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LncRNA HOST2 enhances gefitinib-resistance in non-small cell lung cancer by down-regulating miRNA-621

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Abstract. – OBJECTIVE: The aim of this study was to clarify whether long non-coding RNA (lncRNA) human ovarian cancer-specific transcript 2 (HOST2) could enhance gefitinib-resistance in non-small cell lung cancer (NSCLC) by down-regulating microRNA-621 (miRNA-621).

MATERIALS AND METHODS: The relative expression levels of HOST2, miRNA-621 and SYF2 in NSCLC cell lines were determined by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The regulatory effects of HOST2 and miRNA-621 on the proliferative ability and cell cycle of NSCLC cells were evaluated by Cell Counting Kit-8 (CCK-8) assay and flow cytometry, respectively. Meanwhile, the binding relationship between miRNA-621 to HOST2 and SYF2 was verified by Dual-Luciferase reporter gene assay. Furthermore, rescue experiments were conducted to verify whether HOST2 regulated the proliferative ability and cell cycle of NSCLC cells by absorbing miRNA-621 to up-regulate SYF2 level.

RESULTS: HOST2 showed significantly greater abundance in gefitinib-resistant PC9 cells (PC9/GR) relative to parental cells. The up-regulation of HOST2 markedly enhanced gefitinib-resistance, the proliferative ability and cell cycle progression of PC9 cells. Subsequent Dual-Luciferase reporter gene assay showed the binding relationship between HOST2 and miRNA-621. Moreover, miRNA-621 was lowly expressed in PC9/GR cells compared with parental cells. Up-regulation of miRNA-621 significantly suppressed the proliferative ability and cell cycle progression, as well as reversed gefitinib-sensitivity of PC9 cells. More importantly, miRNA-621 up-regulation abolished the biological function of HOST2 in NSCLC. SYF2 was confirmed as the target gene of miRNA-621 in the same way. In addition, the overexpression of SYF2 remarkably enhanced gefitinib-resistance, while reversed the inhibitory effects of miRNA-621 on the proliferative ability and cell cycle of NSCLC cells.

CONCLUSIONS: HOST2 elevates gefitinib-resistance in NSCLC by degrading miRNA-621 to upregulate SYF2.

Key Words:
Non-small cell lung cancer (NSCLC), Gefitinib, HOST2, MiRNA-621, SYF2.

Introduction

Lung cancer is a major threat to human health and life, with high metastatic and recurrent rates as well as extensive drug resistance[1]. Non-small cell lung cancer (NSCLC) accounts for about 85% to 90% of lung cancer cases, which is the most common pathological type[2]. Currently, platinum-based combined chemotherapy is the standardized treatment for NSCLC. However, the improved efficiency of chemotherapy drugs on the survival of advanced patients is far from satisfactory[3]. Due to the lack of early diagnosis techniques, NSCLC patients usually aggravate to an advanced stage when initially diagnosed. Eventually, they have lost the chance of surgery due to distant metastasis.

In recent years, with the deepening of studies on tumor-related genes, epidermal growth factor receptor (EGFR) mutation is identified as the initiating factor for tumorigenesis of NSCLC. EGFR-based targeted therapy has been well concerned and widely applied in clinical treatment, including gefitinib, erlotinib, etc. As a representative drug of tyrosine kinase inhibitors (TKIs), gefitinib has been used as the first-line treatment for advanced NSCLC patients with EGFR-sensitive mutation. Meanwhile, gefitinib shows better therapeutic efficacy than traditional chemothera-

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py[4]. Nevertheless, some tumor patients may experience primary resistance after taking EGFR TKIs in a short-term period. Although alleviation is achieved in the initial period, a part of patients inevitably develop acquired drug-resistance after 10-16 months of treatment. This may eventually result in treatment failure[5].

Long non-coding RNA (lncRNA) is a kind of non-coding RNA with over than 200 nt in length. LncRNA participates in tumor development by regulating a variety of cellular biological processes[6]. For example, lncRNA MALAT1 regulates the progression and metastasis of multiple cancers by mediating tumor cell behaviors[7]. In addition, lncRNAs have been proved to regulate drug-sensitivity in NSCLC cells. By analyzing the expression profiles of lncRNAs in human lung adenocarcinoma cell line (A549) and its cisplatin-resistant cell line A549/DDP, a total of 725 and 655 lncRNAs are up-regulated and down-regulated, respectively[8]. Further studies have confirmed that the expressions of AK126688, MEG3 and GAS5 are significantly down-regulated in cisplatin-resistant NSCLC cells. However, the expressions of HOTAIR, CCAT1, SNHG12, XIST and AK001796 are up-regulated. These abnormally expressed lncRNAs are involved in the regulation of cisplatin-sensitivity through various mechanisms[9]. It has been demonstrated[10] that lncRNA HOTAIR enhances cisplatin-resistance of NSCLC cells by promoting proliferation, apoptosis and deoxyribonucleic acid (DNA) synthesis by inhibiting cyclin kinase inhibitor p21. LncRNA ROR up-regulates the expression of anti-apoptotic protein Bcl-2 and down-regulates pro-apoptotic protein Bax, eventually inhibiting the apoptosis of NSCLC cells. Furthermore, ROR promotes proliferative and invasive capacities, and enhances cisplatin-resistance by regulating phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway[11].

In this work, lncRNA HOST2 was found highly expressed in PC9/GR cells (gefitinib-resistant cell line, EGFR T790M). Moreover, we aimed to explore the potential function of HOST2 in drug-resistant NSCLC cells and the possible underlying mechanism.

Materials and Methods

Cell Culture

Human bronchial epithelial cell line (HBE), human lung adenocarcinoma cell line (A549), cisplatin-resistant A549 cell line (A549/DDP), paclitaxel-resistant A549 cell line (A549/R), EGFR-sensitive mutant lung adenocarcinoma cell line (PC9), EGFR T790M lung adenocarcinoma cell line (H1975) and gefitinib-resistant PC9 cell line (PC9/GR, EGFR T790M) were all kept by our laboratory. All cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Grand Island, NY, USA) containing 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA), 100 U/mL penicillin and 0.1 mg/mL streptomycin, and maintained in a 5% CO_2 and 37°C incubator.

Cell Transfection

Cells were first seeded into plates one day prior to transfection. The cells were transfected with si-HOST2, pcDNA-HOST2, pcDNA-SYF2, miRNA-621 mimics, miRNA-621 inhibitor or negative control at a final dose of 50-100 nM according to the instructions of Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA).

RNA Extraction

Tissues or cells were first lysed with 1 mL of TRIzol (Invitrogen, Carlsbad, CA, USA). After incubation at room temperature for 5 min, 200 μL of chloroform was added, mixed and stand at room temperature for 5 min. After centrifugation at 4°C, 12000 rpm for 15 min, the supernatant was transferred into a new RNase-free centrifuge tube. Isopropanol with the same volume of supernatant was added for harvesting RNA precipitate by centrifugation. Subsequently, extracted RNA was air dried and quantified. RNA samples with A260/A280 of 1.8-2.0 were dissolved in 10-20 μL of diethyl pyrocarbonate (DEPC) water (Beyotime, Shanghai, China) for use.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

The expression levels of target genes were determined using an ABI StepOnePlus PCR instrument (Applied Biosystems, Foster City, CA, USA). 10 μL of Polymerase Chain Reaction (PCR) mixture was prepared, including 1 μL of upstream primer, 1 μL of downstream primer, 0.4 μL of 50 × Rox Dye, 2 μL of complementary deoxyribose nucleic acid (cDNA) and 5.6 μL of enzyme-free water. Data were analyzed by StepOne Software version v2.1 (Applied BioSystems, Foster City, CA, USA). The primer sequences used in this study were as follows: MiRNA-621, F: 5'-ACACTCCAGCTGGGGGCTAGCAACAGC-

GC-3', R: 5'-CTCAACTGGTGTCGTGGAGTC-GGCAATTCAGTTGAGAGGTAAGC-3'; U6, F: 5'-CTCGCTTCGGCAGCAGCACATATA-3', R: 5'-AAATATGGAACGCTTCACGA-3'; HOST2, F: 5'-CTCAAATCAATCACGACCCT-3', R: 5'-AATGTAGCAGGACGAGCC-3'; GAPDH, F: 5'-GAAGAGAGAGACCCTCACGCTG-3', R: 5'-ACTGTGAGGAGGGGAGATTCAGT-3'.

Dual-Luciferase Reporter Gene Assay

HOST2/SYF2 WT and HOST2/SYF2 MUT were first constructed. After seeded into 12-well plates, the cells were co-transfected with miRNA-621 mimics/negative control and wild-type/mutant-type HOST2/SYF2. The complete medium was replaced at 6 h. 24 h after transfection, the cells were lysed, followed by centrifugation at 10,000 g for 5 min. Finally, the Luciferase activity was determined using the relative kit (Promega, Madison, WI, USA).

Cell Cycle

Cells were seeded into 96-well plates and digested with trypsin. After washing with cold Phosphate-Buffered Saline (PBS; Gibco, Grand Island, NY, USA) twice, the cells were incubated with 1 ml of DNA staining solution. After 30 min of incubation in the dark, the cell cycle distribution was analyzed using MACS flow cytometry (Partec AG, Arlesheim, Switzerland).

Cell Viability

The cells were first seeded into 96-well plates with 3-5×10^3 cells per well. 10 replicates were set in each group. Absorbance (OD) at 450 nm was recorded using the Cell Counting Kit-8 assay (CCK-8; Dojindo Laboratories, Kumamoto, Japan), and IC_{50} was calculated.

Western Blot

The total protein in cells was extracted using radioimmunoprecipitation assay (RIPA; Beyotime, Shanghai, China). The concentration of extracted protein was quantified by the bicinchoninic acid (BCA) method (Pierce, Waltham, MA, USA). 50 μg of protein sample was loaded for electrophoresis at 80 V for 40 min and 120 V for 60-80 min. After transferring onto polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA), the proteins were blocked in 5% skim milk for 2 hours. Then, the membranes were incubated with primary antibodies at 4°C overnight. On the next day, the membranes were incubated with secondary antibodies at room temperature for 2 h. Immunoreactive bands were exposed by enhanced chemiluminescence (ECL; Thermo Fisher Scientific, Waltham, MA, USA) and analyzed by Image J Software (NIH, Bethesda, MD, USA).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 19.0 software (IBM, Armonk, NY, USA) was used for all statistical analyses. Data were expressed as mean ± standard deviation. Intergroup difference satisfying normality was analyzed by the *t*-test. Differences among multiple groups satisfying normality and homogeneity of variance were analyzed by one-way analysis of variance (ANOVA), followed by post-hoc test (Least Significant Difference); otherwise, a nonparametric test was performed. $p<0.05$ was considered statistically significant.

Results

HOST2 Was Upregulated in PC9/GR Cells

Quantitative Real Time-Polymerase Chain Reaction (QRT-PCR) data revealed that the expression level of HOST2 in PC9/GR cells was significantly higher than parental cells and other NSCLC cells (Figure 1A). To explore the potential function of HOST2 in gefitinib-resistant NSCLC, PC9 and PC9/GR cell lines were selected for *in vitro* assays. Transfection efficacy of pcDNA-HOST2 and si-HOST2 was first verified by qRT-PCR (Figure 1B, 1C). Both PC9 and PC9/GR cells were induced with gefitinib, followed by cytotoxicity determination. A significantly higher IC_{50} was observed in PC9/GR cells compared with that of PC9 cells (Figure 1D). Moreover, PC9/GR cells over-expressing HOST2 showed significantly higher IC_{50} relative to controls (Figure 1D). Next, we evaluated the regulatory effects of HOST2 on the proliferative ability and cell cycle of PC9/GR cells. The results demonstrated that the overexpression of HOST2 markedly accelerated the proliferative ability and cell cycle of PC9/GR cells (Figure 1E, 1F). The above findings suggested that HOST2 exerted its potential function in gefitinib-resistance by promoting cell proliferation and cell cycle.

MiRNA-621 Was the Target Gene of HOST2

The presence of binding sequences between miRNA-621 and HOST2 was identified and verified by online prediction (Figure 2A) and Du-

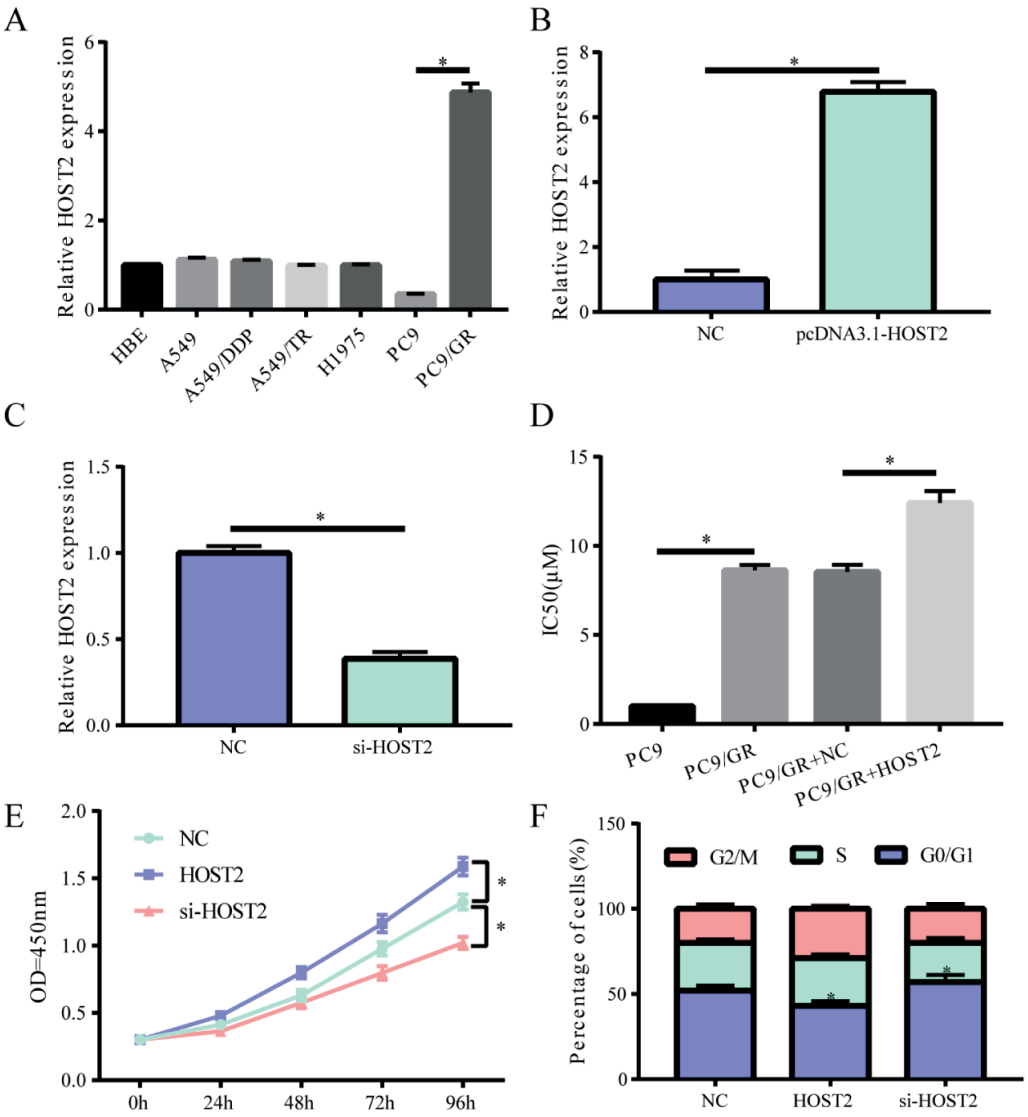

Figure 1. HOST2 was up-regulated in PC9/GR cell line. **A,** HOST2 was highly expressed in PC9/GR cells relative to parental cells and other NSCLC cell lines. **B-C,** Transfection efficacy of pcDNA-HOST2 **B,** and si-HOST2 **C,** in PC9/GR cells. **D,** PC9/GR cells showed significantly higher IC_{50} than that of PC9 cells. PC9/GR cells overexpressing HOST2 showed markedly higher IC_{50} relative to controls. **E-F,** Overexpression of HOST2 remarkably accelerated the proliferative ability **E,** and cell cycle **F,** of PC9/GR cells.

al-Luciferase reporter gene assay (Figure 2B, 2C), respectively. MiRNA-621 level was significantly down-regulated in PC9 and PC9/GR cells transfected with pcDNA-HOST2. This showed that miRNA-621 was negatively regulated by HOST2 (Figure 2D). Subsequently, we examined miRNA-621 expression in other NSCLC cell lines by qRT-PCR as well. A higher expression level of miRNA-621 was observed in PC9 cells than that of PC9/GR cells and other cell lines (Figure 2E). Meanwhile, IC_{50} was significantly higher in PC9/GR cells relative to parental cells (Figure 2F). Besides, PC9/GR cells overexpressing miRNA-621 showed remarkably lower IC_{50} than that of controls (Figure 2E). The above data demonstrated that the downstream gene of HOST2, miRNA-621, was also involved in gefitinib-resistant NSCLC.

HOST2 Exerted Its Function by Absorbing MiRNA-621

To explore whether HOST2 served as a ceRNA to absorb miRNA-621, we evaluated the effect of miRNA-621 on the proliferative ability and cell cycle of NSCLC cells. Transfection efficacy

of miRNA-621 mimics and inhibitor in PC9/GR cells was confirmed by qRT-PCR (Figure 3A, 3B). Overexpression of miRNA-621 markedly inhibited the proliferative ability and cell cycle of PC9/GR cells. Meanwhile, miRNA-621 knockdown markedly promoted cell proliferation and cell cycle progression (Figure 3C, 3D). Subsequently, the cells were transfected with pcDNA-NC, pcDNA-HOST2 or pcDNA-HOST2 + miRNA-621 mimics, respectively. The results indicated that miRNA-621 overexpression could partially reverse the promotive role of HOST2 in cellular behaviors of PC9/GR cells (Figure 3E, 3F). Hence, HOST2 exerted its function in gefinitib-resistant NSCLC by absorbing miRNA-621.

SYF2 Was the Target Gene of MiRNA-621

Current studies have shown that miRNAs exert their biological functions by degrading target genes. In this study, online prediction software predicted that SYF2 was a potential target gene of miRNA-621 (Figure 4A). Dual-Luciferase reporter gene assay confirmed the binding relationship between SYF2 and miRNA-621 (Figure 4B, 4C). Western blot found that the protein expression of SYF2 was markedly down-regulated in PC9 and PC9/GR cells overexpressing miRNA-621. This suggested that miRNA-621 negatively regulated SYF2 level (Figure 4D). In addition, SYF2 expression in PC9/GR cells was significantly higher relative to parental cells and HBE cells (Figure 4E). Therefore, SYF2 might play a crucial role in drug-resistant NSCLC. Subsequently, IC_{50} in PC9/GR cells was found markedly higher than that of parental cells. More importantly, it was remarkably higher in PC9/GR cells overexpressing SYF2 (Figure 4F). Subsequent *in vitro* results indicated that SYF2 overexpression promoted the proliferative ability and cell cycle of NSCLC cells. Furthermore, it partially reversed the inhibitory effects of miRNA-621 on gefitinib-resistant NSCLC cells (Figure 4G, 4H).

Discussion

At present, lncRNAs have been reported to regulate tumor cell behaviors as ceRNAs. This may, in turn, influence the occurrence and development of tumors[12]. Proposed ceRNA hypothesis confers broader biological functions of miRNAs and non-coding RNAs. LncRNA forms a complex post-transcriptional regulatory network of lncRNA-miRNA-mRNA by competitively binding to corresponding miRNA response element (MRE). Meanwhile, changes in expressions or activities eventually affect a series of physio-

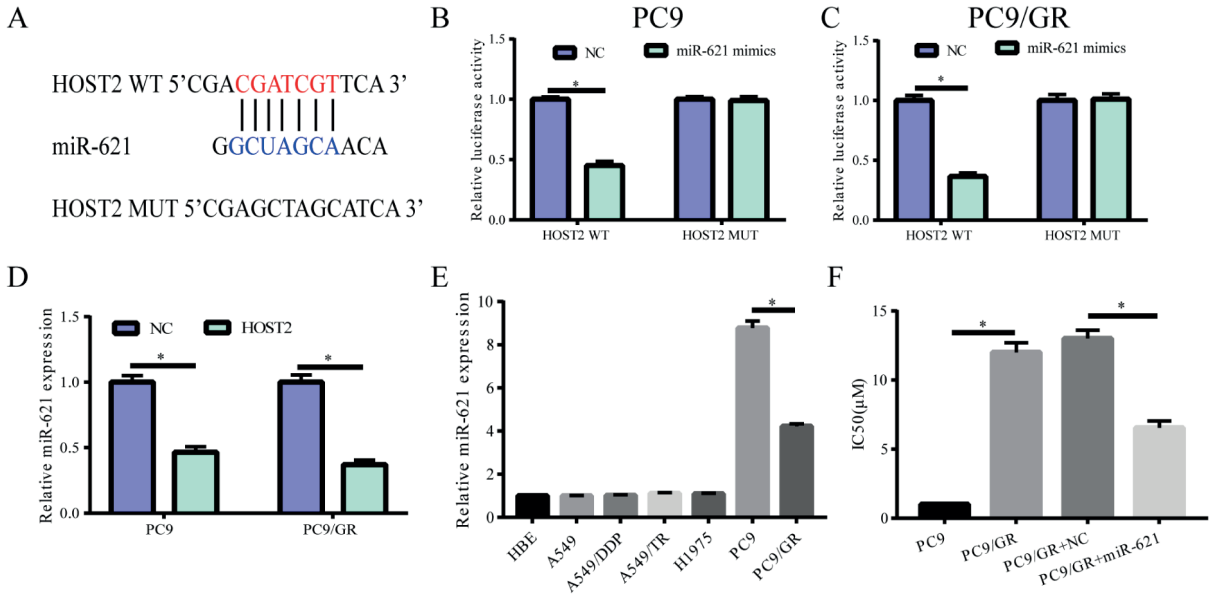

Figure 2. MiR-621 was the target gene of HOST2. **A,** Binding sequences between miR-621 and HOST2. **B-C,** Dual-Luciferase reporter gene assay showed the binding between miR-621 and HOST2. **D,** Transfection of pcDNA-HOST2 downregulated miR-621 level in PC9 and PC9/GR cells. **E,** MiR-621 expression in PC9 cells was higher than that of PC9/GR cells and other cell lines. F, CCK-8 assay indicated that IC50 in PC9/GR cells was higher relative to parental cells. Besides, PC9/GR cells overexpressing miR-621 lowers significantly lower IC50 than that of controls.

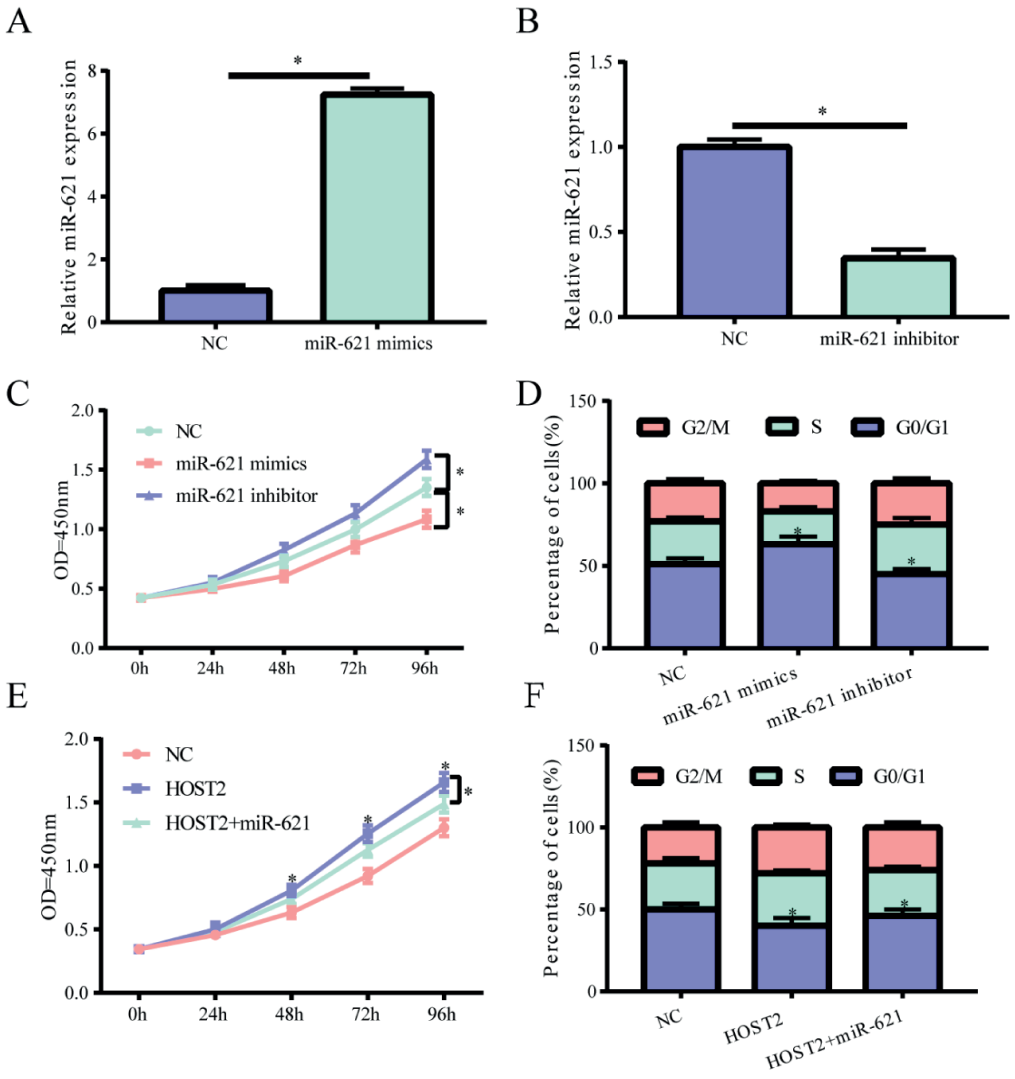

Figure 3. HOST2 exerted its function by absorbing miR-621. **A-B,** Transfection efficacy of miR-621 mimics **A,** and inhibitor **B,** in PC9/GR cells. **C-D,** Overexpression of miR-621 markedly inhibited the proliferative ability **C,** and cell cycle **D,** of PC9/GR cells. **E-F,** MiR-621 overexpression could partially reverse the promotive role of HOST2 in the proliferative ability **E**, and cell cycle **F,** of PC9/GR cells.

logical and pathological processes. CeRNA not only exerts a crucial function in tumor progression[13,14], but also provides a new guiding theory for the study of tumor resistance. For example, studies have found that lncRNA GAS5 binds to miR-21 by indirectly competing with PTEN, thereby enhancing cisplatin-sensitivity of NSCLC cells[15]. LncRNA XIST mediates the proliferation and apoptosis of NSCLC cells, further elevating cisplatin-resistance by inhibiting let-7i/BAG-1 axis. Conversely, XIST knockdown leads to cisplatin-sensitivity by suppressing autophagy of NSCLC cells[16]. LncRNA HOST2 was the first lncRNA identified correlated with breast cancer. The knockdown of HOST2 markedly inhibits the proliferative ability of breast cancer cells, indicating its potential role in tumor progression[17]. However, the specific function of HOST2 in NSCLC remains unclear.

In this work, we first discovered that HOST2 was highly expressed in gefitinib-resistant NSCLC cells. Overexpression of HOST2 significantly enhanced the drug-resistance of NSCLC cells by promoting cell proliferation rate and cell cycle. To elucidate whether HOST2 served as a ceRNA, bioinformatics method was used to predict its potential

gene. Subsequently, Dual-Luciferase reporter gene assay confirmed the binding relationship between miRNA-621 and HOST2. Further results indicated that miRNA-621 was regulated by HOST2 as well. Current studies have shown the tumor-suppressor effect of miRNA-621. For instance, miRNA-621 inhibits the proliferative ability of liver cancer cells by targeting CAPRIN1[18]. MiRNA-621 enhances drug-sensitivity in breast cancer by suppressing FBXO11 expression[19].

Based on the above results, we detected miRNA-621 expression in NSCLC cell lines as well. QRT-PCR results showed that miRNA-621 was lowly expressed in PC9/GR cells when compared with parental cells. Further studies showed that the up-regulation of miR-629 significantly enhanced gefitinib-sensitivity of PC9/GR cells, while inhibited proliferative ability and cell cycle. Down-regulation of miRNA-621, conversely, obtained opposite results. Therefore, we suggested that miRNA-621 exerted a crucial function in the drug-resistance of NSCLC. Meanwhile, rescue experiments were conducted to verify whether HOST2 served as a ceRNA to absorb miRNA-621. The data demonstrated that miRNA-621 overexpression partially reversed the regulatory effects of HOST2 on NSCLC, which confirmed our speculation.

SYF2 is a cell cycle-associated protein that participates in the progression of multiple tumors, such as breast cancer and liver cancer[20,21]. In this paper, SYF2 was predicted and verified as a potential target gene of miRNA-621 through bioinformatics and Dual-Luciferase reporter gene assay, respectively. Meanwhile, SYF2 expression was regulated by miRNA-621 as well. SYF2 showed markedly higher abundance in PC9/GR cells relative to parental cells. These results illustrated its potential function in drug-resistance of NSCLC. Subsequently, SYF2 upregulation remarkably promoted cell proliferation rate and cell cycle. More importantly, the upregulation of

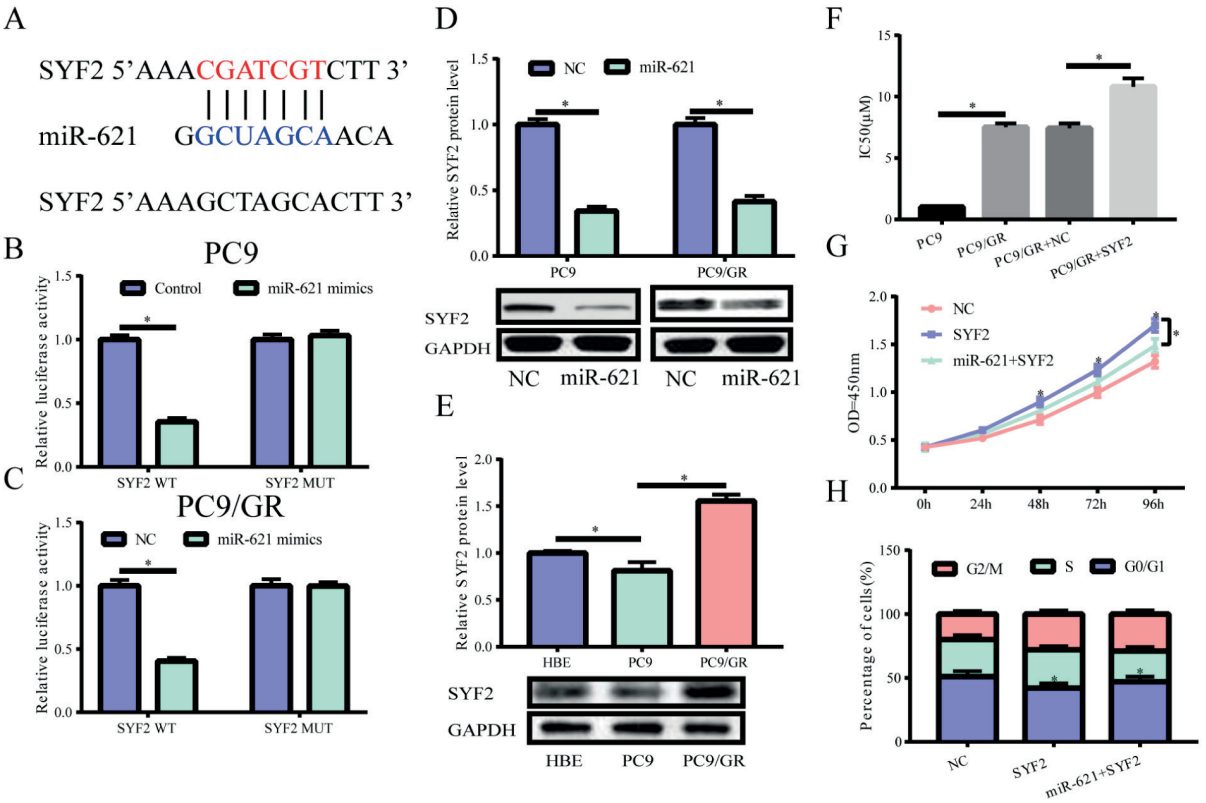

Figure 4. SYF2 was the target gene of miR-621. **A,** Binding sequences between miR-621 and SYF2. **B-C,** Dual-Luciferase reporter gene assay confirmed the binding between miR-621 and SYF2. **D,** The protein expression of SYF2 was markedly downregulated in PC9 and PC9/GR cells overexpressing miR-621. **E,** SYF2 expression in PC9/GR cells was higher relative to parental cells and HBE cells. **F,** IC_{50} in PC9/GR cells was higher than that of parental cells. Meanwhile, it was higher in PC9/GR cells overexpressing SYF2. **G-H,** SYF2 overexpression partially reversed the inhibitory effects of miR-621 on gefitinib-resistant NSCLC cells.

SYF2 elevated gefitinib-resistance. Interestingly, SYF2 overexpression could partially reverse the inhibitory effect of miRNA-621 on NSCLC cells. It was suggested that miRNA-621 exerted its function by down-regulating SYF2.

Conclusions

In this study it has been observed that HOST2 elevates gefitinib-resistance in NSCLC by degrading miRNA-621 to up-regulate SYF2. Our findings may provide novel directions for the prevention of EGFR-TKI-resistance in NSCLC.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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