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Original Paper

Increased KIF15 Expression Predicts a Poor Prognosis in Patients with Lung Adenocarcinoma

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Key Words
Cell cycle • Cell growth • Clinical outcome • KIF15 • Lung cancer

Abstract
Background/Aims: Lung cancer is the leading cause of cancer-related deaths worldwide. The outcome of patients with non-small cell lung cancer remains poor; the 5-year survival rate for stage IV non-small cell lung cancer is only 1.0%. KIF15 is a tetrameric kinesin spindle motor that has been investigated for its regulation of mitosis. While the roles of kinesin motor proteins in the regulation of mitosis and their potentials as therapeutic targets in pancreatic cancer have been described previously, the role of KIF15 in lung cancer development remains unknown. ***Methods:*** Paired lung carcinoma specimens and matched adjacent normal tissues were used for protein analysis. Clinical data were obtained from medical records. We first examined *KIF15* messenger RNA expression in The Cancer Genome Atlas database, and then determined KIF15 protein levels using immunohistochemistry and western blotting. Differences between the groups were analyzed using repeated measures analysis of variance. Overall survival was analyzed using the Kaplan–Meier method. Cell-cycle and proliferation assays were conducted using A549, NCI-H1299, and NCI-H226 cells. ***Results:*** KIF15 was significantly upregulated at both the messenger RNA and protein levels in human lung tumor tissues. In patients with lung adenocarcinoma, KIF15 expression was positively associated with disease stages; high KIF15 expression predicted a poor prognosis. KIF15 knockdown using short hairpin RNA in two human lung adenocarcinoma cell lines induced G1/S phase cell cycle arrest and inhibited cell growth, but there was no effect in human lung squamous cell carcinoma. ***Conclusion:*** Our findings show that KIF15 is involved in lung cancer carcinogenesis. KIF15 could therefore serve as a specific prognostic marker for patients with lung adenocarcinoma.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with a 5-year survival rate of <15.0% [1]. The disease can be broadly divided into non-small cell lung cancer (NSCLC), which accounts for approximately 80.0% of cases, and small cell lung cancer, which accounts for the remaining 20.0% of cases. Lung squamous cell carcinoma (LSCC), large cell carcinoma, and lung adenocarcinoma (LUAD) are the most common NSCLC subtypes [2]. The incidence rate of LUAD has been increasing in recent decades [3].

Lung cancer is usually detected in its late stages; thus, the outcomes of patients with NSCLC remain poor, with 5-year survival rate of only 1.0% for patients with stage IV disease [4]. Therefore, it is essential to identify highly sensitive and specific biomarkers that serve as prognostic predictors for patients with this disease. Various tumor biomarkers (such as *EGFR*, *ALK*, and *ROS*/*MET*/*BRAF*) have already been identified, and biomarker-driven immunotherapy has yielded major advances. However, acquired resistance to these therapies limits their long-term benefits [5].

The abnormal, uncontrolled proliferation of cancer cells is a major event in cancer development. Recent studies have focused on the regulation of mitosis, and mitotic inhibitors (such as taxanes) that target microtubules have been developed for the treatment of various carcinomas [6]. Recently, the role of kinesin motor proteins in the regulation of mitosis, and their suitability as potential therapeutic targets, have also been investigated [7].

The kinesin superfamily proteins (KIFs) are conserved class of microtubule-dependent motor proteins. To date, over 45 members comprising 14 families have been identified in mammalian cells [8]. Kinesin motor proteins play key roles in different stages of mitosis and cytokinesis. It has been reported that the overexpression of some kinesins can induce premature sister chromatid separation prior to anaphase. This results in an unequal distribution of genetic material that can lead to aneuploidy [9]. Furthermore, aneuploidy in daughter cells that carry altered genetic material promotes aggressive cancer development [10]. In contrast, the downregulation of kinesins, such as *KIF11* and *KIF20B*, causes cell cycle arrest, cytokinesis defects, or spindle assembly failure in some cancer cell lines; this can eventually lead to apoptosis via the tumor repressor protein p53 or other pathways [11, 12].

KIF15, which plays an important role in several types of cancer, is a tetrameric spindle motor; its motor-domain structure was first captured in an "ATP-like" configuration with the neck linker docked to the catalytic core. KIF15 interacts with TPX2 to cross-link and slide between two microtubules, leading to centrosome separation during bipolar spindle assembly [13]. It has been reported that KIF15 is induced by estrogen and that its upregulation, together with *ANCCA* that is also induced by estrogen, is associated with breast cancer cell growth, survival, and resistance to tamoxifen [14]. Recently, KIF15 was found to be overexpressed in pancreatic cancer, where it promotes tumor cell proliferation via the MEK-ERK signaling pathway [15]. Bidkhori et al. reconstructed a "genome-scale co-expression network" [16] to test their bioinformatics-derived prediction that KIF15 is overexpressed in LUAD and that it may be important for cell cycle regulation. However, the clinicopathological significance of KIF15 expression in lung cancer remains unknown, and no studies have demonstrated whether the overexpression of KIF15 is a factor in the development of lung cancer.

In this study, we analyzed KIF15 expression in human lung tumor tissues and matched adjacent normal tissues at both the mRNA and protein levels to evaluate the correlations of clinical outcomes with KIF15 expression status. Additionally, we knocked down KIF15 expression and investigated its roles in cancer cell growth and survival in the human lung cancer cell lines A549, NCI-H1299, and NCI-H226. Our findings demonstrate the involvement of KIF15 expression in lung adenocarcinoma progression as well as lung cancer cell growth and survival *in vitro*.

Materials and Methods

Clinical samples

For immunohistochemistry (IHC), 119 tumor tissues and matched adjacent normal tissues were collected and frozen at –80°C between February 2015 and January 2016. Specimens were analyzed at the Department of Pathology of The First Hospital of Jilin University (Changchun, China). For western blotting, 19 paired fresh tissues were collected and stored at –80°C between February 2016 and April 2016. Clinical data were obtained from medical records. Tumor-node-metastasis stage was determined according to the American Joint Committee on Cancer staging manual (7th edition).

IHC

Four-micrometer-thick sections of paraffin-embedded tissues were deparaffinized in xylene and dehydrated in alcohol. The tissues were treated with 3.0% hydrogen peroxide/methanol and incubated with hydrogen peroxide block for 15 min, followed by Ultra V block for 5 min. Anti-KIF15 antibody (dilution, 1:100; Proteintech, Wuhan, China; catalogue no. 55407-1-AP) was added and the samples were incubated at 4°C overnight. IHC staining was performed using a rabbit-specific horseradish peroxidase/3, 3′-diaminobenzidine (avidin-biotin complex) detection IHC kit (Cobioer Biosciences Co., Ltd., Nanjing, China) according to the manufacturer's protocol.

To evaluate KIF15 expression, positive staining was quantified by scoring the percentage of tumor cells showing specific staining. The IHC scores were graded as follows: none (0), weak (1), moderate (2), and strong (3). The percentages of positive cells were divided into 5 categories: 0.0% (0), 1.0–25.0% (1), 26.0–50.0% (2), 51.0–75.0% (3), and >75.0% (4). Cells were considered positive for KIF15 if the product of the IHC and percentage scores was >4.

Western blotting

Tissues and cells were lysed in lysis buffer containing protease inhibitors and NP-40. The protein concentrations were measured using a Pierce Bicinchoninic Acid Protein Assay kit (Thermo Scientific, Rockford, IL, USA; catalog no. 23227). Next, the protein samples (40.0 μg per lane) were subjected to SDS-PAGE and then transferred to a polyvinylidene fluoride membrane. The membrane was blocked for 1 h at room temperature in 5.0% non-fat milk and then incubated with monoclonal antibody against KIF15 (dilution, 1:1000) (Proteintech, Wuhan, China; catalogue no. 55407-1-AP) or beta-actin (dilution, 1:2000) (TransGen Biotech Co., Ltd., Beijing, China) at 4°C overnight. The corresponding horseradish peroxidase-conjugated secondary antibody was added after washing three times with phosphate-buffered saline (PBS) containing 0.1% Tween-20. The blots were visualized using enhanced chemiluminescence (Perkin Elmer, Boston, MA, USA).

Cell culture

Human lung cancer cell lines (A549, NCI-H1299, and NCI-H226) were obtained from the American Type Culture Collection and cultured in RPMI1640 medium (GIBCO, New York, NY, USA) with 10.0% fetal bovine serum (HyClone Laboratories Inc., South Logan, UT, USA), penicillin G (100.0 U/mL), and streptomycin (100.0 μg/mL) (Sigma-Aldrich, Shanghai, China) in a 5.0% CO_2 incubator at 37°C. The cell lines were mycoplasma-free and authenticated by STR profiling (Microread Company, Beijing, China).

RNA extraction and quantitative real-time polymerase chain reaction

Total RNA was extracted and purified using an RNA extraction kit (TransGen Biotech Co., Ltd., Beijing, China). Reverse transcription was performed to generate complementary DNA using EasyScript First-Strand cDNA Synthesis SuperMix (TransGen Biotech Co., Ltd., Beijing, China) according to the manufacturer's protocol. *KIF15* mRNA expression was measured by quantitative real-time polymerase chain reaction using the ABI Prism StepOnePlus System (Applied Biosystems, Foster City, CA, USA). The two sets of predesigned primers were as follows: *GAPDH* forward, 5′-TGACTTCAACAGCGACACCCA-3′; *GAPDH* reverse, 5′-CACCCTGTTGCTGTAGCCAAA-3′; *KIF15* forward, 5′-CTCTCACAGTTGAATGTCCTTG-3′; and *KIF15* reverse: 5′-CTCCTTGTCAGCAGAATGAAG-3′. *GAPDH* was included as an internal reference. The relative expression of *KIF15* was calculated using the $2^{(-\Delta\Delta Ct)}$ method.

Lentiviral transduction

Short hairpin RNA (shRNA) targeting KIF15 was packaged into a lentiviral vector (GeneChem Co., Ltd., Shanghai, China). Cells were infected with viral supernatants at a multiplicity of infection of 20–100. Two days later, the infected cells were examined for KIF15 knockdown efficiency and were used in further experiments.

Cell growth assay

Cells were seeded in 96-well plates at a density of 2.0×10^3 cells per well and incubated at 37°C. At separate time points, (1, 2, 3, 4, and 5 days), 3-(4, 5-dimethyl-2-yl)-2, 5-diphenyltetrazolium bromide solution (MTT; 20.0 μL) was added at a concentration of 5.0 mg/mL into each well, and the cells were incubated at 37°C for an additional 4 h. Next, the supernatant in each well was removed and replaced with 150.0 μL dimethyl sulfoxide to solubilize the formazan salt. Ten minutes later, the absorbance in each well was measured at 490 nm using a microplate reader (BioTek, Winooski, USA). All experiments were performed in quintuplicate.

Cell cycle assay

Cells were collected and centrifuged at 1, 500 rpm for 5 min, resuspended with PBS, and fixed with 75.0% precooled alcohol for at least 1 h. The fixed cells were centrifuged at 6, 000 rpm for 5 min, washed twice with PBS, and stained with viability staining solution containing propidium iodide (0.5 μg/mL), RNase (20.0 μg/mL), and 1× PBS in the dark for 30 min. Cell cycle analysis was performed using flow cytometry. The data were analyzed using Modfit LT 5.0 software (Verity Software House, Topsham, ME, USA).

Statistical analysis

All data are shown as the mean ± standard deviation. Statistical differences between the groups were determined by repeated measures analysis of variance. Overall survival rates were calculated using the Kaplan–Meier method. All statistical analysis were conducted using GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA). A P-value < 0.05 was considered statistically significant. The data shown are representative of at least three independent experiments.

Results

KIF15 expression is upregulated in human lung cancer

To investigate *KIF15* mRNA expression in human lung tumor tissues, we first examined its expression using data from The Cancer Genome Atlas database. Paired human LUAD (n = 57) and LSCC (n = 50) tissues as well as matched adjacent normal tissues were analyzed. We found that *KIF15* mRNA expression was significantly higher in LUAD and LSCC tissues than in the matched adjacent normal tissues (P < 0.0001, Fig. 1a).

We used IHC to examine KIF15 protein expression in paired human LUAD (n = 89) and LSCC (n = 30) tissues and their matched adjacent normal tissues. We found that KIF15 protein expression was significantly higher in LUAD and LSCC tissues than in the matched adjacent normal tissues (P < 0.0001, Fig. 1b–c). Western blotting revealed that KIF15 protein expression was upregulated in 14 out of 19 (73.7%) malignant tumor samples (Fig. 1d). Taken together, these results indicate that KIF15 is upregulated in human lung tumor tissues.

Clinicopathological significance of KIF15 expression in human lung tumor tissues

Next, we analyzed the relationship between KIF15 expression and the clinicopathological characteristics of patients with lung cancer. As shown in table 1, KIF15 expression was significantly correlated with primary tumor stage (P=0.044), but not with age, sex, pathological type, tumor-node-metastasis classification, or distant metastasis (P > 0.05).

Correlation between KIF15 expression and overall survival

Given that a significant correlation was found between the KIF15 expression level and primary tumor stage, we further evaluated whether KIF15 expression was associated

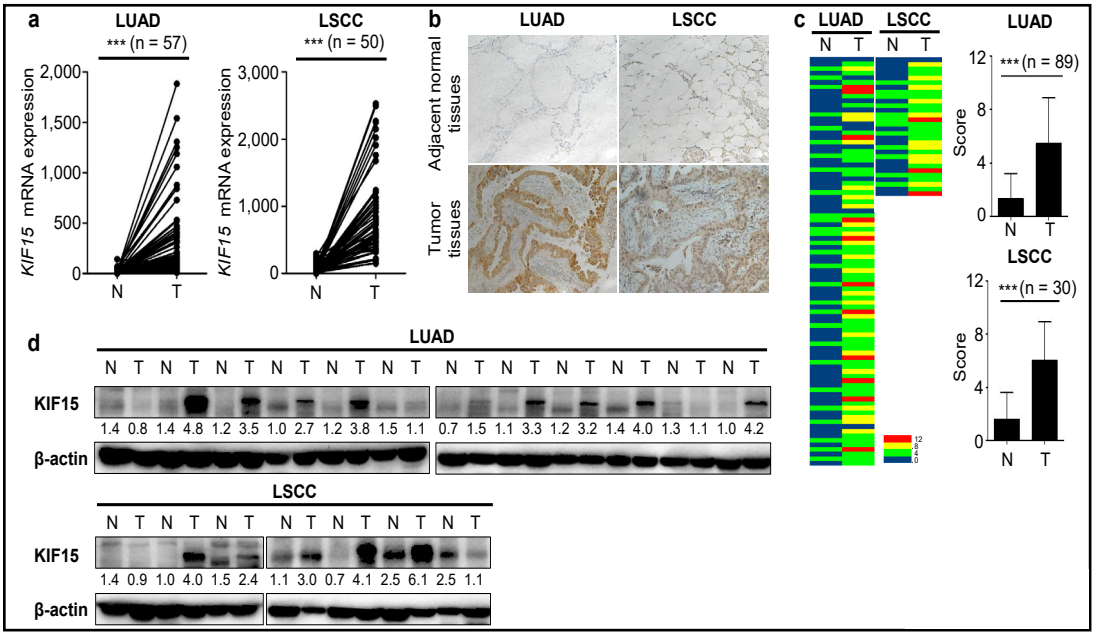

Fig. 1. Upregulation of KIF15 expression in human lung tumor tissues. (a) RNA sequencing data were obtained from The Cancer Genome Atlas. Statistical differences in expression between human lung tumor tissues (T) and paired adjacent normal tissues (N) were analyzed (***P<0.001). (b) KIF15 expression was detected by immunohistochemistry. The images represent typical staining patterns. (c) Individual staining intensities are represented by the heat map (left panel). Statistical differences between T and N were quantitated (right panel) (***P<0.001). (d) Proteins were extracted and subjected to SDS-PAGE and western blotting to determine KIF15 expression levels. Beta-actin (β-actin) was used as a loading control. mRNA: messenger RNA; LSCC: lung squamous cell carcinoma; LUAD: lung adenocarcinoma.

with clinical outcome in patients with lung cancer. Kaplan–Meier analysis revealed that the overall survival of patients with low KIF15 expression was significantly longer than that of patients with high KIF15 expression (P = 0.0025, Fig. 2a). However, when analyzed according to subtypes, KIF15 expression correlated with overall survival in patients with LUAD (P = 0.0007, Fig. 2b), but not in patients with LSCC (P = 0.94. Fig. 2c). These results suggested that high KIF15 expression is a potential indicator of a poor clinical outcome in patients with LUAD, but not in those with LSCC.

KIF15 knockdown reduces human lung adenocarcinoma cell growth

To investigate the role of KIF15 expression in human lung cancer cell growth, we knocked down KIF15 expression using shRNA targeting KIF15 in three human lung cancer cell lines (A549, NCI-H1299, and NCI-H226). The silencing efficiency was determined at both the mRNA and protein levels. KIF15 expression was significantly reduced in human lung cancer cells infected with a lentivirus targeting KIF15, at both the mRNA and protein levels (A549: P = 0.0047; NCI-H1299: P = 0.001; NCI-H226: P = 0.0175, Fig. 3a–c). Next, cell growth in the KIF15-knockdown human lung cancer cells was examined by MTT assays. We found that cell growth was significantly reduced in human LUAD cells (A549 and NCI-H1299) infected with the lentivirus targeting KIF15 (Fig. 3d–e), however, knockdown of KIF15 had no effect on human LSCC cell growth (Fig. 3f). These results indicate that KIF15 knockdown reduces human LUAD cell growth.

KIF15 knockdown inhibits G1/S phase transition

KIF15 is a member of a family of motor proteins that maintain the bipolar microtubule spindle apparatus in dividing cells. Based on bioinformatics analysis, Bidkhori et al. [16] predicted that KIF15 played a crucial role in cell cycle progression in human LUAD cells.

Table 1. Clinicopathological significance of KIF15 expression in lung cancer. *P < 0.05. Abbreviations: cStage, clinical stage; LSCC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; N, lymph node; T, tumor

Characteristics	KIF15 expression		P-value
	None or low (n = 73)	High (n = 46)	
Sex, n			
Male	38	27	
Female	35	19	0.571
Pathology, n			
LUAD	54	35	
LSCC	19	11	0.832
cStage, n			
I	34	11	
II	18	14	
III	20	21	
IV	1	0	0.044*
T classification, n			
1	16	7	
2	41	28	
3	12	8	
4	4	3	0.838
N classification, n			
0	42	20	
1	17	10	
2	11	14	
3	3	2	0.230
Distant metastasis, n			
Yes	1	0	
No	72	46	1.000

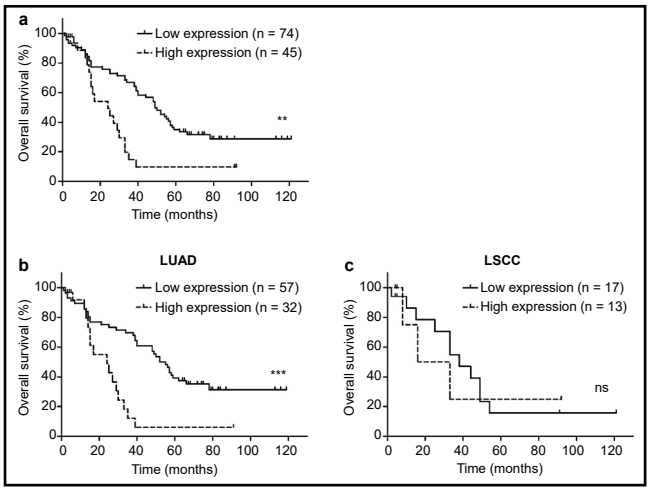

Fig. 2. Overall survival rates of patients with lung cancer. Kaplan-Meier curves of overall survival according to KIF15 expression in patients with (a) lung cancer (**P<0.01), (b) lung adenocarcinoma (LUAD) (***P<0.001), and (c) lung squamous cell carcinoma (LSCC). ns: not significant.

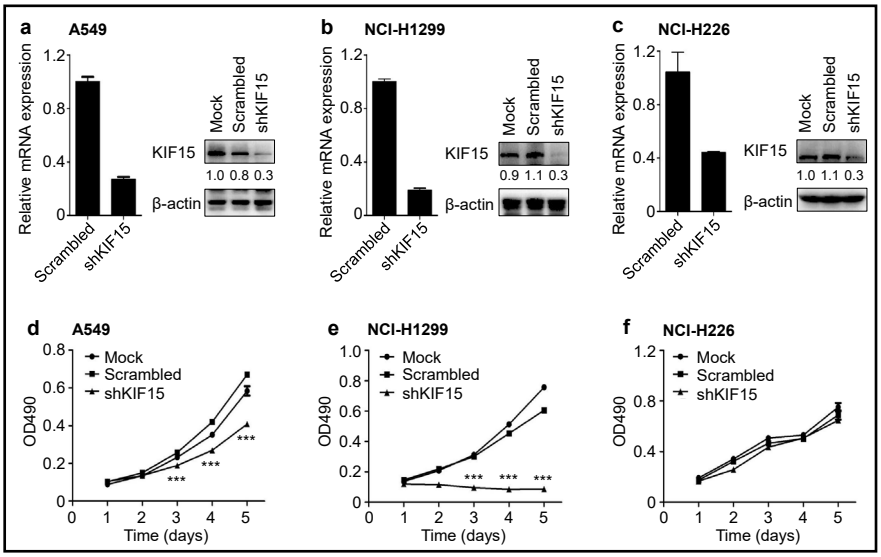

Fig. 3. KIF15 knockdown reduced cell growth in human lung adenocarcinoma cancer cells. RNA was extracted from (a) shKIF15-A549 (KIF15-silenced), (b) shKIF15-NCI-H1299 and (c) shKIF15-NCI-H226 cells and the corresponding control cells (mock and scrambled shRNA) (left panels). *KIF15* expression was examined by quantitative real-time polymerase chain reaction. Knockdown levels were calculated using the $2^{(-\Delta\Delta Ct)}$ method. Proteins from shKIF15-A549, shKIF15-NCI-H1299 and shKIF15-NCI-H226 cells and the corresponding control cells were extracted and subjected to SDS-PAGE and western blotting to determine KIF15 expression levels (right panels). KIF15 protein knockdown efficiency was compared to control cells. Beta-actin (β-actin) was used as a loading control. (d) shKIF15-A549, (e) shKIF15-NCI-H1299 and (f) shKIF15-NCI-H226 cells and the corresponding control cells were cultured in 96-well plates. Cell growth was analyzed using a 3-(4,5-dimethyl-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (***P<0.001). Data are shown as the mean ± standard deviation of quintuplicate experiments. mRNA: messenger RNA; OD490: optical densities at 490 nm; shRNA: short hairpin RNA.

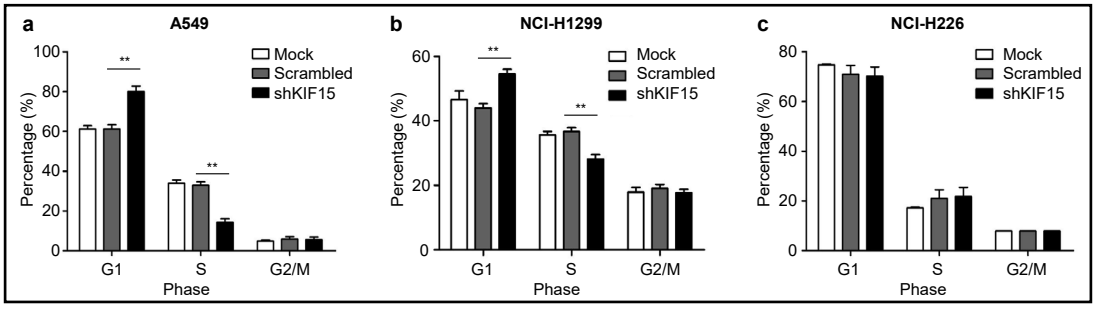

Fig. 4. KIF15 knockdown induced G1 cell cycle arrest in human lung adenocarcinoma cancer cells. The cell cycle was examined by flow cytometry in (a) shKIF15-A549, (b) shKIF15-NCI-H1299 and (c) shKIF15-NCI-H226 cells and the corresponding control cells (mock and scramble shRNA) ($^{**}P<0.01$ and $^{***}P<0.001$). The data were analyzed using Modfit LT 5.0 software (Verity Software House, Topsham, ME, USA). Data are shown as the mean ± standard deviation of at least three independent experiments. shRNA: short hairpin RNA.

Therefore, we tested whether KIF15 knockdown would impair the cell cycle in human lung cancer cells. Flow cytometry revealed that cells with silenced KIF15 comprised more G1 phase cells and fewer S phase cells than control (mock or scramble shRNA) cells in human LUAD cells (Fig. 4a–b), but not in human LSCC cells (Fig. 4c). These results indicate that KIF15 knockdown induces cell cycle arrest in human LUAD cells.

Discussion

In this study, we report that the recently identified kinesin motor protein KIF15 is involved in the carcinogenesis of human LUAD. Our findings suggest that KIF15 may serve as a novel prognostic marker for LUAD and could be a potential target for the treatment of this disease.

Previous studies have revealed that many KIFs are involved in the carcinogenesis of multiple human cancers, including lung cancer [17-22]. For example, *KIFC1* is upregulated in human breast cancer [19], whereas *KIF2C* is upregulated in esophageal squamous cell carcinoma and is associated with poor prognosis [22]. *KIF14* expression is significantly increased in cervical tumor tissues, and its expression is positively associated with a high tumor stage, lymph node metastasis, and chemoresistance [23]. *KIF18A* is upregulated in breast cancer, colorectal cancer, hepatocellular carcinoma, and renal cell carcinoma; its overexpression correlates with cancer development, carcinogenesis, and poor prognosis [17, 24-27]. *KIF22* is upregulated in human breast tumor tissues, and its inhibition leads to a significant accumulation of cells in the G2/M phase, resulting in suppressed cancer cell proliferation [28]. Previous studies of KIF15 provided a rationale to evaluate the potential relationship between its expression and the prognosis of patients with lung cancer; KIF15 is overexpressed in breast cancer, pancreatic cancer, and LUAD, and therefore represents a potential therapeutic target. Our results showed that KIF15 was indeed upregulated in human lung tumor tissues as compared to matched adjacent normal tissues, and that KIF15 expression was positively correlated with lung tumor grade. Interestingly, Kaplan–Meier analysis suggested that KIF15 expression was positively associated with overall survival in patients with LUAD, but not in those with LSCC. This suggests that KIF15 may function as a specific prognostic marker for patients with LUAD.

Kinesins function by travelling along microtubules that are involved in the transport of cellular molecules. Many kinesins play important roles in cell division during the different stages of mitosis [29]. Inspired by the prediction by Bidkhori et al. that KIF15 is critically important for cell cycle progression in human LUAD cells [16], we knocked down KIF15

expression using shRNA to investigate its function in the cell cycle. We found that KIF15 knockdown resulted in G1 phase arrest of the human LUAD cell lines A549 and NCI-H1299, but not of the human LSCC cell line NCI-H226, which validated the previous prediction.

LUAD and LSCC are the two major subtypes of lung cancer; they have distinct features, including location, cell origin, pathology, oncogenic drivers, and molecular markers [30]. In this study, although KIF15 was overexpressed in both LUAD and LSCC tissues, it correlated with patient's overall survival only in LUAD, but not LSCC. Moreover, knockdown of KIF15 inhibited cell growth and induced G1 cell arrest in LUAD, but not in LSCC, which was consistent with the survival data, indicating KIF15 is a specific marker for LUAD.

The first kinesin inhibitor to be developed was monastrol, which targets KIF11 [31], and several new inhibitors are currently under development [32-36]. For example, HR22C16, which is also a KIF11 inhibitor, targets taxol-sensitive and -resistant ovarian cancer cells [37]. Based on our results, inhibitors of KIF15 may also be effective against human LUAD. Small interfering RNA therapy in cancer treatment is thought to be a feasible approach for inhibiting the expression of cancer-specific genes [38]. We showed that KIF15 knockdown resulted in the suppression of human LUAD cell growth. Alternatively, microtubules have been considered as potential targets for cancer therapy [39], and a number of microtubule-inhibiting drugs have been developed, with impressive preclinical results [40]. Hence, targeting KIF15 may be a treatment strategy for patients with LUAD.

Cancer progression is a complex process that involves cell growth, migration, invasion, metastasis, colony formation, and adhesion [41, 42]. In our study, we detected KIF15 expression in lung tumor tissues and investigated its role in LUAD cell growth; however, the molecular signaling pathways through which KIF15 functions remain unclear. Furthermore, the number of samples in our study was limited. Besides, the expression patterns of KIF15 in other types of cancer, such as gastric, colorectal, and hepatocellular cancers, as well as its roles in cancer cell migration, invasion, metastasis, colony formation, and adhesion, remain unknown. Thus, further studies of KIF15 are warranted.

Conclusion

KIF15 is upregulated in human lung tumor tissues, and its overexpression is correlated with tumor grade and a poor clinical outcome in patients with LUAD. Furthermore, KIF15 knockdown significantly inhibits cell growth and results in G1 phase arrest in human LUAD cell lines. Thus, KIF15 is a novel prognostic marker of human LUAD and could be a promising therapeutic target for the treatment of human LUAD.

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Disclosure Statement

The authors declare that they have no competing interests.

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