Research Article

Kinesin Family Member 18A (KIF18A) Contributes to the Proliferation, Migration, and Invasion of Lung Adenocarcinoma Cells In Vitro and In Vivo

Fu-Tao Chen and Fu-Kuan Zhong

Department of Respiratory Medicine, The Second People’s Hospital of Lianyungang, No. 161, Xingfu Road, Haizhou District, Lianyungang City, 222023 Jiangsu Province, China

Correspondence should be addressed to Fu-Kuan Zhong; zhongfukuan555@sina.com

Received 27 January 2019; Revised 13 April 2019; Accepted 16 September 2019; Published 22 October 2019

Academic Editor: Giuseppe Biondi-Zoccai

Copyright © 2019 Fu-Tao Chen and Fu-Kuan Zhong. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. To determine the expression levels of KIF18A in lung adenocarcinoma and its relationship with the clinicopathologic features of patients undergoing radical colectomy and explore the potential role in the progression of lung adenocarcinoma.

Methods. Immunohistochemical assays were performed to explore the expression levels of KIF18A in 82 samples of lung adenocarcinoma and corresponding normal tissues. According to the levels of KIF18A expression in lung adenocarcinoma tissue samples, patients were classified into the KIF18A high expression group and low expression group. Clinical data related to the perioperative clinical features (age, gender, smoking, tumor size, differentiation, clinical stage, and lymph node metastasis), the potential correlation between KIF18A expression levels, and clinical features were analyzed, and the effects of KIF18A on lung adenocarcinoma cell proliferation, migration, and invasion were measured by colony formation assay, MTT assay, wound healing assay, and transwell assays. The possible effects of KIF18A on tumor growth and metastasis were measured in mice through tumor growth and tumor metastasis assays in vivo.

Results. KIF18A in lung adenocarcinoma tissues. Further, KIF18A was significantly associated to clinical characteristic features including the tumor size \( P = 0.033 \) and clinical stage \( P = 0.041 \) of patients with lung adenocarcinoma. Our data also investigated that KIF18A depletion dramatically impairs the proliferation, migration, and invasion capacity of lung adenocarcinoma cells in vitro and inhibits tumor growth and metastasis in mice.

Conclusions. Our study reveals the involvement of KIF18A in the progression and metastasis of lung adenocarcinoma and provides a novel therapeutic target for the treatment of lung adenocarcinoma.

1. Introduction

Lung cancer is one of the common tumors worldwide, with approximately 10 million people worldwide who died because of it in 2018 [1, 2]. Lung cancer is histologically classified into squamous cell carcinoma, small undifferentiated carcinoma, large undifferentiated carcinoma, and adenocarcinoma [3]. Lung adenocarcinoma is thought as the primary histological type of lung cancer and comprises most of lung cancer [4]. In recent years, it was widely reported that lung adenocarcinoma had both low early diagnosis rates and high death rates, which was mainly caused by the lack of early symptoms and difficult to be effectively treated in the advanced stage [5, 6]. Existing treatment methods for lung adenocarcinoma, such as surgical treatment, radiotherapy, and chemotherapy, could hardly meet the survival expectation of patients with advanced lung adenocarcinoma [7]. Recently, targeted therapy exhibits a promising prospect in the treatment of this disease [8, 9]. To reduce mortality and improve prognosis, novel and promising therapeutic targets are also badly needed.

Kinesin family containing 45 members, which are involved in the transport of proteins and organelles based on microtubule, was first discovered in the brains of mammals [10]. Previous studies confirmed that kinesins were involved in cell division, ciliogenesis, and neural signaling
transducing [11, 12]. Kinesin family member 18A (KIF18A) is one of the 45 kinesins and a member of the kinesin-8 family together with KIF18B [13]. A study has indicated that KIF18A possesses core functions related to cell development in multiple species [14]. Additionally, KIF18A could regulate kinetochore-microtubule attachment and further affect chromosome positioning during cell division, and the defects of KIF18A resulted in chromosome instability [15, 16].

Interestingly, the promising role of KIF18A in the progression of multiple cancers has been widely revealed. Several studies indicated that KIF18A has high expression and is associated with the prognosis of patients with breast cancer, clear cell renal carcinoma, and colorectal cancer [14, 17, 18]. KIF18A was also involved in the invasion and metastasis of hepatocellular carcinoma [19]. KIF18A is correlated with cell proliferation, tumor staging, and the prognosis of multiple tumors [20, 21]. However, the possible role of KIF18A in lung cancer is still unclear.

Herein, we revealed the high expression of KIF18A in human lung adenocarcinoma tissues and explored the possible link between KIF18A expression level and clinical features of patients with lung adenocarcinoma. We also found that KIF18A depletion dramatically suppressed the cell proliferation, migration, and invasion of lung adenocarcinoma cells and inhibited tumor growth and metastasis in mice. Therefore, KIF18A could serve as a promising therapeutic target for the treatment of lung adenocarcinoma.

2. Materials and Methods (We Mainly Referred to the Research Methods of Li et al. [22])

2.1. Antibodies, Primers, and shRNA Plasmids. Anti-KIF18A antibody (for immunoblot: 1:200 dilution; #19245, Proteintech, Chicago, USA) and anti-β-actin (1:2000 dilution; #ab8226, Abcam, Cambridge, UK) were used.

The quantitative PCR primer sequences of KIF18A were as follows: forward: 5′-AAAAAGGTGGTATGTGGCTGA-3′ and reverse: 5′-CTTTCAAGGGAGATGGCATTAG-3′. The quantitative PCR primer sequences of GAPDH were as follows: forward: 5′-GAGTCAACGGATTTGGTCGT-3′ and reverse: 5′-TTGATTTGGAGGATCTCG-3′.

Ready-to-package AAV shRNA clone for KIF18A was purchased from Addgene; the targeted sequence was as follows: 5′-AAAGCACTGGATTTCTATAAGT-3′.

2.2. Ethics Approval and Consent to Participate. All applicable international, national, and/or institutional guidelines for the care and use of human specimens and animals were followed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. The animal study was carried out in accordance with the guidelines approved by the Animal Experimentation Ethics Committee of The Second People’s Hospital of Lianyungang. The protocol was approved by the Committee, all surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

2.3. Human Tissue Samples and IHC Assays. Human lung adenocarcinoma (LA) tissues and adjacent tissues were collected from the patients receiving surgical resection in The Second People’s Hospital of Lianyungang from April 2014 to May 2018.

The clinical pathologic features, including patient age, gender, clinical pTNM stage, tumor size, and grade, are precisely recorded and listed in Table 1.

Subsequently, immunohistochemical (IHC) assays were performed to assess the potential correlations between KIF18A expression and LA progression, and we mainly referred to the research methods of Li et al. [22]. Briefly, sections were fixed with 4% PFA at room temperature for 30 minutes and blocked with 2% BSA in PBS for 20 minutes. Slides were incubated with anti-KIF18A antibodies at room temperature for 2 hours. Then the sections were incubated with biotinylated secondary antibody for 1.5 hours at room temperature, and diaminobenzidine was used as a chromogen substrate, and according to our results, KIF18A was mainly expressed in the cytoplasm of lung adenocarcinoma cells.

We used a score method to evaluate the expression level of KIF18A. The proportion of positively stained cells was scored as follows: <10% positive tumor cells score 0, 10%-50% positive staining tumor cells score 1, and >50% positive tumor cells score 2. The staining intensity was classified as follows: 0 means negative staining, 1 means intermediate staining, and 2 means high staining. The staining intensity score was the staining intensity score plus the percentage score. After all, we defined the following KIF18A expression levels as follows: 0-2 was low expression and 3-4 was high expression.

2.4. Cell Culture and Transfection. Both A549 and H1975 human lung adenocarcinoma cells were bought from the Committee of Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). A549 and H1975 cells were all maintained in RPMI-1640 culture medium (Gibco, Grand Island, USA) and supplemented with 10% of fetal bovine serum (FBS, Gibco, Grand Island, USA). Cells were cultured at 37°C in a 5% CO2 incubator. Cells were classified according to the transfection of overexpression resistin plasmid for the resistin group and untransfected cells for the control group. KIF18A stable depleted cells were screened by the infection of its shRNA lentivirus and used for tumor growth and metastasis assays.

2.5. Quantitative PCR Assay. We use TRIZol reagent (#15596026, Invitrogen, Carlsbad, CA, USA) to extract total RNA from LA cells. Then the total RNA was reverse-transcribed by M-MLV reverse transcriptase (M1701, Promega, Madison, Wisconsin, USA).
The involvement of KIF18A in lung adenocarcinoma tissues and associated with the clinical features of patients with lung adenocarcinoma. The involvement of KIF18A in...
the progression and development of various types of cancers has been widely reported. To investigate the potential effects of KIF18A in lung adenocarcinoma development, bioinformatics analysis was performed in an interactive web server GEPIA with the sequencing expression data of 483 tumors. The mRNA expression level of KIF18A in lung adenocarcinoma showed significantly higher than normal tissues ($P < 0.05$, number = 483, normal tissues, number = 347, Figure 1(a) above). And we also found that the disease-free survival time was shorter in the high expression of KIF18A than in the low expression of KIF18A ($P = 0.0059$, $P < 0.05$; Figure 1(a) below). Then we detected the expression

**Figure 1: KIF18A has high expression in human lung adenocarcinoma tissues.** (a) Shown above is the mRNA expression level of KIF18A in cancer and normal tissues in the GEPIA (LUAD: lung adenocarcinoma). Shown below is the disease survival time of low and high mRNA expression of KIF18A in the 483 cases of lung adenocarcinoma in the GEPIA. (b) Immunohistochemical assays were performed, and the representative photographs of KIF18A expression levels in human lung adenocarcinoma tissues were exhibited ($\times 100$ and $\times 200$ magnifications, respectively). (c) IHC staining results revealed the expression levels of KIF18A in the adjacent nontumor tissues ($\times 100$ and $\times 200$ magnifications, respectively).
levels of KIF18A in lung adenocarcinoma tissues from patients who underwent surgical resection through IHC assays. Notably, the results revealed that KIF18A was mainly located in the cytoplasm of lung adenocarcinoma cells (Figure 1(b)). We further explored the difference of KIF18A expression levels in between lung adenocarcinoma tissues and adjacent nontumor tissues through IHC assays. As we expected, adjacent nontumor tissues exhibited significantly low expression levels of KIF18A compared with lung adenocarcinoma tissues (Figures 1(b) and 1(c)).

According to the results, 102 tissue samples from lung adenocarcinoma patients who underwent surgical resection were divided into the KIF18A low expression and KIF18A high expression groups, based on the staining intensity (Figure 1(b) and Table 1). According to the staining results, 42 patients exhibited low expression of KIF18A, whereas 60 showed high expression of KIF18A (Table 1).

We further evaluated the clinical features of KIF18A in patients with lung adenocarcinoma. Patient age, gender, tumor size, and clinical stage were recorded and analyzed, respectively. According to the results, no obvious difference was found in clinical characteristics such as patient age and gender between the KIF18A low expression and KIF18A high expression groups (Table 1). Notably, our data revealed that KIF18A expression was inversely associated with tumor size (P = 0.033) and clinical stage (P = 0.041) in lung adenocarcinoma patients (Table 1). In conclusion, these results suggested the possible involvement of KIF18A in the progression of lung adenocarcinoma.

3.2. Ablation of KIF18A Blocks Cell Proliferation, Migration, and Invasion of Lung Adenocarcinoma In Vitro. To explore the possible regulatory mechanism underlying KIF18A affecting the progression of lung adenocarcinoma, the shRNA plasmids specifically targeting KIF18A were transfected into 2 types of human lung adenocarcinoma cells, A549 and H1975 cells, to block its expression. According to the results of quantitative PCR assays (Figure 2(a)), the transfection of KIF18A shRNA plasmids effectively inhibited its expression in both A549 and H1975 cells. Consistent with the results of quantitative assays, the immunoblot assays confirmed the obviously decreased expression levels of KIF18A in these 2 types of lung adenocarcinoma cells transfected with KIF18A shRNA plasmids (Figure 2(b)).

Next, we detected the effects of KIF18A on the proliferation of A549 and H1975 cells. Both colony formation assays and MTT assays were performed to evaluate cell proliferation capacity of lung adenocarcinoma. Data of colony formation assays exhibited that KIF18A depletion obviously reduced colony number (Figure 3(a)). Similarly, an obvious decrease absorbance value at 570 nm was detected in these 2 types of lung adenocarcinoma cells through MTT assays (Figure 3(b)). All these results confirmed the impaired proliferation capacity caused by KIF18A depletion.

We then performed wound healing and transwell assays to evaluate the effects of KIF18A on the migration and invasion of lung adenocarcinoma cells. Interestingly, our results exhibited that KIF18A depletion dramatically suppressed the extent of wound healing in both A549 and H1975 cells (Figure 3(c)). Additionally, KIF18A depletion significantly blocked the invasion of these 2 types of lung cancer cells through membranes, with dramatically dropped cell number (Figure 3(d)), confirmed by transwell assays.

Collectively, our results indicated that KIF18A contributes to cell proliferation, migration, and invasion of lung adenocarcinoma in vitro.

3.3. KIF18A Induces the Growth and Metastasis of Lung Adenocarcinoma in Mice. Based on the previous results, KIF18A depletion resulted in the inhibition of the proliferation, migration, and invasion of lung adenocarcinoma cells; we further evaluated the possible effects of KIF18A in the growth and metastasis of lung adenocarcinoma in mice.

Tumor growth assays were firstly performed in mice to explore the possible effects of KIF18A on the growth of lung adenocarcinoma in mice. A549 cells were infected with control or KIF18A shRNA lentivirus and subcutaneously injected into nude mice. After 2 weeks, tumors were isolated from mice and photographed, and the volume of tumors was measured every week. Representative photographs were
Figure 3: KIF18A promotes the proliferation, migration and invasion of lung adenocarcinoma cells in vitro. (a) A549 and H1975 cells transfected with control or KIF18A shRNA, and the proliferation capacity was quantified by colony number through colony formation assays. (b) The OD value generated by MTT assays showed the inhibition of cell proliferation caused by KIF18A ablation. (c) KIF18A depletion resulted in the lower migration degree in A549 and H1975 cells. Photographs showed that at 0- and 24-hour time points, migrated cells were present. (d) Transwell assays using both A549 and H1975 human lung adenocarcinoma cells transfected with control or KIF18A shRNA plasmids, and the degree of invasion was quantified by the invasion cell number. Results are presented as the mean ± SD; * P < 0.05.
shown (Figure 4(a)). The growth curve is calculated and exhibited in Figure 4(a). According to the results, the volume of tumors isolated from KIF18A knockdown groups was significantly smaller than that in control groups (Figure 4(a)).

We further performed lung metastasis assay in mice. A549 cells were infected with KIF18A shRNA lentivirus to stably knockdown its expression. Subsequently, control or KIF18A stably depletion A549 cells injected into the caudal vein of nude mice. After 7 weeks, we found that the incidence of lung metastasis for A549 cells was obviously decreased compared with control (Figure 4(b)).

To confirm the silencing efficiency of KIF18A shRNA lentivirus in mice, we detected KIF18A expression levels in tumor tissues through IHC assays. As we expected, the expression levels of KIF18A in the depletion groups were obviously reduced compared with the control groups (Figure 4(c)).

In conclusion, these results confirmed that KIF18A induces the growth and metastasis of lung adenocarcinoma in mice.

4. Discussion

Although the improvement of early detection and combined therapy has resulted in a decrease of lung cancer death, the development and metastasis of advanced lung cancer are still the main cause of high mortality rates [23]. As various studies reported, kinesins were involved in the development and metastasis of multiple tumors [24]. Interestingly, we identified a member of the kinesin superfamily, KIF18A, which promoted the proliferation, migration, and invasion capacity of lung adenocarcinoma cells. Due to the lack of clinical effects of traditional therapeutic drugs, the implementation of a novel promising drug is highly desirable for better treatment of advanced lung adenocarcinoma [25]. KIF18A as a potential antitumor therapeutic target has been widely reported. Our study proved KIF18A as a novel and promising molecular target for the treatment of lung adenocarcinoma.

In our study, we found the high expression of KIF18A in lung adenocarcinoma tissues compared with corresponding normal tissue. Through IHC assays and clinical feature analysis, we also found that the expression of KIF18A was correlated with clinical features including the tumor size and clinical stage, which induced the poor prognosis of lung adenocarcinoma. Consistent with our findings, KIF18A has a reported high expression in tumor tissues and promoted cell proliferation and migration of many types of cancers, such as gastric cancer and breast cancer. Whether KIF18A has similar effects in different tumors is also worthy of further study.

The kinesins are associated with microtubules and involved in various cellular processes related to spindle
organization and chromosome movement [26]. Further, kinesins could be involved in the regulation of cell cycle, proliferation, and migration [26]. Previous studies revealed that microtubule dynamics is critical for the establishment of the interphase polarized cytoskeleton and therefore stabilized the plus ends of the microtubule in the array at the leading edges, which is necessary for cell proliferation and migration [27]. Notably, KIF18A has been found to suppress dynamic instability of interphase microtubules [28]. Therefore, as a member of the kinesin superfamily, KIF18A might affect cell proliferation, migration, and invasion of lung adenocarcinoma in a microtubule-dependent manner, and the precise regulatory mechanism underlying KIF18A promoting lung adenocarcinoma needs further study.

In addition to KIF18A, various types of kinesins are reported to be involved in tumor progression. In previous studies, KIF1B and KIF14 promoted the growth of hepatocellular carcinoma (HCC) and are correlated with the prognosis of patients with HCC [29, 30]. KIF20B could regulate tongue squamous cell carcinoma (HCC) and are correlated with the prognosis [29, 30]. KIF18A might affect the clinical features of patients with lung adenocarcinoma needs further study.

In conclusion, our current study reveals the high expression of KIF18A in lung adenocarcinoma tissues, correlated with the clinical features of patients with lung adenocarcinoma. Furthermore, we found that KIF18A contributed to the proliferation, migration, and invasion of lung adenocarcinoma cells in vitro and promoted the growth and metastasis of lung adenocarcinoma in mice. These results help in providing a better understanding of the possible regulatory mechanisms of tumor progression and a promising therapeutic target for lung adenocarcinoma-targeted therapy.

Data Availability

The data used to support the findings of this study are included within the article.

Ethical Approval

All applicable international, national, and/or institutional guidelines for the care and use of human specimens and animals were followed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. The animal study was carried out in accordance with the guidelines approved by the Animal Experiment Ethics Committee of The Second People’s Hospital of Lianyungang. The protocol was approved by the Committee, all surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

Consent

All of the authors have agreed to publish this article in your journal if it is accepted.

Conflicts of Interest

The authors have declared that no competing financial interest exists.

Authors’ Contributions

Fu-Tao Chen carried out the experiment of molecular biology and drafted the manuscript. Fu-Tao Chen and Fu-Kuan Zhong carried out the animal experiment. Fu-Kuan Zhong participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

References

[1] P. F. Pinsky and B. S. Kramer, "Lung cancer risk and demographic characteristics of current 20-29 pack-year smokers: implications for screening," JNCI: Journal of the National Cancer Institute, vol. 107, no. 11, 2015.
[2] D. D. Kim, J. T. Cohen, J. B. Wong et al., "Targeted incentive programs for lung cancer screening can improve population health and economic efficiency," Health Affairs, vol. 38, no. 1, pp. 66–67, 2019.
[3] T. D. O'Brien, P. Jia, M. C. Aldrich, and Z. Zhao, "Lung cancer: one disease or many," Human Heredity, vol. 83, no. 2, pp. 65–70, 2018.
[4] W. He, D. Xu, Z. Wang et al., "Three-dimensional nanostructured substrates enable dynamic detection of ALK-rearrangement in circulating tumor cells from treatment-naive patients with stage III/IV lung adenocarcinoma," Journal of Translational Medicine, vol. 17, no. 1, pp. 32, 2019.
[5] Y. Ma, M. Fan, L. Dai et al., "The expression of TTF-1 and napsin A in early-stage lung adenocarcinoma correlates with the results of surgical treatment," Tumour Biology, vol. 36, no. 10, pp. 8085–8092, 2015.
[6] L. Xie, Y. Dang, J. Guo et al., "High KRT8 expression independently predicts poor prognosis for lung adenocarcinoma patients," Genes, vol. 10, no. 1, pp. 36, 2019.
[7] X. Zhou, L. Cai, J. Liu et al., "Analyzing EGFR mutations and their association with clinicopathological characteristics and prognosis of patients with lung adenocarcinoma," Oncology Letters, vol. 16, no. 1, pp. 362–370, 2018.
[8] R. Salgia, "Mutation testing for directing upfront targeted therapy and post-progression combination therapy strategies in lung adenocarcinoma," Expert Review of Molecular Diagnostics, vol. 16, no. 7, pp. 737–749, 2016.
[9] S. D. Li, A. Martial, A. B. Schrock, and J. J. Liu, "Extraordinary clinical benefit to sequential treatment with targeted therapy and immunotherapy of a BRAF V600E and PD-L1 positive metastatic lung adenocarcinoma," Experimental Hematology & Oncology, vol. 6, no. 29, 2017.
[10] R. D. Vale, T. S. Reese, and M. P. Sheetz, "Identification of a novel force-generating protein, kinesin, involved in microtubule-based motility," Cell, vol. 42, no. 1, pp. 39–50, 1985.
[11] E. J. Tomei and S. M. Wolniak, “Kinesin-2 and kinesin-9 have atypical functions during ciliogenesis in the male gametophyte of Marsilea vestita,” BMC Cell Biology, vol. 17, no. 1, p. 29, 2016.

[12] J. I. MacDonald, A. Dietrich, S. Gamble, T. Hryciw, R. I. Grant, and S. O. Meakin, “Nesca, a novel neuronal adapter protein, links the molecular motor kinesin with the pre-synaptic membrane protein, syntaxin-1, in hippocampal neurons,” Journal of Neurochemistry, vol. 121, no. 6, pp. 861–880, 2012.

[13] V. De Wever, I. Nasa, D. Chamousset et al., “E. J. Tomei and S. M. Wolniak,” Biochemical and Biophysical Research Communications, vol. 453, no. 3, pp. 432–437, 2014.

[14] C. Zhang, C. Zhu, H. Chen et al., “Kif18A is involved in human breast carcinogenesis,” Carcinogenesis, vol. 31, no. 9, pp. 1676–1684, 2010.

[15] A. Czechanski, H. Kim, C. Byers, I. Greenstein, I. Greenstein, and L. G. Reinholdt, “Kif18a is specifically required for mitotic progression during germ line development,” Developmental Biology, vol. 402, no. 2, pp. 253–262, 2015.

[16] Y. Shin, Y. Du, S. E. Collier, M. D. Oh, M. J. Lang, and R. Ohi, “Biased Brownian motion as a mechanism to facilitate nanometer-scale exploration of the microtubule plus end by a kinesin-8,” Proceedings of the National Academy of Sciences of the United States of America, vol. 112, no. 29, pp. E3826–E3835, 2015.

[17] Q. I. Chen, B. Cao, N. Nan et al., “Elevated expression of KIF18A enhances cell proliferation and predicts poor survival in human clear cell renal carcinoma,” Experimental and Therapeutic Medicine, vol. 12, no. 1, pp. 377–383, 2016.

[18] H. Zhu, W. Xu, H. Zhang et al., “Targeted deletion of Kif18a protects from colitis-associated colorectal (CAC) tumors in mice through impairing Akt phosphorylation,” Biochemical and Biophysical Research Communications, vol. 438, no. 1, pp. 97–102, 2013.

[19] W. Luo, M. Liao, Y. Liao et al., “The role of kinesin KIF18A in the invasion and metastasis of hepatocellular carcinoma,” World Journal of Surgical Oncology, vol. 16, no. 1, p. 36, 2018.

[20] M. Kasahara, M. Nagahara, T. Nakagawa et al., “Clinicopathological relevance of kinesin family member 18A expression in invasive breast cancer,” Oncology Letters, vol. 12, no. 3, pp. 1909–1914, 2016.

[21] F. Yang, Y. Chen, and W. Dai, “Sumoylation of Kif18A plays a role in regulating mitotic progression,” BMC Cancer, vol. 15, p. 197, 2015.

[22] G. Li, Z. K. Xie, D. S. Zhu, T. Guo, Q. L. Cai, and Y. Wang, “KIF20B promotes the progression of clear cell renal cell carcinoma by stimulating cell proliferation,” Journal of Cellular Physiology, vol. 25, 2019.

[23] N. Motono, A. Funasaki, A. Sekimura, K. Usuda, and H. Uramoto, “Prognostic value of epidermal growth factor receptor mutations and histologic subtypes with lung adenocarcinoma,” Medical Oncology, vol. 35, no. 3, p. 22, 2018.

[24] O. Rath and F. Kozielski, “Kinesins and cancer,” Nature Reviews Cancer, vol. 12, no. 8, pp. 527–539, 2012.

[25] C. Liu, Z. Li, S. Wang et al., “FUT4 is involved in PD-1-related immunosuppression and leads to worse survival in patients with operable lung adenocarcinoma,” Journal of Cancer Research and Clinical Oncology, vol. 145, no. 1, pp. 65–76, 2019.