**FIGNL1** is overexpressed in small cell lung cancer patients and enhances NCI-H446 cell resistance to cisplatin and etoposide

**Abstract.** Abnormal DNA repair plays an important role in tumor occurrence, progression and resistance to therapy. Fidgetin-like 1 (**FIGNL1**) expression was assayed in 42 small cell lung cancer (SCLC) and 45 normal lung specimens from Chinese patients by qRT-PCR. Notably, **FIGNL1** was upregulated by 1.5-fold in the SCLC specimens compared to that noted in the normal counterparts. The SCLC cell line NCI-H446 that overexpresses **FIGNL1** was adopted to explore the biological significance of **FIGNL1** in SCLC. Even when **FIGNL1** expression was suppressed by up to 48.6%, H446 cell growth was increased by only 10-16%. Although no significant changes in cell cycle distribution were observed in the H446 cells, the levels of cyclin E1 and CDK2, key cell cycle regulators, were significantly reduced. After downregulation of **FIGNL1** expression by 13.5% in the H446 cells, the cells were 61.8% (24 h) to 29.1% (48 h) more sensitive to etoposide and cisplatin, respectively, consistent with the **FIGNL1** function of DNA double-strand repair. The sensitivity of H446 cells to etoposide and cisplatin was negatively correlated with **FIGNL1** expression. Meanwhile, an obvious positive correlation between DNA damage severity and the sensitization effect of **FIGNL1** knockdown was observed. Since **FIGNL1** is essential in the homologous recombination (HR) pathway, these findings suggest that abnormal activation of the HR pathway featured by **FIGNL1** overexpression contributes to rapid progression and relapse of SCLC in addition to chemotherapy resistance. Further research assessing the functions and mechanisms of **FIGNL1**, and other HR pathway genes may disclose unique pathological characteristics of SCLC, and help identify potential therapeutic targets and biomarkers.

**Introduction**

Small cell lung cancer (SCLC), accounting for ~15-20% of all lung cancer cases, is characterized by its neuroendocrine origin, rapid development and early metastasis. SCLC has the lowest differentiation and highest malignant degree among lung cancers (1). Approximately 70% of SCLC patients are diagnosed at a late stage with accompanying metastasis. Therefore, the 5-year survival rate of patients with SCLC is only 5-10% (2). The development of novel targeted therapeutics for SCLC is one of the promising strategies by which to improve the outcome of SCLC treatment.

Genomic instability and high frequency of p53 mutations are two common characteristics of most human tumors (3). Genomic instability is an important impetus for tumor occurrence and development (4,5). Genomic instability is principally acquired through reprogramming the DNA repair pathway by oncogenes (6).

Research has demonstrated that certain DNA repair pathways, such as transcription-coupled and expression-linked repairs (10), are inactivated, while others are upregulated in...
various SCLC cell lines. For example, PARP expression in SCLC is 2.06 times higher than that in NSCLC (11). Thus, differences in DNA repair pathways and repair ability between tumor and normal cells have been increasingly assessed to identify promising targets (2,12).

Homologous recombination (HR) repairs DNA double-strand breaks with high fidelity. RAD51, the core protein of HR, is expressed 4-6 times higher in the majority of tumor cells both at the gene and protein levels, compared with corresponding normal cells, with its activity increasing by up to 840-fold (13). Abnormal expression of RAD51 can lead to diminished fidelity of HR repair, and promote occurrence of translocation and other chromosome mutations (14). Due to the close correlation between the aberrant activity of RAD51 and tumor occurrence, regulation of the activity of RAD51 has attracted increased attention from scientists.

Fidgetin-like 1 (FIGNL1) belongs to the AAA-ATPase protein family (15), and plays an important role in meiosis and mitosis (16,17). FIGNL1 is an indispensable component of HR, specifically interacting with RAD51 via its conserved RAD51 binding domain (18). The above findings indicate that FIGNL1 can directly regulate the activity of RAD51 and indirectly modulate that of HR in DNA DSB repair. The present study aimed to assess FIGNL1 in SCLC patients and cell lines to explore the function of HR in SCLC.

Materials and methods

Patients and tissue samples. Specimens were collected from patients who underwent surgical resection for lung cancer or suspected lung cancer patients through bronchoscopic biopsy at Shanghai Pulmonary Hospital from 2013 to 2015, with the approval of the Ethics Committee of Tong Ji University. All patients involved in the present study had provided written informed consent for the use of their tissue samples in the present study. The specimens that were confirmed to be SCLC or normal (tumor negative) by pathological examination were used for the following experiments. Detailed clinical information is shown in Table I. All specimens were immediately preserved in RNAstore reagent (Tiangen Biotech, Beijing, China) at 4°C until total RNA extraction.

Cell culture. The human SCLC NCI-H446 cell line was obtained from the Cell Bank of the Chinese Academy of Sciences and was cultured in RPMI-1640 medium (HyClone, Logan, UT, USA) containing 10% fetal bovine serum (FBS) (Gibco, Grand Island, NY, USA). The human embryonic lung fibroblast MRC-5 cell line was a kind gift from Professor Zhiyong Li at the College of Life Science and Technology, Shanghai Jiao Tong University, and was cultured in Minimum essential medium (MEM) containing 10% FBS. The human embryonic lung fibroblast MRC-5 cell line was a kind gift from Professor Zhiyong Li at the College of Life Science and Technology, Shanghai Jiao Tong University, and was cultured in Minimum essential medium (MEM) containing 10% FBS. The human embryonic lung fibroblast MRC-5 cell line was a kind gift from Professor Zhiyong Li at the College of Life Science and Technology, Shanghai Jiao Tong University, and was cultured in Minimum essential medium (MEM) containing 10% FBS.

Chemical and reagents. The chemicals used in the present study were purchased from Sigma-Aldrich.

Table I. Specimens assayed for FIGNL1 expression.

| Variables (n) | Normal | SCLC | P-value |
|--------------|--------|------|---------|
| Total        | 45     | 42   | 0.2853  |
| Gender       |        |      |         |
| Male         | 34     | 36   |         |
| Female       | 11     | 6    |         |
| Age (years)  |        |      |         |
| ≤60          | 26     | 18   | 0.2005  |
| >60          | 19     | 24   |         |
| TNM stage    |        |      |         |
| I-Ia         | -      | 0    |         |
| IIb-IIIa     | -      | 13   |         |
| Ila-IV       | -      | 29   |         |

FIGNL1, fidgetin-like 1; SCLC, small cell lung cancer; TNM, tumor-node-metastasis.

Total RNA extraction and real-time PCR. Total RNA extraction kit was used for total RNA extraction. Approximately 1,000 ng total RNA was reverse transcribed in 20 µl volume using FastQuant cDNA First Chain Synthesis kit (both from Tiangen) according to the manufacturer’s instructions. Quantitative real-time PCR (qPCR) was performed using Super Real Premix Plus (SYBR-Green) (Tiangen) on Eppendorf Mastercycler ep realplex4, with GAPDH as an internal control. The PCR program was as following: 3 min at 95°C, followed by 40 cycles at 95°C for 30 sec, 60°C for 30 sec and 72°C for 15 sec, and last step was the melting curve analysis program. All experiments were independently performed three times, and three replicates each time. The following primers were used: 5’-TCTTCAGGATCCACACTCCGCTT-3’ (forward) and 5’-GGGGCCATCCACAGTCTTCTGCT-3’ (reverse) for FIGNL1; 5’-CTCAGGCTGTCATCGGTC-3’ (forward) and 5’-CTGCTCTCCACCATCGCT-3’ (reverse) for GAPDH; 5’-GTGGCCTCTCTGGAAAGCAGCAACATGTA-3’ (forward) and 5’-CAGGGGATCTTCAGCTTAT-3’ (reverse) for cdc25A; 5’-AGGAAATGGCAAAATCAGCA-3’ (forward) and 5’-CCGGTCTCATCTCTTTTG-3’ (reverse) for cyclin E1; 5’-TATGCTGTATTACAAGCAGCAATGTTTC-3’ (forward) and 5’-GATAACAGCTCCTCCTATCTCAT-3’ (reverse) for cyclin A2; 5’-ATCCGCTGTCATCTCTTTTG-3’ (reverse) for cyclin D1; 5’-AGCTCCTCGTCGTCCTTCA-3’ (forward) and 5’-AGCAGGATCTTACGCTTCGAGTGTGGAG-3’ (reverse) for cdc25A. Relative gene expression was calculated by the 2^-ACt method.

Western blotting. Cells were lysed using RIPA lysis solution (Tiangen Biotech). After the protein concentrations were determined, the protein samples were separated by 10% SDS-PAGE, transferred onto 0.45-µm polyvinylidene fluoride (PVDF) membranes (Millipore, Darmstadt, Germany) and probed with relevant antibodies. Anti-FIGNL1 (cat. no. 7604-1-AP; 1:1,000) and anti-GAPDH (cat. no. 10494-1-AP; 1:2,000) were obtained from Proteintech (Chicago, IL, USA). After incubation with the primary antibody overnight at 4°C, the membranes were washed with Tris-buffered saline with
Tween-20 (TBST) three times, 5 min each. HRP-labeled secondary antibodies (cat. no. 111-035-003; 1:2,000) were obtained from Jackson ImmunoResearch (West Grove, PA, USA). After incubation with the secondary antibody for 2 h at room temperature, the membranes were washed for three time with TBST for 10 min each. Protein bands were detected by enhanced chemiluminescence (ECL; Sigma-Aldrich) and quantitated using Gel-Pro Analyzer 4.0 (Media Cybernetics, Rockville, MD, USA), and the results were obtained from three independent experiments.

shRNA and SCLC cell transfection. Short hairpin RNA (shRNA) targeting FIGHL1 and a negative control were designed by Origene Technologies, Inc. (Rockville, MD, USA). shRNA sequences for FIGHL1 were: 5'-AGCACATCCAGTGATGAGCGTCTGAAGA-3' for shFIGNL1-B, 5'-CAGACTCCAGCCAGGAAACAGATAGTA-3' for shFIGNL-D, and 5'-GCACTACCAGAGCTAACTCAGATAGTACT-3 for sh-control.

H446 cells were transfected using 0.45 µM filtered and Polybrene supplemented (8 µg/ml final concentration) culture media of the Platinum-A Retroviral Packaging Cell Line transfected with the shRNA plasmid for 48 h by Lipofectamine 2000. H446 cells were screened with complete culture medium containing puromycin at 1.0 µg/ml for 6 days. Afterwards, the cells were cultured with complete medium with 0.5 µg/ml puromycin.

Cell cycle analysis. The cells were cultured for ~2 days following synchronization for 12 h. Then, the cells were collected, washed with PBS and fixed with 75% ethanol at -20°C overnight. After incubation with 0.1 mg/ml RNase A at 37°C for 30 min and staining with 40 µg/ml PI (Sigma, St. Louis, MO, USA) in the dark for 30 min, DNA content was detected by flow cytometry (FACSCalibur; Becton-Dickinson, San Jose, CA, USA). Cell cycle distribution was analyzed and calculated by ModFit (Verity Software House, Topsham, ME, USA).

Cell proliferation assay. Cells were plated at 3x10^3/well in 96-well plates. MTT assay was adopted to assess cell viability. Absorbance was measured on an EnSpire 2300 microplate reader (Perkin Elmer, Waltham, MA, USA) at 550 nm. For drug sensitivity assay, cells were seeded in 96-well plates at a density of 3x10^3 cells/well and cultured for 24 h. Then, the cells were exposed to 0, 20, 40, 80 and 160 µM etoposide, respectively, for 24 h, or 0, 1.25, 2.5, 5, 10 and 20 µM, respectively, for 48 h; cisplatin was assayed at 0, 2, 4, 8, 16 and 32 µM, respectively, for 24 h, or 0.5, 1, 2, 4, and 8 µM, respectively, for 48 h. Cell survival was measured by the MTT assay, and half maximal inhibitory concentration (IC50) values of etoposide or cisplatin were calculated by GraphPad Prism 5.0.

Statistical analysis. Statistical analysis was performed using SPSS 17.0 or GraphPad Prism 5.0. Two groups of data, such as FIGNL1 expression between normal and SCLC specimens, was analyzed using a t-test to determine statistical significance. For three or more groups of data, such as comparison of FIGNL1 expression among the different H446 transfected cells, one-way analysis of variance (ANOVA) with Bonferoni post test was adopted. Results are presented as mean ± SD. P<0.05 was considered to indicate a statistically significant result.

Results

FIGNL1 expression in SCLC specimens. A total of 45 normal lung samples was assessed, from 34 male and 11 female patients, respectively. In these specimens, the relative expression level of FIGNL1 was 6.965±3.204x10^-3. Meanwhile, 42 SCLC samples from 36 males and 6 females were assessed, and yielded a value of 11.197± 8.466x10^-3 (Table I). Comparison of the FIGNL1 expression levels between normal and SCLC samples showed a statistical significance (P=0.004; Fig. 1A). A similar result was obtained for comparison between normal and SCLC specimens from the male patients (P=0.014; Fig. 1B). No significant difference in FIGNL1 expression levels was observed between age groups below and above 60 years and early and advanced stage groups (data not shown).

FIGNL1 expression in SCLC and normal lung fibroblast cell lines. The FIGNL1 transcription level was 3.46-fold
in the SCLC H446 cells [9.83±0.12 (ΔCt)] compared to this level in the normal lung fibroblast MRC-5 cells [11.13±0.04 (ΔCt)] (P<0.001; Fig. 2A).

Moreover, FIGNL1 protein expression was assessed in the different cell lines. Notably, the FIGNL1 protein level (FIGNL1/GAPDH) in the H446 cells (0.808±0.035) was 2.84 times higher compared to amounts obtained in the MRC-5 cells (0.285±0.035) (P<0.001; Fig. 2B).

**Effect of FIGNL1 knockdown on the growth and cell cycle distribution of H446 cells.** To further explore the biological function of FIGNL1 overexpression in SCLC cells, shRNA was used to silence FIGNL1 in the H446 cell line.

ΔCt values for FIGNL1 were 10.81±0.11 and 9.98±0.06 in the H446 cells transfected with shFIGNL1-B and shFIGNL1-D, respectively. Compared to the control group [9.77±0.10 (shCtrl)], FIGNL1 mRNA amounts were reduced by 48.6% (P=0.006) and 13.5% (P>0.05) in the shFIGNL1-B and shFIGNL1-D group cells, respectively (Fig. 3A). Western blot results further confirmed that the FIGNL1 protein level (FIGNL1/GAPDH) was reduced by 55.5% (P=0.002) and 46.5% (P=0.002), respectively, in the H446 cells transfected with shFIGNL1-B (0.359±0.087) or shFIGNL1-D (0.431±0.117) compared to the control (0.806±0.059) (Fig. 3B and C).

**FIGNL1 silencing slightly affects H446 cell growth.** Three groups of H446 cells with the same initial density were cultured for two days, and 13.8 and 12.5% more cells were transfected with shFIGNL1-B (P=0.0011) or shFIGNL1-D (P=0.0017) compared with the control group. After three days of culture, 12.8 and 11.5% more cells were found in the shFIGNL1-B (P=0.003) and shFIGNL1-D (P=0.002) groups compared with the control group. After culture for four days, 17.1% (P=0.003) and 15.6% (P=0.004) more cells, respectively, were obtained in the shFIGNL1-B and shFIGNL1-D groups compared with the control group. These findings indicated that FIGNL1 suppression slightly accelerated growth in the H446 cells (Fig. 4).

**FIGNL1 silencing alters the expression of key genes involved in cell cycle regulation.** To assess whether FIGNL1 expression affects the cell cycle, cyclin A2, cyclin E1, CDK2 and cdc25A expression levels were quantified in the H446 cells transfected with the different shRNAs.

As shown in Fig. 5, in the H446 cells transfected with shFIGNL1-D, no significant change in the expression of cyclin A2, cdc25A, cyclin E1 and CDK2 was observed. However, in the shFIGNL1-B-transfected cells, cyclin E1 and CDK2 mRNA amounts decreased by 34.94% (P=0.016) and 53.03% (P=0.018), respectively, at the same time the expression of cyclin A2 and cdc25A remained unchanged.

Cyclin-dependent kinases (CDKs) function mainly in S and G1 phases of the cell cycle and most tumors abrogate the cell cycle regulatory mechanism by directly or indirectly enhancing the activity of CDKs (19,20). Thus, cell cycle analysis was conducted to assess whether this downregulation impacted the H446 cell cycle.

**Effect of FIGNL1 silencing on H446 cell cycle distribution.** Flow cytometry was used to assess the cell cycle distribution of H446 cells transfected with the different shRNAs. As shown in Fig. 6, cell cycle distribution was not significantly different among the groups. Although, FIGNL1 knockdown greatly reduced cyclin E1 and CDK2 expression, it did not affect the cell cycle.

**FIGNL1 silencing sensitizes H446 cells to etoposide and cisplatin.** Following treatment with etoposide for 24 h, the sensitivity to etoposide of H446 cells transfected with shFIGNL1-B or shFIGNL1-D was increased by 65.6 and 61.8%, respectively, compared to the control group (Fig. 7A; Table II).

After treatment with etoposide for 48 h, sensitivity of the H446 cells transfected with shFIGNL1-B or shFIGNL1-D to etoposide was increased by 47.8 and 24.3%, respectively, compared to the control group (Fig. 7B; Table II).

**Changes in the sensitivity to cisplatin in H446 cells after FIGNL1 silencing.** As shown in Fig. 7C and Table III, H446

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**Figure 2.** FIGNL1 expression was higher in the NCI-H446 SCLC cell line than that noted in the MRC-5 normal cell line at both the mRNA and protein levels. (A) Comparison of FIGNL1 expression in MRC-5 and NCI-H446 cell lines; ***P<0.001. (B) Comparison of FIGNL1 in H446 and MRC-5 cells by western blotting; **P<0.001. Values provided were calculated from three independent experiments.
cells treated with cisplatin for 24 h showed IC₅₀ values of 6.463, 5.157 and 5.446 µM in the shCtrl, shFIGNL1-B and shFIGNL1-D groups, respectively. Compared with the control group, sensitivity of H446 cells to cisplatin was increased by 20.1 and 15.6% after FIGNL1 suppression by 48.6 or 13.5%, respectively.

H446 cells treated with cisplatin for 48 h showed IC₅₀ values of 1.889, 1.046 and 1.342 µM in the shCtrl, shFIGNL1-B and shFIGNL1-D groups, respectively (Fig. 7D; Table III). Compared with the control group, the sensitivity of shFIGNL1-B- and shFIGNL1-D-transfected cells to cisplatin was increased by 44.4 and 29.1%, respectively.

The above results showed a negative correlation between the FIGNL1 expression level in H446 cells and H446 cell sensitivity to etoposide and cisplatin.

Figure 3. Suppression efficiency of different shRNAs targeting FIGNL1. (A) Comparison of FIGNL1 expression in H446 cells transfected with shRNA-ctrl, shFIGNL1-B or shFIGNL1-D. **P=0.006. (B) FIGNL1 protein level in the H446 cells transfected with shRNA-ctrl, shFIGNL1-B or shFIGNL1-D calculated from three independent experiments; **P<0.01. (C) Western blot results of FIGNL1 protein expressed in the H446 cells transfected with shRNA-ctrl, shShFIGNL1-B or shFIGNL1-D.

Figure 4. Comparison of cell growth among the H446 cells transfected with shRNA-control, shFIGNL1-B or shFIGNL1-D; **P<0.01.

Figure 5. FIGNL1 knockdown suppressed the expression of cyclin E1, CDK2 and cdc25A in the H446 cells; *P<0.05.
Assessment of 45 normal lung and 42 SCLC clinical specimens revealed that FIGNL1 expression in the SCLC samples was 1.5 times increased in the SCLC specimens when compared to that noted in the normal lung tissue specimens.

As an AAA-ATPase protein family member (21), FIGNL1 is involved in various important cellular activities.
induction of DNA damage is different. Etoposide functions by abnormally enhanced. That in SCLC, DNA double-strand break repair pathways are agents. These results further support the previous notion the sensitivity of cells to etoposide/cisplatin (DNA damaging silencing. Indeed, the lower the sensitivity to etoposide and cisplatin (DNA damaging of the main mechanisms underlying the clinical features of SCLC as mentioned above. As shown above, a significant increase in H446 cell sensitivity to etoposide and cisplatin was found after FIGNL1 silencing. Indeed, the lower the FIGNL1 expression, the higher the sensitivity of cells to etoposide/cisplatin (DNA damaging agents). These results further support the previous notion that in SCLC, DNA double-strand break repair pathways are abnormally enhanced. The mechanism of etoposide and cisplatin involving the induction of DNA damage is different. Etoposide functions by inactivating DNA topoisomerase II (31), whereas the action of cisplatin is due to its ability to promote intra-strand and inter-strand crosslinking between adjacent purine bases of the DNA strand (32). Once topoisomerase II in tumor cells is inhibited by etoposide, DNA damage occurs immediately. However, for cisplatin, DNA damage in tumor cells may gradually occur and accumulate in DNA replication and transcription process after increasing DNA adducts are formed.

In the present study, FIGNL1 knockdown sensitized H446 cells to etoposide and cisplatin in different patterns (Tables II and III). For etoposide, the sensitization reached its highest level at an earlier stage (24 h), while cisplatin showed an opposite pattern. In addition, there was an obvious positive correlation between the severity of DNA damage and sensitization. These results are consistent with the mechanism of these two chemotherapeutic agents. The results mentioned above were obtained using NCI-H446 cells, and may be verified in more SCLC cell lines, i.e. NCI-H1688, in future research.

DNA repair pathway abnormalities contribute directly to the main causes of the poor outcome of cancer treatment, i.e. chemoresistance, radioresistance and relapse (28,29). Therefore, several studies aimed to identify targets of cancer therapy and biomarkers in the DNA repair pathway (33,34). Although the cell cycle was not effected, FIGNL1 knockdown significantly inhibited the expression of cyclin E1 and CDK2. This implies that FIGNL1-mediated regulation of the expression of cell cycle genes may exist, and our future research aims to investigate the underlying mechanisms.

Based on the finding of the present study and studies from other investigators, we suggest that DNA double-strand break repair HR pathways are abnormally enhanced in SCLC and the activity can be markedly suppressed through manipulation of FIGNL1. Thus, FIGNL1 is a promising target for SCLC.

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Table II. IC_{50} values of etoposide in the H446 cells transfected with the different shRNAs.

| Construct transfected | IC_{50} (24 h) (µM) | IC_{50} (48 h) (µM) |
|-----------------------|---------------------|---------------------|
| shRNA-Ctrl            | 87.44               | 2.76                |
| shRNA-FIGNL1-B        | 30.10               | 1.44                |
| shRNA-FIGNL1-D        | 33.39               | 2.09                |

Table III. IC_{50} value of cisplatin in the H446 cells transfected with the different shRNAs.

| Construct transfected | IC_{50} (24 h) (µM) | IC_{50} (48 h) (µM) |
|-----------------------|---------------------|---------------------|
| shRNA-Ctrl            | 6.46                | 1.89                |
| shRNA-FIGNL1-B        | 5.16                | 1.05                |
| shRNA-FIGNL1-D        | 5.45                | 1.34                |
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