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Original Article

Long non-coding RNA NKILA inhibits proliferation and migration of lung cancer via IL-11/STAT3 signaling

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Abstract: Background: MicroRNAs (miRNAs) play an important role in the development and progression of lots of cancer. Non-small cell lung cancer (NSCLC) is all lung cancer except small cell lung cancer (SCLC). The most common non-small cell lung cancer types include squamous cell carcinoma, large cell carcinoma and adenocarcinoma, and some other common types. Increasing studies identified that a long non-coding RNA NKILA was negatively correlated with breast cancer metastasis while its clinical significance and potential role in non-small cell lung cancer (NSCLC) remain unclear. In the present study, we confirmed the function of lncRNA NKILA as well as the underlying mechanism in regulating the NSCLC. Methods: The expression of lncRNA NKILA was detected in both Lung cancer tissues and cell line including A549 and NCI-H1299 by quantitative real-time reverse transcription. A small interfering RNA (siRNA) that targeted NKILA was transfected into cells to inhibit the expression of NKILA. MTT (3-(4,5-dimethylthiazol- 2-yl)-2,5-diphenyltetrazolium bromide) assay and scratch experiments were performed to analyze the migration and proliferation of NCI-H1299 which were transfected with si-NKILA. Protein levels of genes that related with G0/G1 arrest markers p16, p21, and p27 markers were measured. Results: The expression of NKILA was significantly down regulated in lung cancer tissues when compared to matched normal tissue. Conclusion: In summary, our results confirmed that low expression of lncRNA NKILA plays a role in the deterioration of NSCLC cells and this effect depends on IL-11/STAT3 signaling.

Keywords: Non-small cell lung cancer (NSCLC), lncRNA NKILA, IL-11/STAT3 signaling

Introduction

Long non-coding RNAs (lncRNAs), which were regarded as “transcriptional noise”, have been recently demonstrated to be a functional molecular [1, 2]. They regulate gene expression levels at a variety of levels including epigenetics, transcriptional regulation, and post-transcriptional regulation [3-5]. Non-coding RNAs functions in many aspects, such as participating in X chromosome inactivation, regulating mRNA degradation [6], constituting the skeletal structure of the nuclear sub-structure, as a regulator of chromatin remodeling and so on [7]. A growing volume of literatures has indicated the important roles of lncRNAs in cancer biology [8]. Non-small cell lung cancer (non-small cell carcinoma) and “non-small cell carcinoma” are all lung cancer, which include adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. Compared with small cell carcinoma, the growth rate is slower and diffusion is relatively late [9, 10]. Non-small cell lung cancer accounts for approximately 80-85% of the total lung cancer. The identification of activating mutations and amplifications of oncogenes, including KRAS [11, 12], EGFR, KARS [13], as well as inactivating mutations in tumor-suppressive genes, such as p53, helped understanding of NSCLC pathogenesis. It has been reported that IL-11 exhibits a wide variety of biological effects in the hematopoietic and immune systems. It has been reported that IL-11 promotes the development of gastric, breast, and colorectal cancer and contributes to the bone metastasis of HCC. STAT proteins are potent, conserved transcription factors. Seven STAT proteins have been identified as latent cytoplasmic transcription factors activated by tyrosine phosphorylation in response to cytokine and growth factor stimulation STAT sig-

naling plays an important role in the transfer of extracellular signals into the nucleus, resulting in transcriptional regulation and is essential in the uncontrolled growth of cancer cells, angiogenesis, and metastasis. However, the relationship between lncRNA-NKILA and IL-11 on the development of NSCLC remains unclear and requires further investigation.

Several lncRNAs have been reported to modulate tumor metastases, the specific roles of lncRNAs in mediating the prometastatic role of NSCLC and regulating proliferation are not well studied. In this study, we focus on the role of LncRNA-NKILA in the invasion-metastasis cascade of NSCLC and the mechanism in it.

Materials and methods

Animals

Male nude mice (4-5 weeks old) were used for animal studies. NCI-H1975 cells were suspended in PBS and the cell concentration was adjusted to 5×10^6/mL. Disinfection of the skin of the nude mice and inoculate 0.2 mL of the cell suspension with a syringe was performed. When the subcutaneous transplanted tumors grew to a diameter of approximately 10 mm, the transplanted tumors were removed, and the tumor-bearing nude mice with well-growth and no tumor rupture were selected. In the clean bench, the tumors were completely dissected under aseptic conditions. Blood stains were washed away. The tumor knots were cut off, necrotic tissue from the center was removed, and the tumor was cut into small pieces with a diameter of about 1 mm. Twenty nude mice received surgical orthotopic transplantation. Nude mice were returned to their original cages and kept. This study had received the ethical approval of the Ethics Committee of Lianyungang TCM Hospital.

Cell culture

A normal human bronchial epithelial cell line (16HBE) and NSCLC adenocarcinoma cell lines (A549, NCI-H1975) were purchased from the Biopike Biological company. DMEM or RPMI 1640 (Gibco Company) were used as cell culture mediums, containing 10% fetal bovine serum (FBS, HyClone) as well as 100 U/ml penicillin and 100 U/ml streptomycin (Invitrogen). Cells were cultured in a humidified cell incubator at 37°C in the presence of 5% CO_2.

Reverse-transcription quantitative real-time PCR (RT-qPCR)

Total RNA from tissues or cell lines was extracted using TRIzol reagent (Invitrogen, CA). The concentration of isolated total RNA was measured by NanoDrop ND-1000 Spectrophotometer (Agilent, CA). cDNA was obtained with the Total RNA as a templet by using the reverse transcription kit (Sigma) according to manufacturer instructions. This reaction was carried out in the real-time PCR detection system (Bio-Rad, CA, USA). GADPH and ACTIN were used as the reference and normalization control.

MTT assay

Cells transfected with si-NKILA or si-NC were digested by trypsin and collected by the termination of centrifugal seeding into 96-well plates. The cell suspension was adjusted to a concentration of 5-10 × 10^4/ml. 5% CO_2, then incubated at 37°C for 16-48 hours, and the effect of the drug was observed. An addition of 10 μM of MTT solution (5 mg/ml, 0.5% MTT) to each well and continued incubation for 4 hours was the next step. After the drug and MTT reaction, the culture medium was centrifuged, discarded, and carefully washed with PBS 2-3 times. The reaction was stopped to measure the absorbance at 490 nm using a microplate reader (Bio-Rad Laboratories, California, USA).

Western blotting

Human cells NCI-H1299 were harvested, washed twice with ice-cold PBS, total protein was extracted by adding protein lysate (RIPA lysate, 1% NP-40, 1 × protease inhibitor cocktail, phosphatase/protease inhibitors, PMSF) put on ice, and supplemented with a protease inhibitor cocktail tablet (Roche, USA). Equal amounts (50-80 μg) of protein were applied to an 8-12% SDS-polyacrylamide separating gel and cut the size of 6 × 9 cm gel, transferred to a PVDF membrane (Millipore). The protein was transferred to the PVDF membrane. Imprinted membranes were incubated at room temperature for one hour with a blocking solution of milk. The primary antibody was diluted at a concentration of 1:200 to 1:1000 and the blot was incubated overnight at 4°C. The PVDF membrane was washed 3 times with 0.05% TBST. The secondary antibody was diluted at a concentration of 1:8000 and the PVDF membrane

was incubated at room temperature for one hour. The PVDF membrane was washed 3 times with 0.05% TBST. Antibodies and their sources were as follows: STAT3 (no. 2532; Cell Signaling), phosphorylated STAT3 (p-STAT3 Thr172, no. 2531; Cell Signaling), BCL2 (no. 45174; Abcam), β-actin (no2066; Sigma-Aldrich).

Cell scratches

Cells were seeded in the 6-well plate. Several lines were drawn behind the plate with a ruler. After the cells attached, another line was drawn straight across the middle of the hole. The cells were washed with PBS 3 times, removing the cells on the surface, and adding a serum-free medium. Cells were put into the 37°C 5% CO_2 incubator and pictures were taken after transfecting with si-NKILA or control at different time points.

siRNA and transfection

lncRNA-NKILA siRNA and the scramble siRNA were designed and synthesized as previously reported (13). Cells were grown to ~60% confluency in 6-well plates (NEST Biotechnology Co., Ltd., Wuxi, China) one day before transfection. According to the manufacturer's instructions, we diluted the siRNAs with the appropriate concentration in Opti-MEM I to form complexes. NCI-H1299 cells were transiently transfected with the complexes obtained by Oligofectamine. Cells were cultured with serum-free medium supplemented with 10% FBS 6-h post transfection, and then incubated at 37°C in air containing 5% CO_2 for 48-72 h.

Defination of disease-free survival

Non-small cell lung cancer dataset analysis. The Kaplan-Meier method was used to estimate survival curves for NSCLC patients. The log-rank test was used to compare the differences between curves. The top 50% samples with the highest expression were considered as the high-expression group, and the remaining 50% of the samples as the low-expression group.

IL-11 ELISA

IL-11 levels in normal culture medium were collected after 48 h from different cells were detected with the Human IL-11 ELISA Kit (ab189569; Abcam, CA, USA) according to the manufacturer's instructions.

Statistical analyses

Statistical analysis was performed using Prism 5.0 (GraphPad Prism) Software. Experimental results are presented as means ± standard deviation. The comparisons between the groups were conducted with Student's t-test or ANOVA with multiple comparison with *P* value less than 0.05 considered statistically significant.

Results

NKILA was down-regulated and was associated with mice' survivals

Previous study suggested that the metastasis and clinical invasion of breast cancer has a relation with reduced expression of NKILA [14]. However, its function was barely known in the development of NSCLC. Next, we examined the expression of NKILA in the NSCLC cell line and matched noncancerous cells. We found that, as shown in **Figure 1A** and **1B**, the expression of NKILA was higher in normal human bronchial epithelial cell line (16HBE) or low metastatic cell lines (CAL27) but was significantly reduced in high-metastatic cell lines (A549, NCI-H1299, NCI-H1975). Interestingly, the result was also observed in the NSCLC tissues from the mice model that was described in the beginning (**Figure 1C**). The low level of NKILA had a strong relation with shorter disease-free survival (DFS) of mice with NSCLC (**Figure 1D**). Collectively, this data indicated that NKILA may have effect on the pathology development of NSCLC.

Effect of NKILA overexpression on the proliferation and migration of NSCLC adenocarcinoma cell lines

To reveal the potential role of NKILA in lung adenocarcinoma, we transfected NSCLC cells A549 with adenovirus to overexpress lncRNA NKILA. Then we investigated whether NKILA affected lung adenocarcinoma cell growth. The RT-PCR results showed that transfection of NKILA adenovirus could significantly enhance the level of NKILA in A549 cells, as compared to their respective control groups (**Figure 2A**). MTT assay showed that up-regulation of NKILA significantly inhibited cell *proliferation* of A549

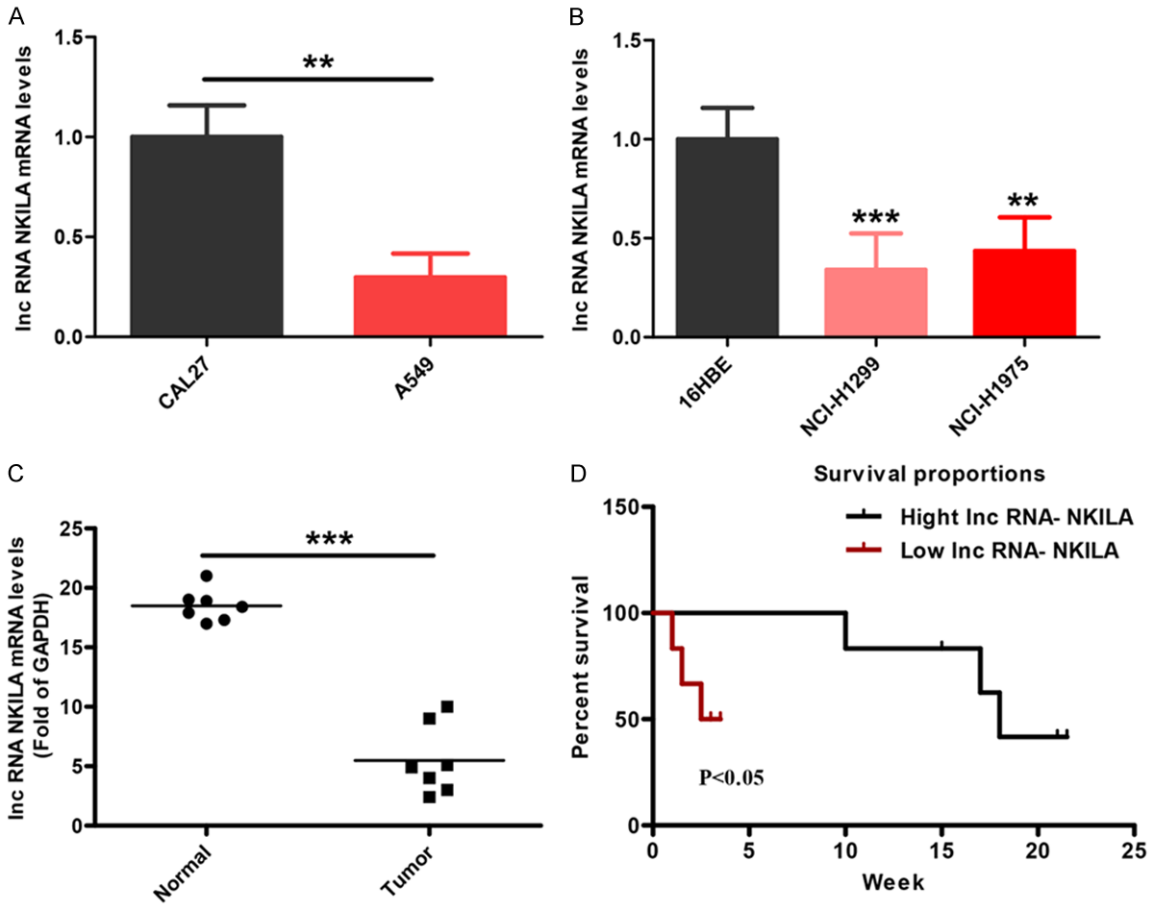

Figure 1. The expression of NKILA was higher in normal human bronchial epithelial cell line. For (A) and (B), the expression level of lncRNA-NKILA was analyzed by Q-PCR. The expression of NKILA was analyzed in NSCLC tissues (C), Kaplan-Meier analyses of the correlations between lncRNA-NKILA expression level and survival (D). Values are means ± SEM for n = 7-8. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control.

cells (**Figure 2B**). Apart from the above results, the cell scratches experiments demonstrated that up-regulation of NKILA significantly inhibited the migration of A549. These results suggested that NKILA inhibit the developments of lung adenocarcinoma cells (**Figure 2C**, **2D**).

NKILA inhibits IL-11 mRNA expression in NSCLC cells

We next explored the mechanisms behind the potent effect of lncRNA-NKILA on metastatic colonization. Recently, KEGG_JAK_STAT signaling pathway in Molecular Signatures Database has been published that IL-11/STAT3, which modifies gene signatures, were significantly changed in several different cells with lncRNA overexpressed [15-17]. This led us to measure IL-11 mRNA levels in different clones of A549 and NCI-H1975 cells and we found that the overexpression of lncRNA-NKILA significantly decreased IL-11 mRNA levels in a dose-dependent manner (**Figure 3A**, **3B**). Interestingly, we also discovered that the stability of LI-11 was severely repressed, causing autocrine reduction and activates STAT3 signaling (**Figure 3C**). Reciprocally, the depletion of lncRNA-NKILA significantly increased IL-11 mRNA levels in a dose-dependent manner in A549 and NCI-H1975 cells (**Figure 3D**, **3E**). These results demonstrated that IL-11 may be associated with the metastasis of NSCLC.

NKILA decrease IL-11 secretion and inhibit IL-11/STAT3 signaling

To examine whether lncRNA-NKILA decrease IL-11 secretion and inhibits IL-11/STAT3 signaling, we measured IL-11 levels in the cell supernatants and phosphorylation levels of STAT3 in

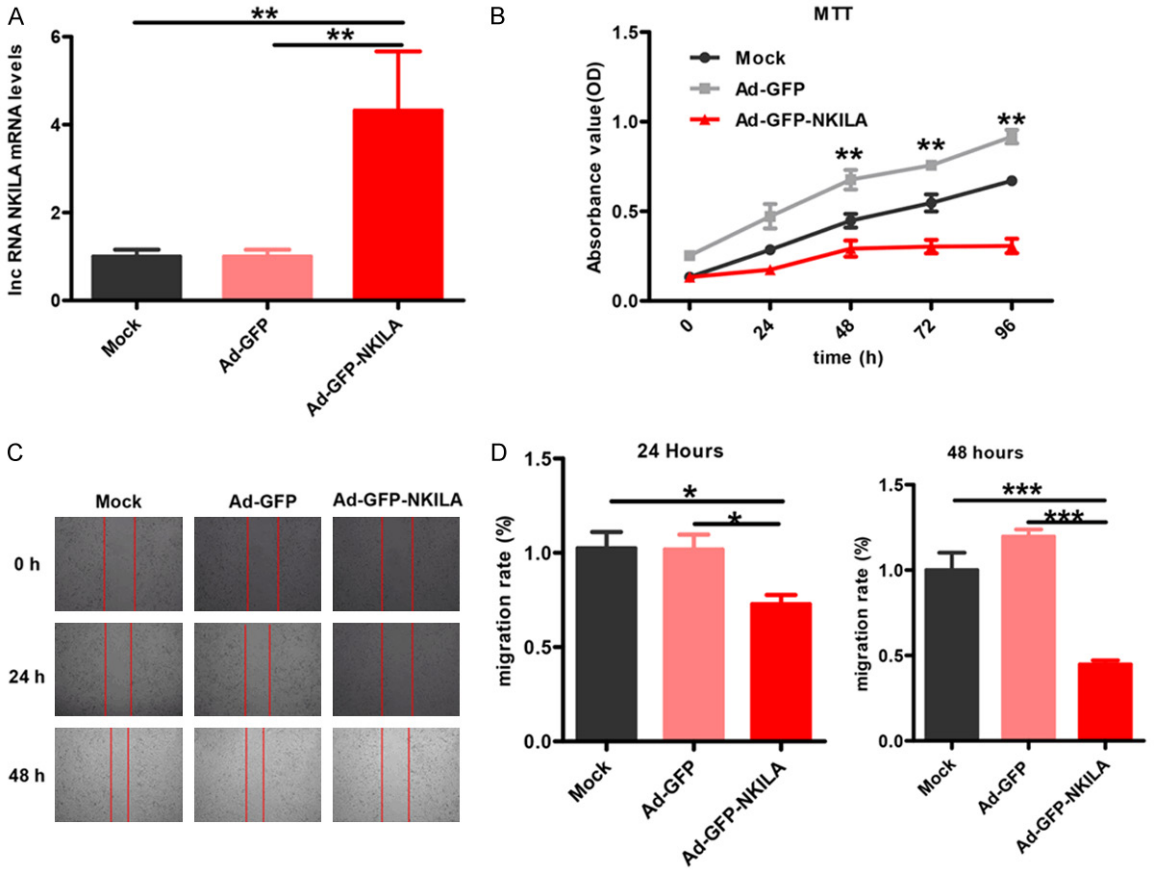

Figure 2. NKILA inhibited the proliferation and migration of NSCLC adenocarcinoma cell lines. A. The expression of NKILA after transfected with Ad-GFP or Ad-GFP-NKILA. B. MTT assay was performed after transfected with Ad-GFP or Ad-GFP-NKILA. C, D. The migration of NSCLC cells after transfected with Ad-GFP or Ad-GFP-NKILA. Values are means ± SEM for n = 7-8. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control.

different NSCLC cells. The overexpression of lncRNA-NKILA, leads to decreased IL-11 levels in the cell supernatants and decreased phosphorylation levels of STAT3 in a dose-dependent manner (**Figure 4A-D**). Reciprocally, the IL-11 levels in the cell supernatants and phosphorylation levels of STAT3 were increased after depletion of lncRNA-NKILA in a dose-dependent manner. STAT3 downstream target protein BCL2 was also down regulated by over expression of lncRNA-NKILA, and was up regulated by depletion of lncRNA-NKILA (**Figure 4E** and **4F**). To test the contribution of down-regulated IL-11 to the positive role of lncRNA-NKILA, we knocked down IL-11 in A549 cells over expressing lncRNA-NKILA. It had no significant effect on lncRNA-NKILA expression. We next measured the effects of IL-11 on cell proliferation, and found that the knockdown of IL-11 significantly decreased the wound healing after scratching. This data demonstrated that lncRNA-NKILA inhibits the metastasis potential of NKILA cells and this effect depends on IL-11.

Discussion

Squamous cell carcinoma, adenocarcinoma, large cell carcinoma are all family members of non-small cell lung cancer (NSCLC). The growth rate of cancer cells is much faster than that of carcinoma and small cells [18]. Non-small cell lung cancer accounts for approximately 80-85% of the total lung cancer [19, 20]. The treatment of non-small cell lung cancer should be based on the clinical stage of lung cancer.

In recent years, long-chain non-coding RNA (long noncoding RNA, lncRNA) played an important role in the process of cancer development [4, 21], which has aroused widespread concern. LncRNA is a non-coding RNA molecule with a length of more than 200nt [20, 22].

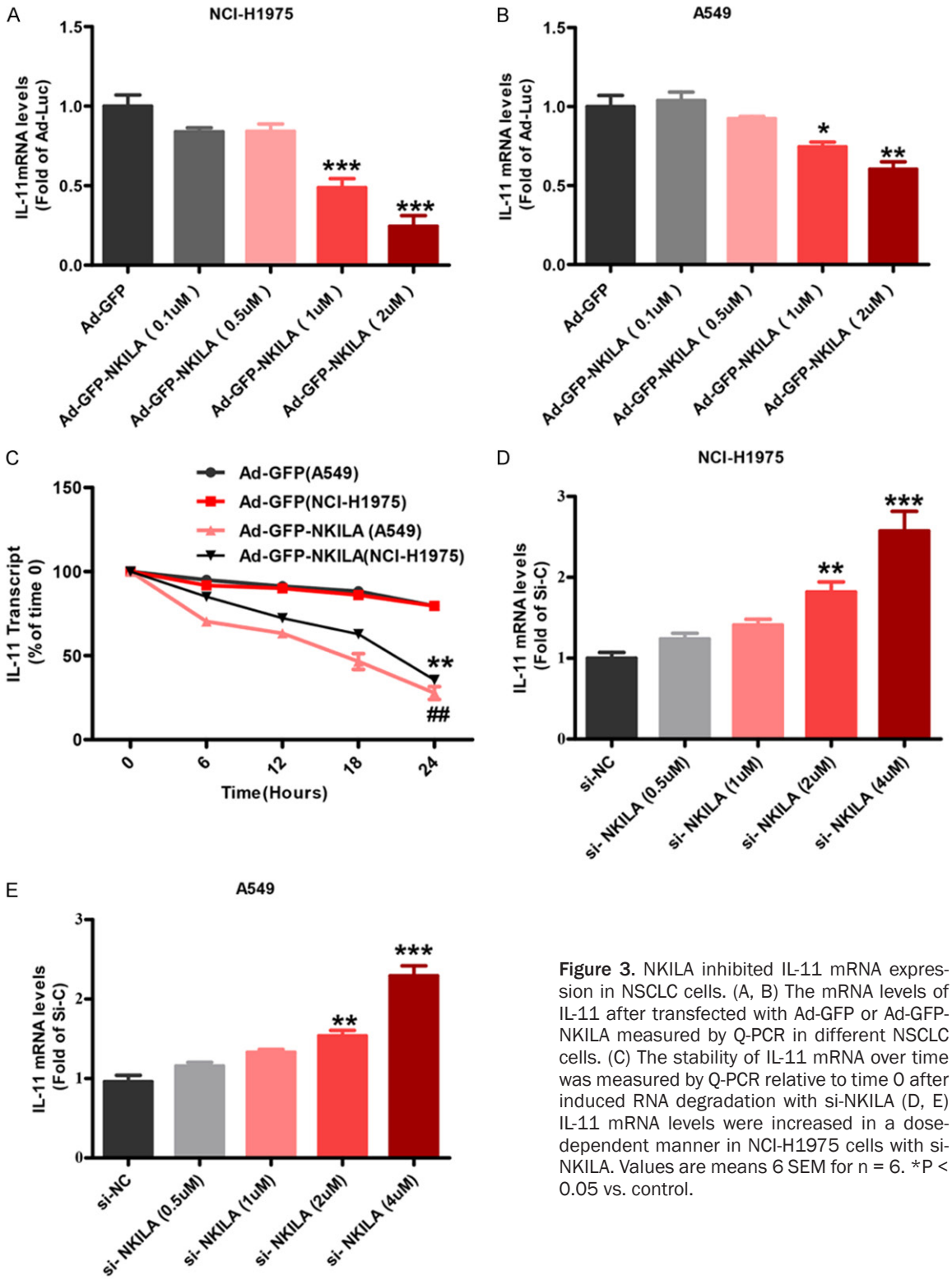

Figure 3. NKILA inhibited IL-11 mRNA expression in NSCLC cells. (A, B) The mRNA levels of IL-11 after transfected with Ad-GFP or Ad-GFP-NKILA measured by Q-PCR in different NSCLC cells. (C) The stability of IL-11 mRNA over time was measured by Q-PCR relative to time 0 after induced RNA degradation with si-NKILA (D, E) IL-11 mRNA levels were increased in a dose-dependent manner in NCI-H1975 cells with si-NKILA. Values are means 6 SEM for n = 6. *P < 0.05 vs. control.

These RNA do not encode proteins or simply encode very short peptides, and at first they are considered to be "noises" of genomic transcription and do not have biological functions. However, more and more studies have shown that lncRNA is involved in genome imprinting,

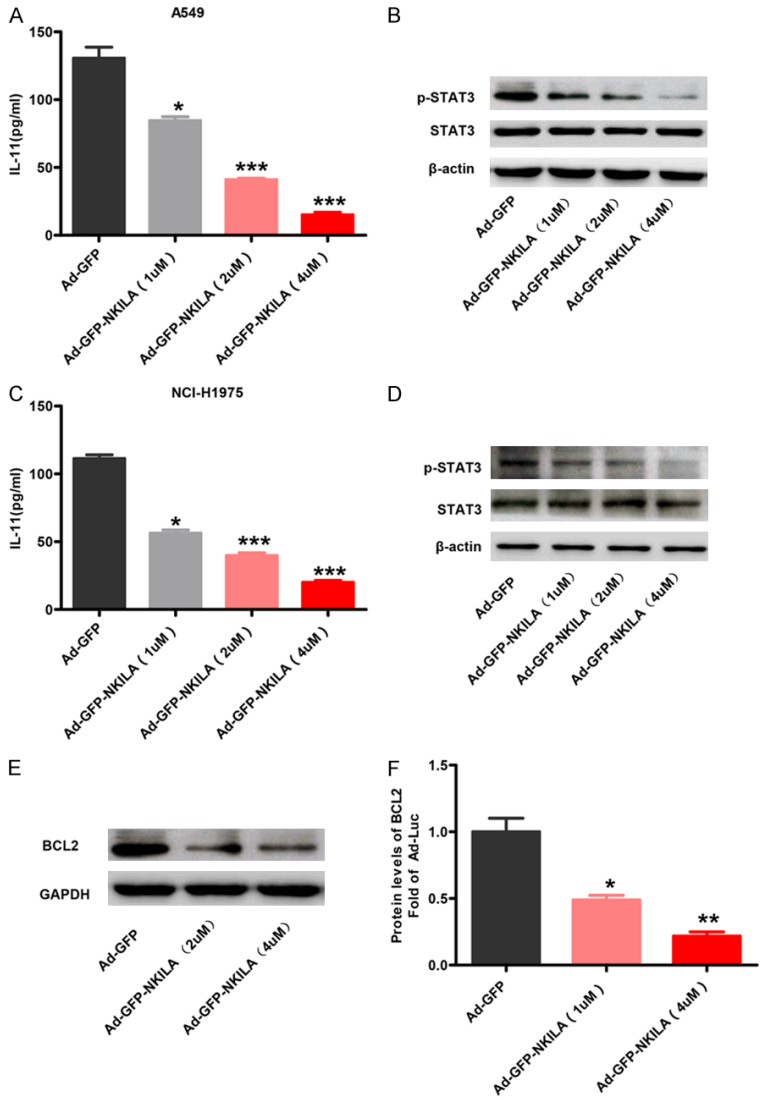

Figure 4. NKILA decrease IL-11 secretion and inhibit IL-11/STAT3 signaling. A-D. Concentrations of IL-11 in the culture medium were measured by ELISA and p-STAT3 levels determined by western blot from A549 or NCI-H1975 cell. E, F. BCL2 levels were determined by western blot from indicated cells. Values are means 6 SEM for n = 6-8. *P < 0.05 vs. control.

transcriptional control, post-transcriptional regulation, and protein function regulation in signal transduction process [21, 23]. The comprehensive understanding of the lncRNA provides a new perspective in tumor clinical treatment [24]. Lots of work had been done on the regulatory network and clinical significance of lncRNA involvement in the development of non-small cell lung cancer [25]. It was found that lncRNA, which was differentially expressed in lung cancer, could distinguish cancer tissue from adjacent tissues, indicating that lncRNA had a characteristic expression profile in cancer tissues. Previous studies had demonstrated that cloning and identification of lncRNA molecules, such as lncRNA-LET [26], lncRNA-HEIH [27], and lncRNA-MVIH [28] have important functions in the development and progression of hepatocellular carcinoma.

Recently, different mechanisms had been documented to regulate progression and metastasis of several long non-coding RNA (lncRNA). lncRNAs are widely present in various tissues of the body and play a key role in the upregulation of multiple expressions such as cytokines, chemical factors, growth factors, cell adhesion molecules, and anti-apoptotic proteins, and in many diseases, especially cancers. H19 has been recently characterized as an oncogenic lncRNA in some tumors and promoted PDAC cell invasion and migration at least partially by increasing HMGA2-mediated epithelial-mesenchymal transition (EMT), providing a new therapeutic target on pancreatic cancer metastasis [29, 30]. Also a study reveals that long non-coding RNA-ATB may act on colon tumorigenesis by suppressing E-cad expression and promoting EMT process [31]. LncRNA-LET as a regulator of hypoxia signaling offers new avenues for therapeutic intervention against cancer progression [32]. LncRNA NKILA could directly interact with signaling protein NF-κB by blocking the IKK phosphorylating sites of IκB and therefore inhibiting NF-κB mediated breast cancer cell apoptosis and migration [33]. They also found that NKILA play an important role in regulating TSCC cells migration and invasion. However, the role of lncRNA NKILA in the NSCLC remains to be explored [34].

The pathogenesis plays an important role. Certain human malignancies are closely relat-

ed to chronic inflammation, such as liver cancer and chronic hepatitis, gastric cancer and gastritis, colon cancer and ulcerative colitis, pancreatic cancer and pancreatitis, melanoma and skin inflammation, and cervical cancer and chronic cervix Inflammation. It is estimated that the malignant tumor associated with chronic inflammation accounts for about 15% of human cancer. Here we find that the expression pattern of lncRNA-NKILA was related with the progression and metastasis of NSCLC. Our experimental data strongly suggested that lncRNA NKILA plays a vital role in regulating NSCLC cells migration and invasion. The *in vivo* experiments data further proved that the clinical significance of NKILA in NSCLC. The results confirmed that the expression of NKILA was significantly down regulated in lung cancer tissues when compared to matched normal tissue. This expression pattern of NKILA in NSCLC was consistent with previous observation in breast cancer. In NSCLC, the low expression level of NKILA was associated with the shorter life expectancy, lymph node metastasis, and poor survival. At the same, the expression of lncRNA-NKILA has an effect on the expression and secretion of IL-11, activating IL-11/STAT3 signaling, which were further verified in our in vitro system.

In general, in this report, we validated that as direct targets of lncRNA-NKILA, IL-11 mediated the role of lncRNA-NKILA in local invasion and distant colonization respectively. The pleiotropic effects of lncRNA-NKILA on the early and late steps of the invasion-metastasis cascade suggest that lncRNA-NKILA could be an effective target for anti-metastasis therapies and serve as a prognostic marker.

Disclosure of conflict of interest

None.

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