INTRODUCTION

Lung cancer divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is accounting for 85% of all lung cancer cases. Clinically, cisplatin-based combined chemotherapy not only serves as adjuvant therapy or neoadjuvant therapy to ameliorate the prognosis of patients, but also is the first-line treatment for patients with advanced NSCLC. However, long-term and...
extensive use has led to the development of cisplatin resistance of NSCLC, greatly limiting its effective clinical application.\textsuperscript{4,5} So, it is vital important to elucidate the mechanism of NSCLC resistance to cisplatin and to search for effective drug resistance markers and therapeutic targets.

Studies have confirmed that super enhancer-associated long non-coding RNA (SE-lncRNA) is a type of IncRNAs produced in the super enhancer region, and its length is about one thousand to several. In kilobases, SE-lncRNA could regulate enhancer activity and promoter activation and initiate and stabilize the enhancer-promoter loop.\textsuperscript{6} Together with super enhancer, this IncRNA regulates genes in the process of specific cell lineage development and identity determination expression. It shows that SE-lncRNA is related to a variety of human diseases, especially playing a key role in the occurring and development of tumors.\textsuperscript{7–9}

Smooth muscle and endothelial cell enriched migration/differentiation-associated IncRNA (SENCR) was a super enhancer-long non-coding RNA that reported to be enriched in smooth muscle cells and endothelial cells, which could not only stabilize the contractile phenotype of smooth muscle cells, but also promote proliferation, the differentiation, and migration of endothelial cells.\textsuperscript{10–12} The SENCr gene contained three exons was a lncRNA transcribed in the direction of antisense from the first intron of friend leukemia virus integration 1 (FLI1) gene.\textsuperscript{10,13,14} FLI1 is a member of the ETS family of transcription factors and was originally found in erythroleukemia cell lines.\textsuperscript{15} In addition, FLI1 had also been reported to induce Ewing's sarcoma,\textsuperscript{16} acute myeloid leukemia,\textsuperscript{17} endometrial cancer,\textsuperscript{18} and so on. It suggested that it was a therapeutic target for tumors. However, SENCr role in cisplatin resistance in NSCLC remained unclear.

2 \ | MATERIALS AND METHODS

2.1 \ | Cell culture

LETP-a, H1975, A549, and A549/DDP cell as well as human normal lung epithelial cell (BEAS-2B) were purchased from the Chinese Academy of Medical Sciences (Shanghai, China). BEAS-2B, LETP-a, H1975, and A549 cell were cultured in 10% fetal bovine serum (FBS) (Thermo Fisher Scientific) and 90% RPMI-1640 medium (Thermo Fisher Scientific), and A549/DDP cell needed to be cultured in the whole medium (including 2 µg/ml cisplatin) to keep cisplatin resistance.

2.2 \ | Human DDP-treated LAD specimens

Human LAD tissues in remission (DDP-sensitive, \( n = 30 \)) and advanced tissues (DDP-resistant, \( n = 21 \)) were collected at the First Affiliated Hospital of Wenzhou Medical University from August 2018 to August 2021 (Table 1). All tissue samples must meet the following criteria. (1) Primary LAD patients with clinical stage IIIB-IV; (2) first-line chemotherapy regimen. DDP 25 mg/m² combined with gemcitabine 1000 mg/m² or paclitaxel 80 mg/m² for 21 days, each patient received 3 cycles of treatment. According to medical imaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI), serum tumor markers and response evaluation criteria for solid tumors (RECIST) criteria.\textsuperscript{19} These patients underwent fiberoptic bronchoscopy after 3 cycles of treatment, and lung cancer tissue was obtained and cryopreserved in liquid nitrogen within 15 min, and all specimens were confirmed by histopathological examination. This study was approved by the Institutional Ethics Review Committee of the First Affiliated Hospital of Wenzhou Medical University (YS2018001) and was conducted in strict accordance with the guidelines of the Declaration of Helsinki.

2.3 \ | Cell transfection

The antisense oligonucleotides (ASO) targeting SENCr (ASO-SENCr) and negative control (ASO-NC) were purchased from Ribobio Company (Guangzhou, China). ASO-SENCr and ASO-NC were transfected into A549/DDP cell using Lipofectamine3000 (Thermo Fisher Scientific, USA), consistent with the manufacturer’s manual. After 12 h, the cell transfection mixed medium was changed to RPMI-1640 medium containing 10% FBS for 48 h. SENCr knockdown efficiency of A549/DDP cell was confirmed by RT-qPCR.

Lentivirus (LV) overexpressing SENCr (LV-SENCr) and negative control (LV-NC) were purchased from Gene Chem (Shanghai, China). LV-SENCr and LV-NC were stably transfected into A549 cells using

| TABLE 1 Clinical features between cisplatin-sensitive group and cisplatin-resistant group of lung adenocarcinoma |
|--------------------------------------------------|------------------|------------------|
| Term                                            | sensitive group  | resistant group  |
| Sex                                             | (n = 30)         | (n = 21)         |
| Male                                            | 17               | 11               |
| Female                                          | 13               | 10               |
| TMN stage                                       |                  |                  |
| IIIb                                            | 16               | 12               |
| IV                                              | 14               | 9                |
| Histological degree                             |                  |                  |
| Poor                                            | 7                | 5                |
| Moderate                                        | 14               | 11               |
| High                                            | 9                | 5                |
| Lymph node metastasis                           |                  |                  |
| Yes                                             | 11               | 7                |
| No                                              | 19               | 14               |
| Smoking                                         |                  |                  |
| Yes                                             | 10               | 6                |
| No                                              | 20               | 15               |
a lentivirus-mediated method. Cell lines successfully transfected with lentiviral-mediated vectors for 48 h were then screened using puromycin screening assay. Finally, the SENCER overexpression efficacy of A549 cells was detected by RT-qPCR.

2.4 | Cisplatin sensitivity test

A total of 100 µl medium containing four thousand cells per group/well of were inoculated into 96-well plates and treated with different concentrations of cisplatin for 48 h. Afterward, each well was replaced with 100 µl of RPMI-1640 medium containing 10% Cell Counting Kit 8 (CCK8, Corning Corporation) and incubated for 40 min, followed by enzyme standardization (Thermo Fisher Scientific (absorbance at 450 nm). Cell viability = (OD cisplatin-OD blank)/(OD control-OD blank) × 100%, cytostatic rate = 1 - cell viability; IC50 is the concentration of cisplatin at which 50% cytostatic rate can be achieved.

2.5 | Cell proliferation assay

Cells 1000/well of A549 each group (1 µg/ml cisplatin or without cisplatin) or 2000/well of A549/DDP each group (2 µg/ml cisplatin or without cisplatin) were inoculated in 96-well plates and at 37°C for 4 days. On day 1, each well was changed into 100 µl RPMI-1640 medium containing 10% CCK8 reagent (CCK8, Corning Corporation) and incubated for 40 min. After incubation, the absorbance at 450 nm was measured on an enzyme marker (Thermo Fisher Scientific). The cell absorbance test procedures on days 2, 3, and 4 were the same as those on day 1.

2.6 | RT-qPCR

Total RNA was extracted using TRIzol reagent (Invitrogen, CA, USA) and then reverse transcribed into total cDNA using Prime Script RT reagent (Takara, Japan). qPCR was performed on a 7500 real-time PCR system (Thermo Fisher Scientific) using SYBR Green Master Mix II reagent (Takara) to detect target RNA levels and repeated three times. RT-qPCR primers were SENCER: 5’-CAGGCTTTGAGCATTGAC-3’ (forward) and 5’-GCCCTCTTGAGACACCCCTTTT-3’ (reverse); FLI1: 5’-GAAGAGGAGCT TGGGGCAATA-3’ (forward) and 5’-AAACAATGCTTCTGC TCT CC-3’ (reverse); β-actin: 5’-GACGCTACCCGATCTCGGCAT-3’ (forward) and 5’-ACCTGAGGGACATTGAC-3’ (reverse). The 20-µl PCR reaction volume included 6 µl double-distilled water, 10 µl SYBR premix (2x), 1 µl PCR forward primer (10 mM), 1 µl PCR reverse primer (10 mM), and 2 µl cDNA template. The qPCR reaction program included a denaturation step at 95°C for 10 min, 40 cycles (5 s at 95°C, 30 s at 60°C), and a final extension at 72°C for 5 min. The relative expression level of the target RNA was analyzed by 2^−ΔΔCT method with β-actin as internal reference.

2.7 | Nuclear/Cytosol Fractionation

Target cells were subjected to nuclear and cytoplasmic separation with the Nuclear/Cytosol Fractionation Kit (BioVision, SF, USA). In summary, 2 × 10^5 target cells at logarithmic growth stage were collected and then the cytoplasmic fraction was extracted with Cytosol Extraction Buffer A Mix (BioVision) and Cytosol Extraction Buffer B (BioVision), and the nuclear fraction was extracted by Nuclear Extraction Buffer Mix (BioVision). Afterward, total RNA was extracted from the nucleus and cytoplasm separately by TRIzol reagent (Invitrogen), followed by reverse transcription by Prime Script RT reagent (Takara). To detect the nuclear and cytoplasmic distribution of the target RNA, qPCR was performed in three replicates using SYBR Green Master Mix II reagent (Takara). RT-qPCR primers were GAPDH, 5’-GACGCTTGAGGACACCCCTTTT-3’ (forward) and 5’- ACCTGAGGGACATTGAC-3’ (reverse); U6, 5’-ACAGAGGAGCT GGGCATGTTACTG-3’ (forward) and 5’-ACCTGAGGGACATTGAC-3’ (reverse). The relative expression levels of target RNA in nucleus and cytoplasm were analyzed by 2^−ΔΔCT method, and GAPDH was as internal reference for cytoplasmic quality control, while U6 was as internal reference for nuclear quality control.

2.8 | Transwell assay

For the migration assay, logarithmic growth phase cells from each A549/DDP group and each A549 group were resuspended with serum-free RPMI-1640 medium and inoculated in the upper chamber of the transwell, respectively. RPMI-1640 medium containing 10% FBS (2 µg/ml cisplatin or no cisplatin per group for A549/DDP; 1 µg/ml cisplatin or no cisplatin per group for A549) was added to the bottom chamber and incubated at 5% CO2 and 37°C for 48 h. After incubation, migrating cells on the basolateral side of the membrane were fixed with 4% paraformaldehyde (Sigma, MO, USA) for 30 min and stained with 0.5% crystal violet (Sigma, MO, USA) for 15 min. After three washes with PBS solution, migrating cells were photographed under the microscope and counted with ImageJ software (Rawak Software Inc., Stuttgart, Germany). For the invasion assay, the operation and procedure were the same as for the migration assay, in addition to matrix gel (BD Biosciences, CA, USA) was added to the upper surface of the transwell chamber.

2.9 | Colony-forming assay

Logarithmic growth phase cells of A549/DDP each group and A549 each group were resuspended in culture medium and gradually diluted to a suitable concentration gradient. Added 1 ml RPMI-1640 medium containing 10% FBS (A549/DDP each group, plus 2 µg/ml cisplatin or without cisplatin; A549 each group, plus 1 µg/ml cisplatin or without cisplatin) to the 12-well plate and then put suspension cells of each group into the corresponding wells (400 cells in A549/DDP each group and 300 cells in A549 each group). After culturing in a 5%
carbon dioxide cell incubator at 37°C for two weeks, fixed the visible colonies with 4% paraformaldehyde (Sigma, MO, USA) for 30 min, and then stained with 0.5% crystal violet (Sigma, MO, USA) 15 min. Finally, the colonies were washed 3 times with PBS solution and photographed. ImageJ software (Rawak Software Inc., Stuttgart, Germany) was used to calculate the number of colonies in each well.

2.10 | Cell apoptosis

The Annexin V-FITC/PI apoptosis detection kit (BD Biosciences, CA, USA) was used to detect the apoptosis of A549/DDP cells in each group. The cells were cultured in RPMI-1640 medium (with or without cisplatin at 2 μg/ml) containing 10% FBS for 48 h. Then about 1 × 10⁶ cells were collected and washed twice with PBS solution. After resuspending in the binding buffer, the cells were stained with Annexin V-FITC and PI. Finally, the apoptosis rate was analyzed by flow cytometry (BD Biosciences, CA, USA). The Annexin V-FITC/PI apoptosis detection kit (BD Biosciences, CA, USA) was used to detect the apoptosis of A549 cells in each group. The cells were cultured in RPMI-1640 medium (with or without cisplatin at 1 μg/ml) containing 10% FBS for 48 h. Then about 1 × 10⁶ cells were collected and washed twice with PBS solution. After resuspending in binding buffer, cells were stained with Annexin V-FITC and PI. Finally, the apoptosis rate was analyzed by flow cytometry (BD Biosciences, CA, USA).

2.11 | Western blot

The total protein of each group of cells was extracted with RIPA lysis buffer (Beyotime, Shanghai, China) containing 1% protease inhibitor (Beyotime), and then the protein concentration was detected with the BCA protein assay kit (Beyotime). After configuring 20 μg/20 μl loading buffer (Beyotime) in the loading system, denatured it at 100°C for 5 min. Next, 20 μg of protein was separated by SDS-PAGE and transferred to a polyvinylidene fluoride (PVDF) membrane (Millipore, MA, USA). After sealing with 5% skimmed milk for 2 h, put the membrane into PCNA (1:1000), MDMX (1:500), P-gly (1:500), FLI1 (1:1000) and β-actin (1:1000) (Protiontech, CA, USA) for overnight incubation. On the next day, the membrane removed from the primary antibody was washed three times with TBST solution and was further incubated with horseradish peroxidase (HRP)-conjugated anti-rabbit IgG secondary antibody (Beyotime) at room temperature for about 1 h. Finally, ECL chemiluminescence solution (Thermo Fisher Scientific) was used to observe the Western blot in the exposure machine, and ImageJ software (Rawak Software Inc., Stuttgart, Germany) was used to analyze the band density.

2.12 | Statistical analysis

The statistical significance between the two groups was analyzed by student’s t test. All data are expressed as mean ± standard deviation (SD) and analyzed with GraphPad Prism 8.0 (GraphPad Software Company, San Diego, California, USA). p < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | SENCr was upregulated in NSCLC cisplatin-resistant A549/DDP cell and was mainly localized in the nucleus

To investigate the role of SENCr in cisplatin resistance in NSCLC cells, we used NSCLC cisplatin-sensitive A549 cells and cisplatin-resistant A549/DDP cells. The CCK8 assay showed that the survival rate of A549/DDP cells was significantly higher than that of A549 cells with increasing cisplatin concentration (Figure 1A), and the IC50 of A549/DDP cells was also higher than that of A549 cells (Figure 1B), indicating the successful establishment of cisplatin-resistant NSCLC cells. Next, RT-qPCR assays showed that SENCr was expressed at lower levels in LETP-a, H1975 and A549 cells of NSCLC than in BEAS-2B cells (Figure 1C). SENCr expression levels were significantly higher in NSCLC cisplatin-resistant A549/DDP cells than in cisplatin-sensitive A549 cells (Figure 1D). In addition, nuclear and cytoplasmic separation experiments showed that the highly expressed SENCr was mainly located in the nucleus of cisplatin-resistant A549/DDP cells (Figure 1E). In addition, compared with DDP-sensitive tissues with disease relief, SENCr expression was higher in DDP-resistant tissues with disease progression from LAD(Figure 1F). These results suggested that SENCr was upregulated in NSCLC cisplatin-resistant A549/DDP cells and is mainly located in the nucleus.

3.2 | SENCr promoted proliferation and cisplatin resistance in NSCLC cells

ASO-SENCr was successfully transfected with A549/DDP cells to inhibit SENCr expression (Figure 2A). CCK8 assays showed that knockdown of SENCr at cisplatin concentrations significantly reduced the survival of A549/DDP cells compared with each control (Figure 2C) and significantly reduced the IC50 of A549/DDP cells (Figure 2D). Next, cell proliferation analysis showed that SENCr knockdown significantly inhibited the proliferative capacity of A549/DDP cells in both the presence and absence of 2 μg/ml cisplatin (Figure 2G). For A549 cells, after successful overexpression of SENCr by LV-SENCr transfection (Figure 2B), the CCK8 assay shown that there was a significant increase in survival at cisplatin concentrations (Figure 2E), and the IC50 of A549 cells was also significantly higher in the negative control (Figure 2F). Then, the cell proliferation assay showed that SENCr overexpression significantly enhanced the proliferation of A549 cells both in the absence and in the presence of 1 μg/ml cisplatin (Figure 2H).

In addition, WB assay shown that knockdown of SENCr significantly reduced the expression of proliferation-related protein PCNA, cisplatin resistance-related proteins MDMX and P-gp.
3.3 SENCRC promoted migration and invasion of NSCLC cells

The effect of SENCRC on the migratory and invasive capacity of NSCLC cells was examined by Transwell assay. For A549/DDP cells, either without cisplatin or containing 2 μg/ml cisplatin, knockdown of SENCRC significantly reduced the migratory capacity compared with the respective control (Figure 3A), and the trend of invasion capacity was consistent with the trend of migratory capacity (Figure 3B).

For A549 cells, the migration ability was significantly enhanced after successful overexpression of SENCRC, both without and with 1 μg/ml cisplatin (Figure 3C), and the trend of invasion ability was the same as that of migration ability (Figure 3D). These results suggested that under the influence of cisplatin, SENCRC promoted the migration and invasive ability of NSCLC cells.

3.4 SENCRC promoted colony formation of NSCLC cells

For A549/DDP cell, after successful knockdown of SENCRC, the colony formation numbers were obviously reduced relative to corresponding controls whether without cisplatin or with 2 μg/ml cisplatin (Figure 4A). For A549 cell, overexpression of SENCRC significantly enhanced the colony formation numbers compared with respective controls whatever without cisplatin or with 1 μg/ml cisplatin (Figure 4B). These results hinted that SENCRC can promote the ability of NSCLC cells to form colonies with or without the influence of cisplatin.

3.5 SENCRC inhibited apoptosis of NSCLC cells

For A549/DDP cell, whatever without cisplatin or with 2 μg/ml cisplatin, knockdown of SENCRC significantly increased cell apoptosis compared with respective controls (Figure 5A). For A549 cell, after successful overexpression of SENCRC, the apoptosis was obviously
reduced relative to corresponding controls whether without cisplatin or with 1 μg/ml cisplatin (Figure 5B). These results suggested that SENCR inhibit apoptosis in NSCLC cells with or without cisplatin.

3.6 | SENCR and FLI1 were positively correlated in NSCLC cells

We first found by RT-qPCR that FLI1 mRNA expression was significantly upregulated in cisplatin-resistant A549/DDP cells compared with A549 cells (Figure 6A), with high expression of FLI1 mRNA detected by nucleus and cytoplasm isolation assays localized mainly in the cisplatin-resistant A549/DDP cell's nucleus (Figure 1D). Then, the database of Gene Expression Profiling Interactive Analysis (GEPIA) predicted a positive correlation between SENCR and FLI1 mRNA expression in lung adenocarcinoma (Figure 6B). Notably, RT-qPCR and protein blotting analysis showed that knockdown of SENCR significantly decreased FLI1 expression at the mRNA and protein levels in A549/DDP cells (Figure 6C and D), while SENCR overexpression significantly increased the expression of FLI1 mRNA and protein in A549 cells (Figure 6E and F). These results indicated that the expression of SENCR were positively correlated to FLI1 in NSCLC cells.

4 | DISCUSSIONS

LncRNAs are a class of non-coding RNAs that are involved in a variety of biological processes and are closely associated with the development of many diseases, especially playing a key role in tumorigenesis, metastasis, and drug resistance.23,24 In NSCLC, LncRNAs directly regulate cisplatin resistance not only by affecting the expression of downstream target proteins,25 but also by affecting the expression of downstream target genes by competitively binding miRNAs.26,27 In our study, we found that although SENCR expression levels were lower in NSCLC LETP-a, H1975, and A549 cells than in human normal lung epithelial cells (BEAS-2B), SENCR expression levels were lower in NSCLC cisplatin than in human normal lung epithelial cells (BEAS-2B). Drug-resistant A549/DDP cells were significantly higher than cisplatin-sensitive A549 cells, suggesting that SENCR may play an important role in the development of cisplatin resistance in NSCLC. In addition, nuclear and cytoplasmic separation experiments showed that the highly expressed SENCR was mainly distributed in the nucleus of A549/DDP cells, laying the foundation for further exploration of the role and mechanism of SENCR in cisplatin resistance.
Antisense oligonucleotide (ASO) is a chemically synthesized single chain molecule containing 13–30 nucleotides, which mainly degrades precursor mRNA in the nucleus of cells. In our study, we found that the highly expressed SENCR was mainly localized in the nucleus of A549/DDP cell. Therefore, in order to knock down SENCR and explore its influence on cisplatin resistance effectively, we chose the ASO technique mainly interfering with the nucleus of A549/DDP cell. After successful knockdown of SENCR levels, the proliferation ability and cisplatin resistance of A549/DDP cell were significantly reduced, reflected by the decreased levels of proliferation-related protein PCNA, cisplatin resistance-related proteins MDMX, and P-gp. Next, whatever without cisplatin or with 2 μg/ml cisplatin, SENCR knockdown obviously reduced the migration, invasion, and colony formation abilities of A549/DDP cell and promoted apoptosis. However, when SENCR was overexpressed in A549 cell by lentiviral vector, all above results were reversed. These findings indicated that SENCR could promote the growth and cisplatin resistance in NSCLC cells.

FLI1, identified as a proto-oncogene, has a site-specific relationship with SENCR at the locus, and studies have also shown that SENCR is associated with FLI1 in a variety of tissues and cells. In our study, we first found that FLI1 mRNA expression was significantly higher in cisplatin-resistant A549/DDP cells than in A549 cells and was mainly localized in the nuclei of A549/DDP cells. Then, database gene expression profile interaction analysis (GEPIA) predicted a positive correlation between SENCR and FLI1 mRNA expression in lung adenocarcinoma. Notably, RT-qPCR and protein blotting analysis showed that knockdown of SENCR significantly decreased FLI1 mRNA expression and protein levels in A549/DDP cells, whereas overexpression of SENCR significantly increased FLI1 mRNA and protein expression in A549 cells, indicating SENCR correlation and FLI1 in NSCLC cells. However, our study only explored the role of SENCR and FLI1 in cisplatin resistance in NSCLC, and the specific signaling pathways need to be further investigated.
FIGURE 5  SENCR inhibits apoptosis in NSCLC cells. A549/DDP cells were transfected with ASO-SENCR or ASO-NC. A549 cells were transfected with LV-SENCR or LV-NC. (A) In the absence or use of 2 μg/ml cisplatin, the ASO-SENCR group significantly increased apoptosis compared with the ASO-NC group ($p < 0.001, p < 0.001$). (B) Compared with the LV-NC group, the apoptosis of the LV-SENCR group was significantly reduced regardless of whether cisplatin was used or 1μg/mL cisplatin was used ($p < 0.01, p < 0.01$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

FIGURE 6  SENCR and FLI1 were positively correlated in NSCLC cells. A549/DDP cells were transfected with ASO-SENCR or ASO-NC. A549 cells were transfected with LV-SENCR or LV-NC. (A) FLI1 mRNA expression was significantly higher in cisplatin-resistant A549/DDP cells than in A549 cells ($p < 0.001$). (B) Positive correlation between SENCR and FLI1 mRNA in lung adenocarcinoma. (C, D) Expression of FLI1 mRNA and protein levels were significantly lower in the ASO-SENCR group compared with the ASO-NC group ($p < 0.05, p < 0.05$). (E, F) FLI1 mRNA and protein expression were significantly higher in the LV-SENCR group than in the LV-NC group ($p < 0.05, p < 0.01$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$
We found that the expression of both SENCR and FLI1 was up-regulated in cisplatin-resistant NSCLC cells and was mainly located in the nucleus. The knockdown of SENCR inhibited NSCLC cell growth and cisplatin resistance by reducing FLI1 expression, while overexpression of SENCR was reversed. Our results suggest that SENCR may be a target for cisplatin resistance in NSCLC.

CONFLICT OF INTEREST
All authors declared no conflict of interest.

PATIENT CONSENT STATEMENT
All patients consent to the retention of samples.

DATA AVAILABILITY STATEMENT
Requests for data, resources, and reagents should be directed to the corresponding author Jie Chen (chenjie991300@163.com).

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