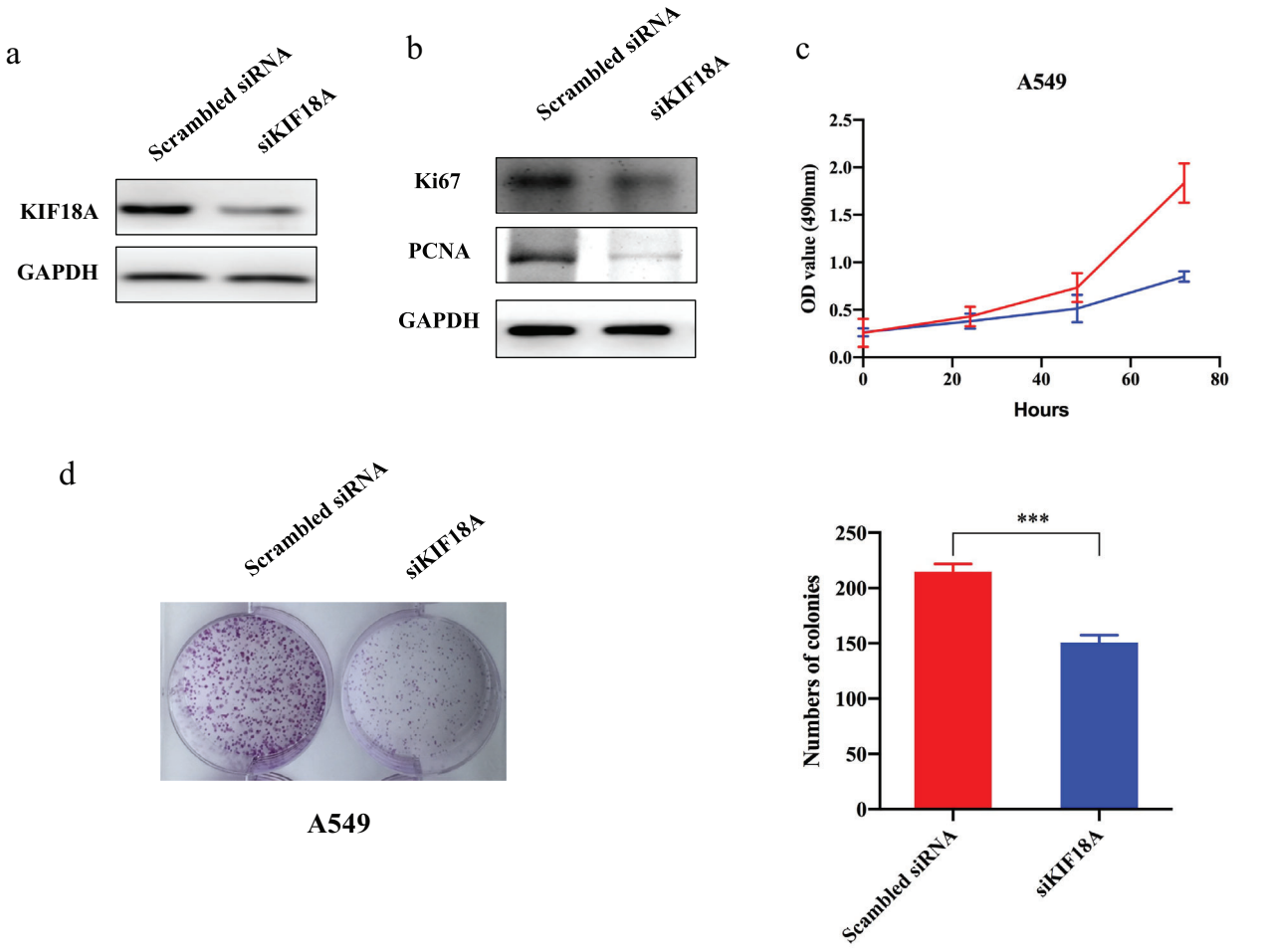

Figure 2 Kinesin family member (18A KIF18A) regulates the proliferation of lung adenocarcinoma (LUAD) cells in vitro. (**a**) Confirmation of RNA interference against KIF18A in A549 cells by Western blot. (**b**) Western blot analysis shows Ki67 and PCNA expression in A549 cells transfected with the indicated small interfering RNA (siRNA). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal control. (**c**) A Cell Counting Kit-8 assay was performed to determine the proliferation of A549 cells in response to knocked down KIF18A. —— Scrambled siRNA, —— siKIF18A. (**d**) Representative image and numbers of colony formation assays of A549 cells transfected with KIF18A siRNA or control plasmids.

Table 1 KIF18A expression in tumor tissues and normal tissues

	KIF18A expression		
Group	Positive	Negative	*P*
Tumor tissues	54	28	< 0.001*
Normal tissues	22	60	

*Statistically significant. KIF18A, kinesin family member 18A.

95% CI 1.124–2.087, $P = 0.007$) were independent predictors for both DFS and OS in LUAD patients.

Discussion

KIFs are known to play a role in the transport of organelles and vesicles, and the movement of chromosomes during mitosis and meiosis.[6,14] However, the altered regulation of KIFs during the cell cycle may lead to overproliferation, highlighting their involvement in tumorigenesis.[15] To date, many studies have demonstrated that the different subtypes of the kinesin protein family may participate in different functions in cells; similarly, the altered expression of different KIFs may participate in different cancers. For example, increased KIF2A expression plays a central role in glioma development[16] Wang *et al.* indicated that KIF26B was remarkably overexpressed and could be a potential biomarker of prognosis.[17] Both *KIF3* and *KIF4* have been identified as tumor suppressor genes in gastric cancer.[18,19] Pike *et al.* demonstrated that chromokinesin KIF22 was coordinated with coxsackievirus and adenovirus receptor (CAR) and EGFR, two key plasma membrane receptors that facilitate cancer cell division, resulting in the

Table 2 Clinicopathologic variables and KIF18A expression in 82 LUAD patients

Variable	Group	KIF18A expression			*P*
		N	High (%)	Low (%)	
Age	< 60	40	26 (65.0)	14 (35.0)	0.874
	≥ 60	42	28 (66.7)	14 (33.3)	
Gender					
	Female	31	21 (67.7)	10 (32.3)	0.779
	Male	51	33 (64.7)	18 (35.3)	
Smoking history					
	No	34	20 (58.8)	14 (41.2)	0.259
	Yes	48	34 (70.8)	14 (29.2)	
Degree of differentiation					
	Low	47	25 (53.2)	22 (46.8)	0.005*
	Moderate or high	35	29 (82.6)	6 (17.4)	
Tumor size					
	≤ 5cm	43	22 (51.2)	21 (48.8)	0.003*
	> 5cm	39	32 (82.1)	7 (17.9)	
Lymph node metastasis					
	Positive	45	25 (55.6)	20 (44.4)	0.03*
	Negative	37	29 (78.4)	8 (21.6)	
Tumor stage					
	I–II	58	23 (39.7)	35 (60.3)	0.026*
	III	24	16 (66.7)	8 (33.3)	

*Statistically significant. KIF18A, kinesin family member 18A; LUAD, lung adenocarcinoma.

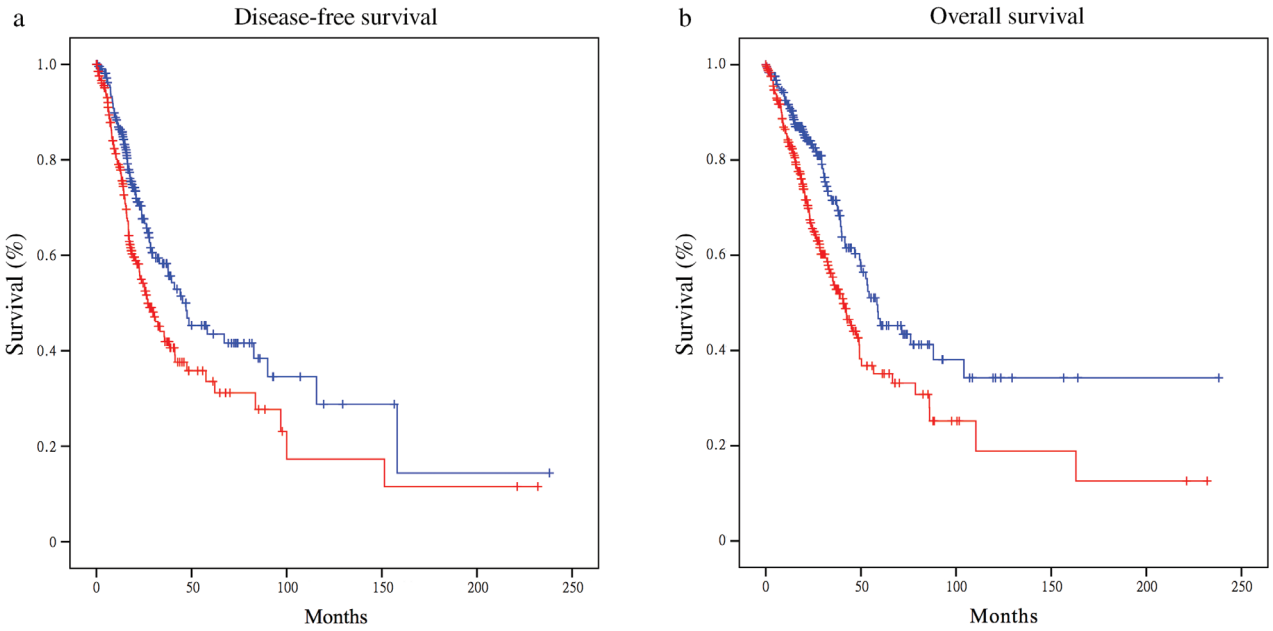

Figure 3 Kaplan–Meier analysis of kinesin family member 18A (KIF18A) expression in lung adenocarcinoma (LUAD) patients (The Cancer Genome Atlas) and survival. Protein levels showed that KIF18A played a prognostic role in (**a**) disease-free survival and (**b**) overall survival. Low KIF18A TPM, high KIF18A TPM, Low censored, high censored. Low KIF18A TPM, high KIF18A TPM, low censored, high censored. TPM, Transcripts per kilobase of exonmodel per million.

promotion of CAR and EGFR dependent tumorigenesis in lung cancer.[20] Hung *et al.* proposed that KIF14 might regulate the recruitment of the adhesive molecule cadherin 11 to the cell membrane in LUAD cell lines.[21]

KIF18A, an important member of KIF8 family, plays key roles in the regulation of chromosome congression during prometaphase and in the maintenance of chromosome alignment during metaphase.[6] Dysfunction of KIF18A may

Table 3 Prognostic value of KIF18A expression for survival

	Univariate analysis			Multivariate analysis		
Covariant	HR	95% CI	*P*	HR	95% CI	*P*
Disease-free survival						
KIF18A	1.535	1.146–2.056	0.004*	1.518	1.120–2.058	0.007*
Age	1.007	0.992–1.023	0.354	1.012	0.997–1.028	0.111
Smoking history	1.119	0.970–1.290	0.123	—	—	—
Tumor size	1.573	1.299–1.904	< 0.001*	1.476	1.175–1.854	0.001*
Lymph node metastasis	1.420	1.183–1.704	< 0.001*	1.191	0.905–1.569	0.213
Tumor stage	1.439	1.234–1.677	< 0.001*	1.060	0.807–1.932	0.674
Overall survival						
KIF18A	1.688	1.255–2.270	0.004*	1.537	1.124–2.087	0.007*
Age	1.008	0.992–1.023	0.332	1.012	0.996–1.027	0.144
Smoking history	1.030	0.896–1.184	0.679	—	—	—
Tumor size	1.555	1.294–1.870	< 0.001*	1.226	1.005–1.497	0.045*
Lymph node metastasis	1.711	1.442–2.028	< 0.001*	1.202	0.905–1.530	0.133
Tumor stage	1.683	1.465–1.933	< 0.001*	1.348	1.080–1.682	0.008*

*Statistically significant. CI, confidence interval; HR, hazard ratio; KIF18A, kinesin family member 18A.

influence chromosome segregation and/or chromosome stability. Several studies have revealed that KIF18A plays a key role in the carcinogenesis and progression of tumors.[22] Upregulation of KIF18A increases proliferation in many cancers, such as breast cancer, hepatocellular carcinoma, and colorectal cancer, demonstrating that knockdown of KIF18A significantly suppresses tumor proliferation, migration, and invasion.[4,12,13] Zhu *et al* showed that KIF18A is upregulated in an induced colorectal tumor model, and KIF18A deficient mice are protected from colorectal carcinogenesis via inactivation of the PI3K-AKT pathway, demonstrating the significance of KIF18A in colorectal tumor progression and its role in vivo.[23] To our knowledge, research of KIF18A expression in LUAD is limited.

In our study, we analyzed LUAD KIF18A mRNA expression using data from two databases and investigated KIF18A expression in LUAD patients after surgery. We found that KIF18A expression at both levels was significantly upregulated in primary LUAD tissues compared to adjacent normal lung tissues. Furthermore, treatment of NSCLC cells with specific siRNA to knockdown KIF18A expression resulted in the suppression of cancer cell proliferation in in vitro assays.

Moreover, we analyzed the correlation between KIF18A expression and clinicopathological characteristics, including age, gender, smoking history, tumor size, degree of differentiation, lymph node metastasis, and tumor stage. Our findings indicated that LUAD tissues have higher KIF18A expression than normal lung tissues, which is associated with an advanced malignant phenotype, such as patients' higher T status and harmful components. These results demonstrate that KIF18A may play a crucial role in the carcinogenesis and progression of LUAD. The high transferability and invasiveness of the malignant tumor are key factors in tumor development that influence prognosis.[6] In our study, LUAD patients with lymph node metastasis exhibited higher KIF18A expression compared to those without metastasis. Furthermore, Cox regression analysis suggested that KIF18A is an independent prognostic factor, indicating that KIF18A may be an important modulator involved in LUAD development.

In the future, we will attempt to unravel the mechanism of KIF18A-mediated invasion and migration of LUAD. Meanwhile, it is important to determine the causes of abnormal mitosis in cells, which may lead to a better understanding of the fundamental cell biology.[6] Some studies have demonstrated that some kinesin proteins also play critical roles in taxane resistance.[24,25] This may be a new research direction for future study. Several inhibitors targeting KIF have entered clinical trials.[26,27] Targeting these proteins may be a new antitumor strategy for the effective control of human cancers.

In summary, this study showed that KIF18A is overexpressed in patients with LUAD, further confirming that a high KIF18A expression level is correlated with higher pathologic tumor status stage, poorer tumor differentiation, lymph node metastasis, and tumor stage. KIF18A knockdown significantly inhibited proliferation in A549 cells and upregulation of KIF18A predicted shorter DFS and OS, indicating that high KIF18A expression is correlated with poor prognosis in primary LUAD. These results could help to facilitate curative adjuvant treatment.

Acknowledgments

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Disclosure

No authors report any conflict of interest.

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