

Downregulation of PFTK1 Inhibits Migration and Invasion of Non-Small Cell Lung Cancer

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Background: PFTK1, a novel cyclin-dependent kinase, plays pivotal roles in tumorigenesis. Cell motility and invasiveness could be enhanced by PFTK1 in various tumors. However, the function of PFTK1 in NSCLC metastasis remains unclear. In this study, the potential role of PFTK1 in NSCLC metastasis was determined.

Materials and Methods: In this study, the potential function of PFTK1 in lung cancer patients was analyzed with the Kaplan–Meier plotter database. RNA interference-mediated knockdown of PFTK1 was established in two NSCLC cell lines (H1299 and 95C) to explore the role of PFTK1 in NSCLC. The efficacy of downregulation of PFTK1 was examined by Western blot and immunofluorescence. The role of PFTK1 in cell migration and invasion ability was detected by wound healing and transwell assays. The protein levels in lung cancer cells were determined by Western blot. Immunofluorescence analysis was used to evaluate the structure of filamentous actin.

Results: Overexpression of PFTK1 was associated with the poor survival prognosis in NSCLC patients. PFTK1 knockdown cells were constructed successfully. Suppression of PFTK1 significantly inhibited the cell migration and invasion in H1299 and 95C cells. Notably, after PFTK1 downregulation, the epithelial–mesenchymal transition (EMT) markers vimentin, ZEB1 and β -catenin were obviously decreased. Additionally, immunofluorescence analysis indicated that PFTK1 downregulation remarkably induced filamentous actin depolymerization.

Conclusion: In summary, PFTK1 could significantly promote lung cancer metastasis through changing EMT progress and modulating intracellular cytoskeleton F-actin expression. Taken together, our findings indicated that PFTK1 might serve as a novel therapeutic target for the inhibition of NSCLC progression.

Keywords: non-small cell lung cancer, PFTK1, invasion

Introduction

Lung cancer is the leading cause of all cancer-related deaths worldwide.¹ It can be divided into two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of lung cancers. Although surgery, chemotherapy and radiation therapy effectively control NSCLC at the primary site, the development of metastasis signals poor prognosis.² Metastasis is the primary cause of death due to NSCLC. Increased understanding of the mechanism of NSCLC will facilitate better control of carcinogenesis. However, the NSCLC-related metastatic molecular mechanism remains unclear.

The human *PFTK1* gene, also named *CDK14*, is located at chromosome 7q21.13. Its 6kb transcript is highly expressed in the brain, pancreas, kidney, heart, testis and

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ovary, but at a relatively lower level in other tissues.³ *PFTK1* gene encodes a cell division cycle 2-related serine/threonine protein kinase PFTK1, which has a highly conserved domain homology to Cdc2 kinase.⁴ Though *PFTK1* was identified in 2001, it has been long recognized as a regulatory factor in the control of eukaryotic cell cycle transitions and proliferation. However, its role in cancer is poorly understood. Overexpression of *PFTK1* was detected in various cancers, including hepatocellular carcinoma,⁵⁻⁷ glioma,⁸ esophageal squamous cell carcinoma,⁹ ovarian cancer¹⁰ and breast cancer.¹¹

Metastatic dissemination, one of the most complicated processes during carcinogenesis, is responsible for nearly 90% of cancer-related deaths.^{12,13} Accumulated data indicated that *PFTK1* plays important roles in tumor cell migration, and invasion. Several researchers have investigated the function of *PFTK1* during tumor invasiveness and cell motility, and reported that *PFTK1* promoted invasiveness and cell motility in hepatocellular carcinoma.^{6,7} Similar results were obtained in glioma.⁸ Furthermore, *PFTK1* was found to interact with CCNY, the newest member of the cell cyclin family, and regulate cell cycle progression and cell proliferation.¹⁴ However, the role of *PFTK1* in NSCLC invasion and migration remains unclear.

In the present study, we investigated the function of *PFTK1* in cell migration and invasion by lentivirus-mediated RNA interference approach in NSCLC cell lines to understand its biological roles in lung cancer. Results illustrated that downregulation of *PFTK1* inhibited NSCLC cell migration and invasion as well as EMT *in vivo*. Furthermore, immunofluorescence assay was used to assess the effect of *PFTK1* on cytoskeletal protein. *PFTK1* was found to promote cell motility and invasion by regulating F-actin expression in NSCLC cells.

Materials and Methods

Cell Culture

Human lung large cell neuroendocrine cell line (H1299) and human large cell lung carcinoma cell line (95C) were purchased from the Tumor Center of Chinese Academy of Medical Sciences. The lung cancer cell lines were cultured in RPMI 1640 medium (Invitrogen, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, Los Angeles, CA, USA) and 1% penicillin/streptomycin. The cell lines were maintained at 37°C under a humidified air atmosphere containing 5% CO₂.

Knockdown of PFTK1 by shRNA Interference

Knockdown of *PFTK1* was performed by a lentivirus-based RNAi delivery system. Three candidate *PFTK1*-RNAi lentiviral vectors were constructed (Shanghai Genechem Co. Ltd., Shanghai, China). The target sequences of the oligonucleotides for RNA interference were as follows:

shRNA-*PFTK1*#1, 5'-GTTTCATTCTTTACCACATT-3', shRNA-*PFTK1*#2, 5'-AGGTTGCATCTTTGTTGAA-3', and shRNA-*PFTK1*#3, 5'-CGCCAACAAGTCCCAAATT-3'. A non-silencing-shRNA (5'-TTCTCCGAACGTGT CACGT-3') was designed as a negative control. For transfection, H1299 and 95C cells were plated in 96-well culture plates at a density of 5000/well. The next day, cells were transfected with recombinant virus carrying shRNA-*PFTK1* and shRNA-NS for 8 h. The transfected cells were selected with 5 µg/mL puromycin in H1299 cells or 1 µg/mL puromycin in 95C cells for at least 3 days.

Wound Healing Assay

The cells were plated in 6-well plates overnight. Next day, the confluent cell monolayers were wounded by a sterile pipette tip and cultured in serum-free medium.

The wounds were observed at 0, 24, and 36 h along the scratch, and representative images were acquired with a phase-contrast microscope. The wound areas were calculated using Alpha View Analysis Tools. All experiments were performed in triplicate.

Cell Migration and Invasion Assay

The migration and invasion assays were conducted in a 24-well transwell unit containing 8-µm pore size polycarbonate membrane. For migration assay, after starvation for 12 h, the cells with 200 µL serum-free medium were suspended and plated in the upper compartment, while the lower compartment was filled with 600 µL medium containing 10% FBS. Twenty-four hours later, the cells in the upper compartment were completely removed by gently swabbing with a cotton bud. Cells migrating to the lower surface of the membrane were stained by crystal violet. The number of cells on the lower surface of the membrane was counted in five microscopic fields at 200× magnification. The assay was performed in triplicate and the data were presented as means ± SD.

The invasion assay was similarly performed. Briefly, cells were starved for 24 h, suspended, and then seeded

into the upper compartment whose membrane was coated with Matrigel matrix. RPMI 1640 medium containing 10% FBS was added to the lower compartment and used as a chemoattractant. After incubation for 48 h, cells attached to the lower surface of the membrane were stained by crystal violet and counted in five microscopic fields at 200× magnification. Triplicate samples were assayed and the data were presented as means \pm SD.

Western Blot Analysis

The cells were harvested, washed with PBS and extracted with lysis buffer (150 mM NaCl, 1 mg/mL leupeptin, 1 mM EDTA, 1 mM EGTA, 1 mM natrium glycerophosphoricum, 1 mM sodium vanadate, 2.5 mM sodium pyrophosphate, 1 mM PMSF, 1 mM DTT and 1×cocktail). After the cell debris were removed by centrifugation at 14,000 g for 10 min at 4°C, the protein concentration was measured by Nanodrop. Then the proteins were separated using 10% SDS-PAGE and transferred onto a nitrocellulose filter membrane. To block nonspecific binding, the membranes were incubated with 5% non-fat milk for 2 hours at room temperature. After the membranes were incubated overnight at 4°C with the human anti-PFTK1 (Ab175489; Abcam, UK), anti-ZEB1 (Ab155249; Abcam, UK), anti-vimentin (Ab8978; Abcam, UK) and anti- β -catenin (Ab6302; Abcam, UK), appropriate secondary antibodies conjugated to horseradish peroxidase were diluted 1:3000 and incubated with the membrane. GAPDH was used as an internal reference. After washing three times with TBST, proteins were detected using ECL reagents (Pierce, USA) and exposed to Alpha Innotech Imager.

Immunofluorescence Staining

Cells cultured on glass coverslips were rinsed in PBS and fixed in 4% paraformaldehyde for 10 minutes. After washing three times in PBS, the cells were permeabilized with 0.2% Triton X-100 for 15 minutes. To block nonspecific binding, the coverslips were incubated with 3% BSA for 30 minutes at room temperature, probed with primary antibodies overnight at -4°C followed by FITC-conjugated secondary antibody for 1 h at room temperature. Finally, cells were counterstained with Hoechst 33,342 (10 μ g/mL; Sigma, USA) for 30 min and visualized under a laser confocal microscope (Leica, Germany).

For staining F-actin, cells were washed with PBS and fixed in 3.7% formaldehyde for 10 minutes at room temperature. After permeabilizing with 0.1% Triton X-100 in

PBS for 5 minutes, cells were incubated with rhodamine-conjugated phalloidin for 20 minutes at room temperature. The coverslips were washed and nuclei were stained with Hoechst 33,342 for 20 min. Cells were analyzed with a laser confocal microscope (Leica, Germany).

Statistical Analysis

Data were presented as the means \pm SD of at least three independent experiments. The statistical differences between the two independent groups were analyzed using Student's *t*-test. All statistical analyses were performed with SPSS 16.0, and $p < 0.05$ was considered to be statistically significant.

Results

High PFTK1 Expression Corrected with the Poor Survival Prognosis in Lung Cancer

Firstly, the potential function of PFTK1 in lung cancer patients was analyzed with the Kaplan–Meier plotter database. As shown in Figure 1, the median survival time of PFTK1 was 76 months in the low-expression group ($n=962$), which was higher than that in the high-expression group ($N=963$) at 63 months ($p < 0.05$). The information performed that the high PFTK1 expression was significantly correlated with poor overall survival of lung cancer patients, which showed a significant role of PFTK1 in lung cancer progression.

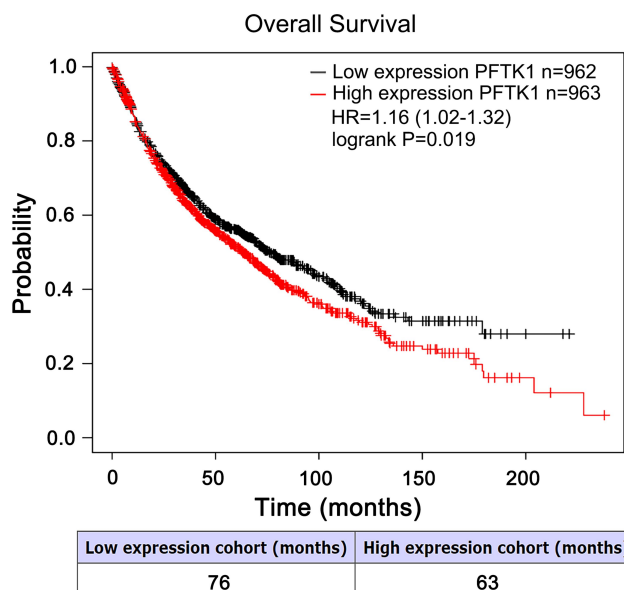


Figure 1 High expression of PFTK1 was associated with the poor overall survival of lung cancer in Kaplan–Meier plotter database.

Lentivirus-Mediated shRNA Effectively Suppressed PFTK1 Expression in NSCLC Cells

To investigate the function of PFTK1 in NSCLC cells, we transfected shRNAs for PFTK1 into lung cancer cell lines H1299 and 95C. The efficiency of lentivirus-mediated PFTK1-shRNA were confirmed by western-blot and immunofluorescence. As shown in **Figure 2A** and **B**, compared to the cells transfected with the control shRNA, the expression levels of PFTK1 in the cells transfected with shRNA for PFTK1 (shPFTK1-1, 2 and 3) were obviously decreased. Moreover, as shown in **Figure 2C** and **D**, PFTK1 was successfully downregulated in H1299 and 95C cells by all three PFTK1-RNAi lentiviral vectors, as determined by immunofluorescence assay. The results showed that PFTK1 expression could be specifically and

effectively suppressed by lentivirus-mediated shRNA against PFTK1 in H1299 and 95C cells.

Downregulation of PFTK1 Suppresses the Migration of NSCLC Cells

To assess the function of PFTK1 on cell metastasis, we first examined the effect of PFTK1 on cell migration ability. We found that PFTK1 significantly inhibited wound closure in H1299 and 95C cells, as compared to the corresponding controls (**Figure 3**). In the transwell assay, the number of cells that migrated to the bottom of the transwell chamber membrane was obviously decreased when PFTK1 was knocked down in H1299 and 95C cells (**Figure 4**, $*p<0.05$). These data suggested that PFTK1 could effectively inhibit the migration of human NSCLC cells.

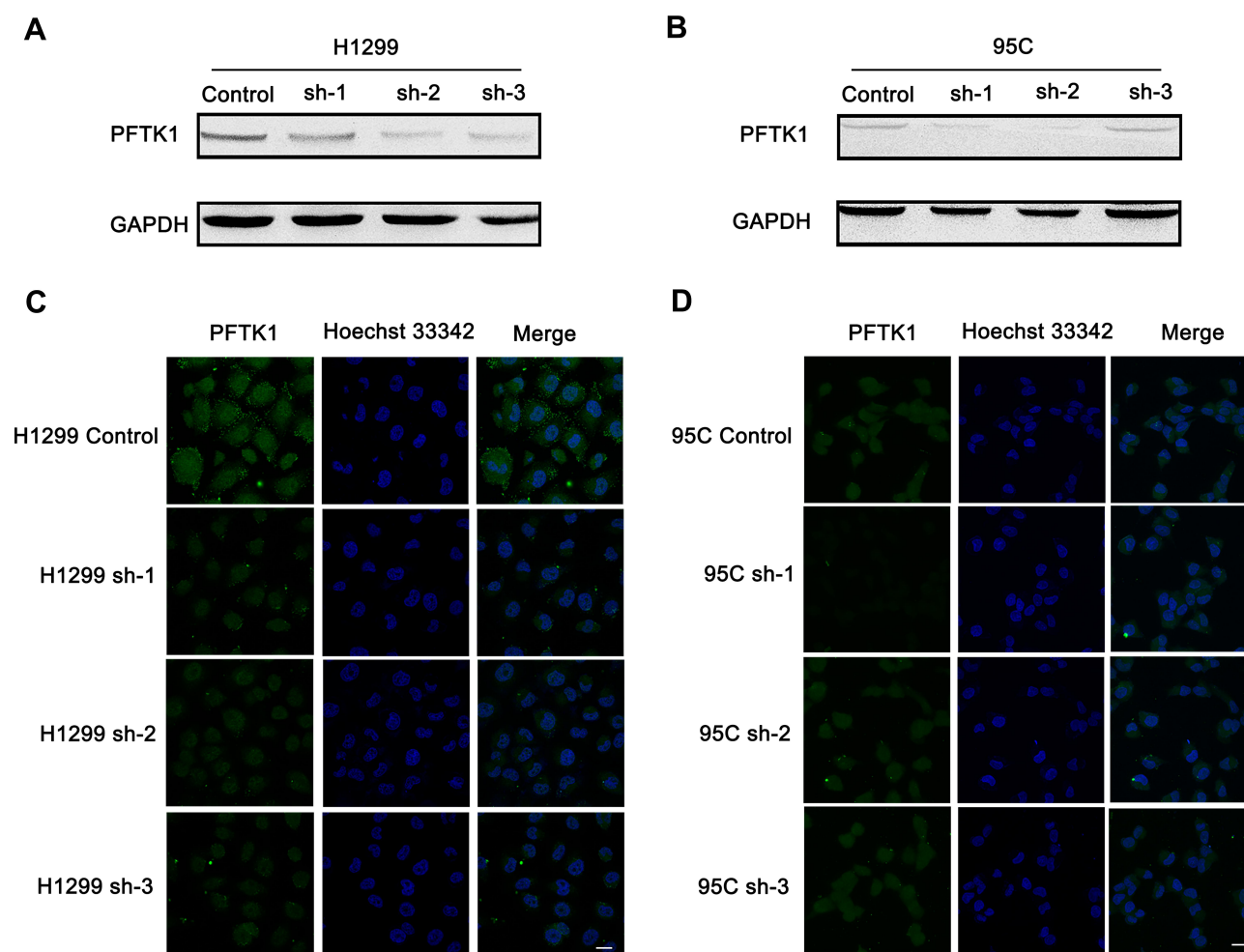


Figure 2 PFTK1 was downregulated by shRNA interference in NSCLC cell lines. (**A**, **B**) The protein levels of PFTK1 in H1299 shRNA PFTK1 (sh-1, 2 and 3), 95C shRNA PFTK1 (sh-1, 2 and 3) cells and control cells were determined by western-blot. GAPDH expression level was detected as a control. (**C**, **D**) PFTK1 protein expression was evaluated by immunofluorescent assay in H1299 shRNA PFTK1 (sh-1, 2 and 3), 95C shRNA PFTK1 (sh-1, 2 and 3) cells and control cells. The green signal represents the staining of PFTK1 and the blue signal represents the nuclear DNA staining by Hoechst 33,342. Bars represent 20 μ m.

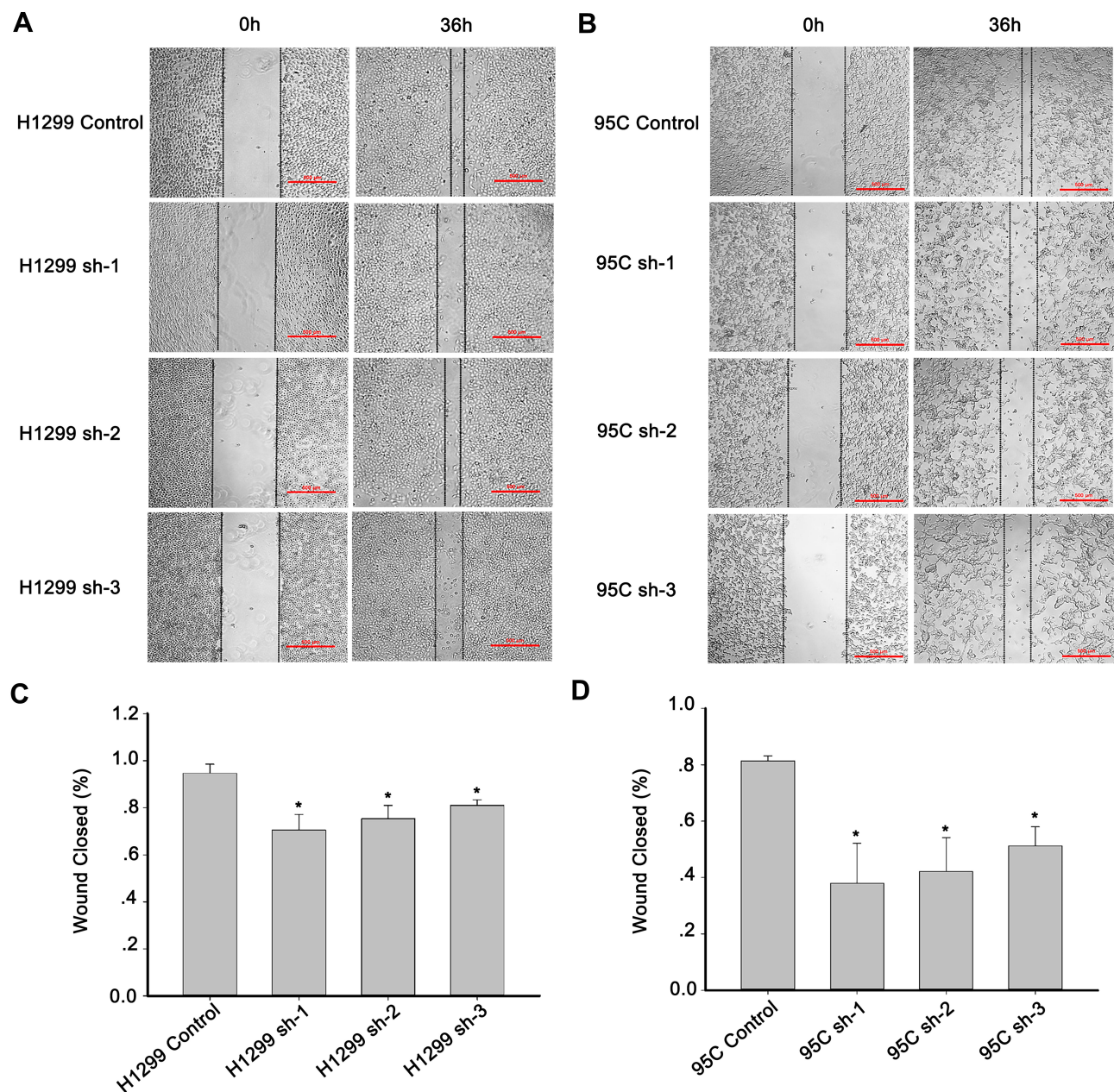


Figure 3 PFTK1 is involved in lung cancer cell migration. (A, B) Wound healing assay was performed in H1299 shRNA PFTK1 (sh-1, 2 and 3), 95C shRNA PFTK1 (sh-1, 2 and 3) cells and control cells for 36 h. Bars represent 500 μ m. (C, D) The wound areas in PFTK1 knockdown cells as well as control cells of H1299 and 95C were calculated using Alpha View Analysis Tools. The data are shown as the means \pm SD of three independent experiments. Significant difference as compared to the control group (* p <0.05).

Downregulation of PFTK1 Suppresses the Invasion of NSCLC Cells

To further explore the influence of PFTK1 on cell metastasis, transwell assay with matrigel was performed. As shown in Figure 5, the invasion abilities of H1299 and 95C cells were remarkably decreased by the downregulation of PFTK1 expression, as compared to the control groups. These results indicated that PFTK1 plays an important role in cell invasion and migration of NSCLC cells.

PFTK1 Regulates Epithelial–Mesenchymal Transition (EMT) in NSCLC Cells

To further investigate the possible molecular mechanism by which PFTK1 promotes migration and invasion of NSCLC cells, we identified a list of EMT-related proteins. Western-blot analysis revealed that the expression of vimentin, ZEB1 and β -catenin were obviously diminished after downregulation of PFTK1 in H1299 and 95C cells as compared to the control cells (Figure 6). Since vimentin, ZEB1 and β -catenin are

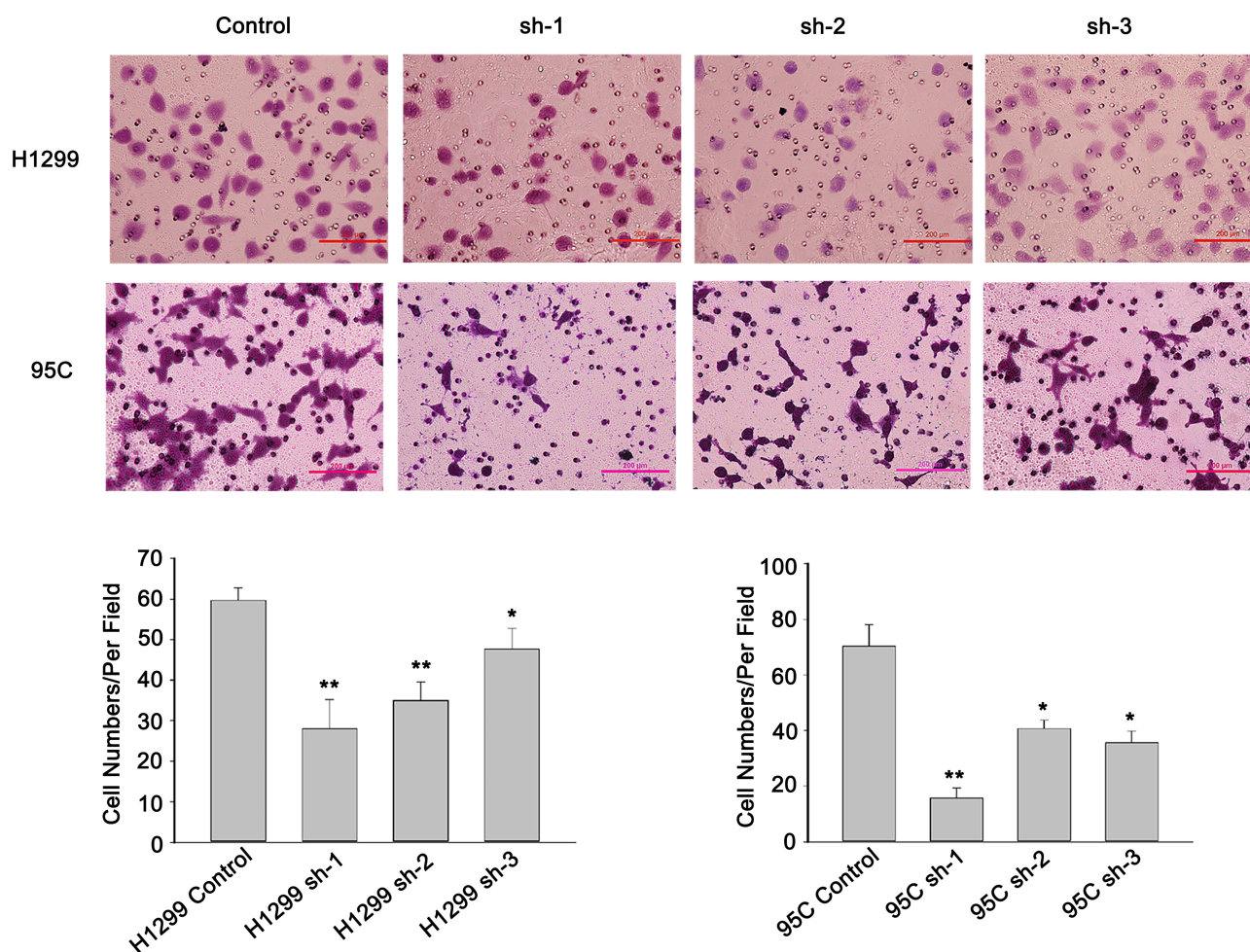


Figure 4 PFTK1 promotes NSCLC cell migration ability. Transwell migration assay was performed in H1299 shRNA PFTK1 (sh-1, 2 and 3), 95C shRNA PFTK1 (sh-1, 2 and 3) cells and control cells over 24 h. The number of cells on the lower surface of the membrane was counted in five microscopic fields at 200× magnification. The assay was performed in triplicate and the data are presented as means \pm SD. Significant difference as compared to the control group (* $p < 0.05$ and ** $p < 0.01$).

mesenchymal cell markers, these results suggested that PFTK1 stimulates cell metastasis by inducing EMT of NSCLC.

PFTK1 Modulates Intracellular Cytoskeleton

To determine the association between PFTK1 and filamentous actin organization, immunofluorescence staining for filamentous actin by phalloidin was performed. As shown in Figure 7, reduced actin stress fiber formation was found in PFTK1 downregulated cells. However, the control cells showed obvious polymerization of actin stress fibers. Our findings strongly indicated that PFTK1 promoted cell motility by modulating cytoskeletal structure in H1299 and 95C cells.

Discussion

The current study was performed to investigate whether PFTK1 is involved in lung cancer progression. Previous

studies have suggested important functions of PFTK1 in various tumors. However, its role in lung cancer and the potential molecular mechanisms remains unclear. The current study demonstrated that PFTK1 promoted cell motility and invasiveness by inducing EMT and modulating cytoskeletal structure.

Accumulating evidence showed that PFTK1 expression is positively associated with cancer progression and patient survival. In various human cancers, high PFTK1 expression indicates a more advanced stage of the disease. For instance, previous investigation analyzed the expression of PFTK1 in gastric cancer by immunohistochemistry and found that up-regulated PFTK1 expression was correlated with lymph node invasion and tumor grade.¹⁵ Another study also noted that high expression of PFTK1 was highly associated with grade and poor overall survival of breast cancer patients.¹¹ In oesophageal squamous cell

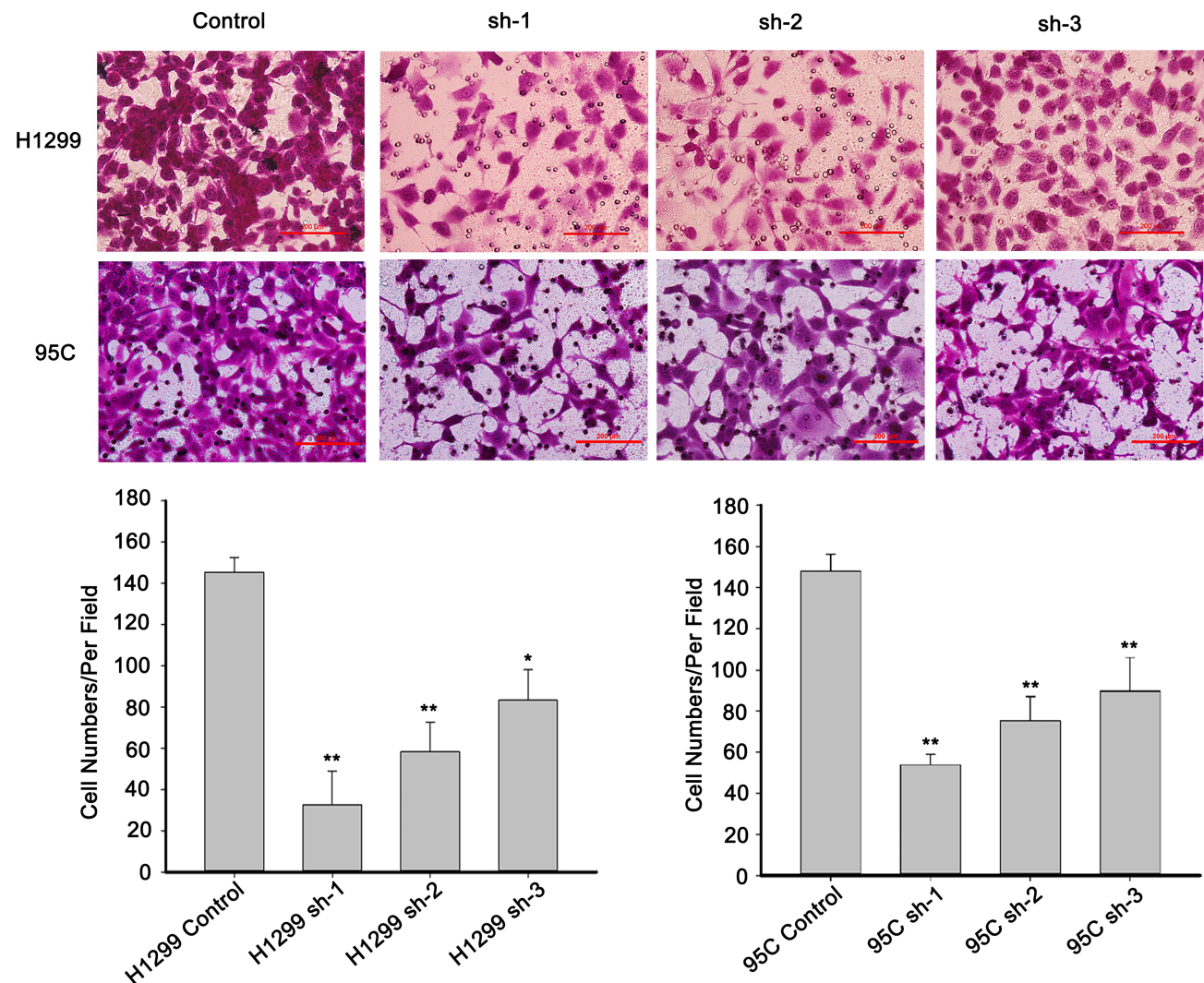


Figure 5 PFTK1 promotes NSCLC cell invasion ability. Transwell invasion assay was performed in H1299 shRNA PFTK1 (sh-1, 2 and 3), 95C shRNA PFTK1 (sh-1, 2 and 3) cells and control cells over 48 h. The number of cells on the lower surface of the membrane was counted in five microscopic fields at 200× magnification. The assay was performed in triplicate and the data are presented as means \pm SD. Significant difference as compared to the control group (* p <0.05 and ** p <0.01).

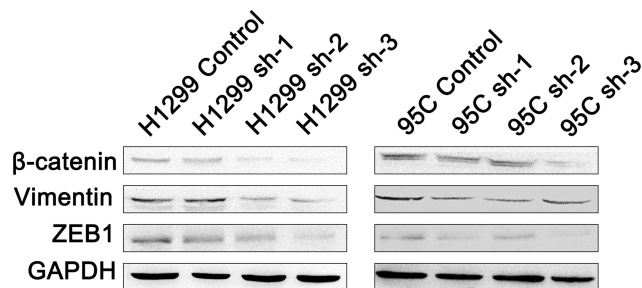


Figure 6 PFTK1 regulates epithelial-mesenchymal transition (EMT) in NSCLC cells. Expression of EMT-related proteins, vimentin, ZEB1 and β-catenin was examined by immunoblotting in H1299 shRNA PFTK1 (sh-1, 2 and 3), 95C shRNA PFTK1 (sh-1, 2 and 3) cells and control cells. GAPDH expression level was detected as a control.

carcinoma, the patients with high expression of PFTK1 showed a poor 5-year overall survival rate.⁹ Similar results were confirmed in liver cancer.⁶ In this study, we firstly

analyzed the function of PFTK1 in lung cancer with the Kaplan-Meier plotter database. The data indicated PFTK1 could be a prognosis marker for lung cancer patients. Moreover, our previous study¹⁶ examined the expression of PFTK1 in 119 cases of NSCLC by immunohistochemistry. We demonstrated that PFTK1 was overexpressed in lung cancers than adjacent normal tissues, and high PFTK1 expression was significantly correlated with T stage and lymph node metastasis. Moreover, overexpression of PFTK1 was associated with poor overall survival of NSCLC patients. Collectively, these findings showed a significant role of PFTK1 in lung cancer progression. To investigate the potential molecular mechanisms in NSCLC, we successfully inhibited the expression of PFTK1 in H1299 and 95C cells.

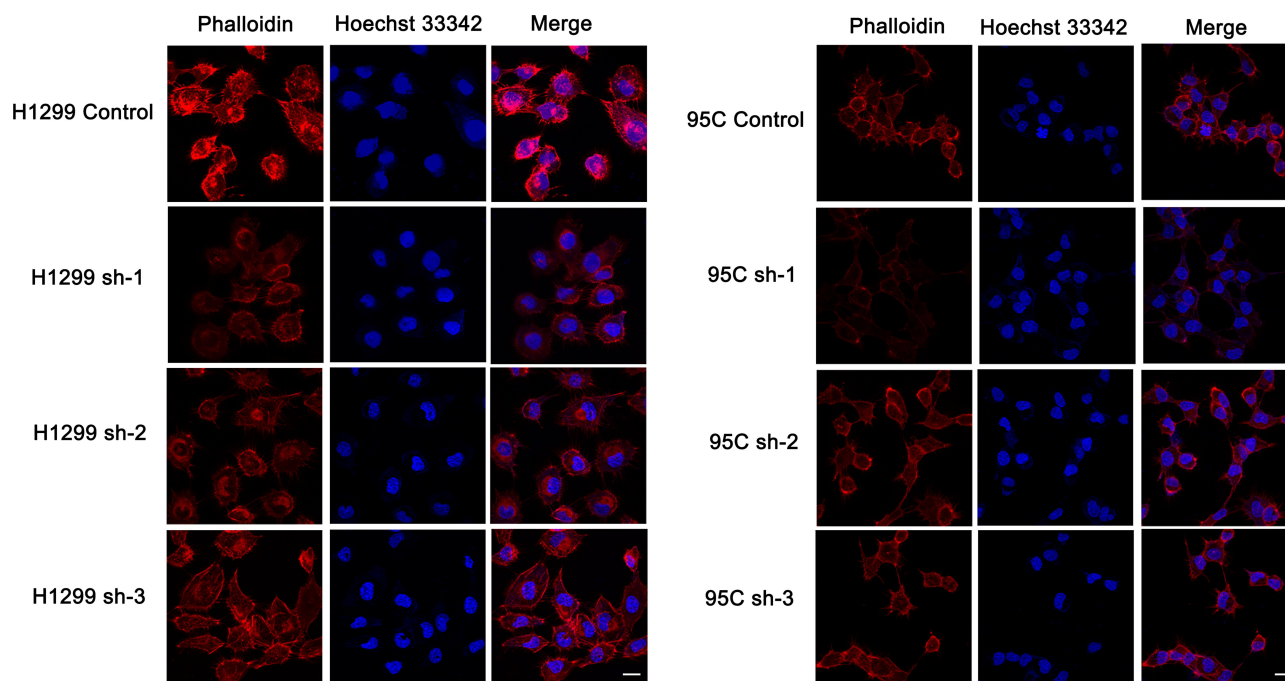


Figure 7 PFTK1 modulates intracellular cytoskeleton of NSCLC cells. F-actin was labelled by immunofluorescence staining in H1299 shRNA PFTK1 (sh-1, 2 and 3), 95C shRNA PFTK1 (sh-1, 2 and 3) cells and control cells. The red signal represents the staining of F-actin and the blue signal represents the nuclear DNA staining by Hoechst 33,342. Bars represent 20 μ m.

Numerous studies have found that epithelial–mesenchymal transition (EMT) plays a crucial role in tumor metastasis. During this process, tumor-associated epithelial cells could become migratory mesenchymal cells by many types of stimuli.¹⁷ Some studies have suggested an important association between PFTK1 and EMT in various cancer cells. For example, knockdown of PFTK1 inhibited the migration and invasion abilities as well as EMT progression in pancreatic cancer,¹⁸ ovarian cancer,¹⁰ gastric cancer,¹⁵ glioma,⁸ breast cancer,¹¹ oesophageal squamous cell carcinoma⁹ and liver cancer.⁶ PFTK1 may be involved in the progression of lung cancer cells. One study demonstrated that knockdown of PFTK1 by RNAi inhibits the proliferation and invasion in A549 cells.¹⁹ However, the mechanism of PFTK1 in NSCLC metastasis has yet been unclear. Our study showed that suppression of PFTK1 significantly inhibited the migration and invasion of NSCLC cells. Furthermore, mesenchymal cell markers vimentin, ZEB1, and β -catenin were obviously diminished after knockdown of PFTK1 in H1299 and 95C cells. Our findings clarified that PFTK1 might promote lung cancer metastasis by inducing EMT. Changes in filamentous actin organization were correlated with cancer metastasis.²⁰ In hepatocellular carcinoma cells, marked filamentous actin polymerization was detected in PFTK1-expressing

cells.^{6,7,21} In the present study, we verified that actin stress fiber formation was reduced in PFTK1 downregulated cells. Conversely, the control cells showed obvious polymerization of actin stress fibers. These findings strongly suggested that PFTK1 promoted cell motility by modulating cytoskeletal structure in NSCLC cells.

In conclusion, we reported that downregulation of PFTK1 in NSCLC could significantly inhibit cell migration and invasion. Our findings further indicated that PFTK1 could regulate cell motility by inducing EMT and modulating cytoskeletal structure of NSCLC. Taken together, these observations highlight the important role of PFTK1 in tumor progression, which might serve as a novel therapeutic target for NSCLC.

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Disclosure

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