Silencing long noncoding RNA OGFRP1 inhibits the proliferation and migration of cervical carcinoma cells

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Cervical cancer is still a serious threat to women’s health and life safety worldwide, and new treatment strategies are urgently needed. Accumulating evidences also imply that long non-coding RNAs (lncRNAs) are involved in a wide range of cellular processes, such as cell proliferation, apoptosis, and cell cycle. We found that the expression of lncOGFRP1 in cervical cancer tissues was significantly higher than that in normal cervical tissues ($P < .05$). Further, CCK8 detection found when lncOGFRP1 was silenced, the proliferation of cells was inhibited. After depleting lncOGFRP1, the proportion of apoptosis cells in C33A (3.71 ± 0.38% VS 11.98 ± 1.26%, $P < .05$) and SiHa (0.69 ± 0.06% VS 11.06 ± 1.03%, $P < .05$) cells increased significantly, and cell cycle was arrested in S phase. On the other hand, migration detection found the migration of cells also was hindered when lncOGFRP1 level was reduced. And the depletion of lncOGFRP1 inhibited the expression of β-catenin, Vimentin, N-cadherin, and SNAIL and promoted the expression of E-cadherin. In summary, we first discovered the high expression of lncOGFRP1 in cervical cancer and revealed that silencing lncOGFRP1 inhibits the proliferation and migration of cervical carcinoma cells.

Significance of the study: We first discovered the high expression of lncOGFRP1 in cervical cancer and revealed that silencing lncOGFRP1 inhibits the proliferation and migration of cervical carcinoma cells. These results help to better understand the pathogenesis and development of cervical cancer and provide insight to develop better diagnosis and treatment strategies.

KEYWORDS
apoptosis, cell cycle, cervical cancer, EMT, lncOGFRP1, migration, proliferation

1 INTRODUCTION

Protein-coding genes are only 2% of the human genome’s transcripts. The ENCODE project suggests that 76% of the human genome is transcribed to produce long non-coding RNAs (lncRNAs), which are widely defined as RNAs over 200 nucleotides in length. They lack the protein-coding ability and can be located in the cytoplasm or nucleus. Genetic mutation, chromosomal rearrangements, reverse transcription, tandem replication, and insertion of transposons are probably the causes of lncRNA production. So far, the vast majority of lncRNAs have not been well characterized. Whereas, lncRNAs have been found to affect various aspects of gene regulation, including epigenetic regulation, transcription, and posttranscriptional splicing. Accumulating evidences also imply that lncRNAs play a role in wide range of cellular processes, such as cell proliferation, apoptosis, and cell cycle.
As one of the most common gynaecological malignancies worldwide, cervical cancer (CC) causes 10% to 15% of female cancer-related deaths. Although, in recent decades, some progress has been made in the prevention, diagnosis, and treatment of CC, the overall survival rate is still poor, especially metastatic patients. The 5-year survival rate of localized CC patients is 91.5%, while the 5-year survival rate decreases to 57.1% and 17.3% with patients who suffer from regional lymph node metastases and distant metastases, respectively. Moreover, the incidence of CC is still high, and 80% patients have developed to invasive cancer at the time of diagnosis. Therefore, it is urgent to further reveal the molecular mechanism of the occurrence and development of CC and find biomarkers for early diagnosis, metastasis and prognosis, and new effective therapeutic targets.

In this study, we first found that lncOGFRP1 was highly expressed in CC. Depletion of lncOGFRP1 inhibited the proliferation of CC cell lines through the induction of cell cycle arrest at S phase and mitochondrial apoptosis pathway and impeded the migration by inhibiting EMT.

2 MATERIALS AND METHODS

2.1 Cell culture and transfection

The CC cell lines C33A and SiHa were provided by the Cell Resource Database of Chinese Academy of Sciences (Shanghai, China). Cells were maintained in DMEM medium (Thermo Scientific DioneX, Shanghai, China) replenished with 10% fetal bovine serum (FBS) (Invitrogen, Carlsbad, CA, USA), 100 U/mL penicillin (Sigma-Aldrich, St. Louis, MO, USA), and 0.1 mg/mL streptomycin (Sigma-Aldrich, St. Louis, MO, USA) at 37°C in 5% CO2. Once the cell density accomplish 60% in USA), and 0.1 mg/mL streptomycin (Sigma Aldrich, St. Louis, MO, USA), 100 U/mL penicillin (Sigma Aldrich, St. Louis, MO, USA), and 0.1 mg/mL streptomycin (Sigma-Aldrich, St. Louis, MO, USA) at 37°C in 5% CO2. The CC cell lines C33A and SiHa were provided by the Cell Resource Database of Chinese Academy of Sciences (Shanghai, China). Cells were maintained in DMEM medium (Thermo Scientific DioneX, Shanghai, China) replenished with 10% fetal bovine serum (FBS) (Invitrogen, Carlsbad, CA, USA), 100 U/mL penicillin (Sigma-Aldrich, St. Louis, MO, USA), and 0.1 mg/mL streptomycin (Sigma-Aldrich, St. Louis, MO, USA) at 37°C in 5% CO2. Once the cell density accomplish 60% in the well plate, the cells were transfected of lncOGFRP1 siRNA using Lipofectamine2000 (si-OGFRP1). A nonsense siRNA was also transfected into cells as a negative control (NC). LncOGFRP1 siRNA was purchased from Ruibo (Guangzhou, China). The siRNAs were synthesized by Guangzhou RiboBio Co, Ltd (Guangzhou, China). The sequences of siRNAs were as follows:

- siRNA1: 5′-GTGCTTCACTGCAAGTAA-3′
- siRNA2: 5′-GGATCTGAGGCTGCAAA-3′
- siRNA3: 5′-CATGACATGTTGGC-3′
- NC: 5′-UUCUCCGAACGUGACGUU-3′

2.2 Real-time quantitative PCR

Total RAN was resolved from C33A and SiHa cells after transfection 24 hours using Trizol reagent (Invitrogen, San Diego, CA, USA) and then reverse transcribed to cDNA. The expression of IncOGFRP1 was performed by SYBR Premix Ex Taq II (Takara Bio, Dalian, China). The relative quantification was identified by the 2^-ΔΔCt method after standardization to the GAPDH level. Primers used are as follows:

- IncOGFRP1 sense: 5′-TGCTGCCCAAGATAATG-3′
- anti-sense: 5′-GCCTCCATCAAAGCCTCT-3′
- GAPDH sense: 5′-TTATGCGCCGCTTATC-3′
- antisense: 5′-CACCCCTGTGCTGATGCAA-3′

2.3 CCK8 assay

For CCK8 assay, 5 × 10^3 cells after transfection for 12 hours were planted into 96-well plate. After cultured for 24, 48, and 72 hours, remove the culture medium, add fresh DMEM containing 10 μL CCK8 solution (Beyotime Biotechnology, Shanghai, China) and incubate at 37°C for 2 hours. OD value at 450 nm determined the proliferation of cells.

2.4 Transwell migration assay

Cells (5 × 10^4) that transfected IncOGFRP1 siRNA for 24 hours were planted in the upper chamber of Boyden chamber (8 μm pore size) (Millipore, Billerica, MA, USA) maintaining by 100 μL DMEM medium with 1% FBS. Then 600 μL DMEM medium with 10% FBS was added to the lower chamber to guide cell migration. Incubate 24 hours and remove the remaining cells on the upper chamber. The migrated cells were fixed by 4% paraformaldehyde for 30 minutes, stained with 0.1% crystal violet for 20 minutes, and photographed under the microscope.

2.5 Flow cytometry for apoptosis detection

Cell apoptosis was detected by Annexin V-FITC Apoptosis Detection kit I (BD Biosciences, Franklin Lakes, NJ, USA). After transfection for 48 hours, cells were gathered and washed with precooled PBS. Cells were resuspended to 1 to 5 × 10^6/mL by Annexin V binding buffer; 100 μL cell suspension was incubated with 5 μL Annexin V/FITC mix for 5 minutes. Then 10 μL PI dye and 400 μL PBS were added, and apoptosis was detected by flow cytometry. Statistical analysis was performed using Flowjo software (Tree Star, Ashland, OR, USA).

2.6 Flow cytometry for cell cycle detection

After transfection for 48 hours, cells were trypsinized (without EDTA) and resuspended in cold PBS. Ten volumes of cold 70% ethanol were vortexed while the cell suspension was dropped drop by drop. Fixed at −20°C for 24 hours, wash twice with cold PBS; 100 μL PBS containing 100 μg/mL RNase resuspend the cells. Incubate for 5 minutes and add 400 μL PBS containing 50 μg/mL PI (Beyotime Biotechnology, Beijing, China). Immediately detect cell cycle progression using a flow cytometer and use FCS Express 4 software (De Novo Software, Los Angeles, CA) to perform cell cycle analysis.

2.7 Western blot

Total proteins from C33A and SiHa cells after transfection 48 hours were extracted by ice-cold RIPA buffer (Beyotime, Shanghai, China).
containing protease inhibitors and phosphatase inhibitors (Roche, Basel, Switzerland). The proteins were separated by SDS-PAGE and transferred to a PVDF membrane. Then, the membrane was preblocked and incubated overnight at 4°C with primary antibodies (1:1000), followed by the secondary antibodies (1:2000) at room temperature for 1 hour. ECL reagent (Amersham, Little Chalfont, UK) generated the chemiluminescent signals of proteins, which were quantified with QUANTITY ONE software.

The primary antibodies used in this study were as follows: anti-Bcl2 (1:1000, ab32124), anti-Bax (1:1000, ab32503), anti-p53 (1:1000, ab32389), anti-E-cadherin (1:1000, ab194982), and anti-SNAL2 (1:1000, ab180714) were rabbit monoclonal antibodies and purchased from Abcam (Cambridge, MA, USA). Anti-Caspase3 (1:1000, ab13847), anti-CyclinA1 (1:1000, ab53699), anti-PCNA (1:1000, ab18197), anti-β-catenin (1:1000, ab16051), and anti-N-cadherin (1:1000, ab18203) were rabbit polyclonal antibody and purchased from Abcam. Anti-GAPDH (1:500, ab8245, Abcam) and anti-Vimentin (1:1000, ab8978) were mouse monoclonal antibodies and purchased from Abcam.

### 2.8 Statistical analysis

All experimental data were analysis by SPSS 20.0 statistical analysis software. Measured data were expressed as mean ± standard deviation (SD). Student t test was used for comparison between the two groups, and \( P < 0.05 \) was considered statistically significant. All experiments were repeated more than three times.

### 3 RESULTS

#### 3.1 IncOGFRP1 is abnormally high in CC but unrelated to prognosis of patients

The expression of IncOGFRP1 in CC was analysed, based on the mRNA expression data of 306 cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) samples, and 13 normal cervical samples contained in the GEPIA database. Online data analysis showed that the expression of IncOGFRP1 in CC tissues was significantly higher than that in normal cervical tissues (\( P < .05 \), Figure 1A). The TCGA database provides information on the overall survival of 290 patients with CC. Based on this, the prognostic value of IncOGFRP1 in tumours was analysed. However, the correlation between high expression of IncOGFRP1 in CC and prognosis was not statistically significant (Figure 1B).

#### 3.2 Deletion of IncOGFRP1 inhibits the proliferation of CC cells and blocks cell migration

CC cell lines C33A and SiHa were selected as in vitro experimental modals, and IncOGFRP1 was depleted using specific siRNA. As shown in Figure 2A,B, both siRNA 1 and 2 (S1 and S2) were effective in reducing the IncOGFRP1 level. Subsequently, S1 was used to subsequent experiments. CCK8 detection found that the absorbance at 450 nm of si-OGFRP1 cells was significantly reduced compared with NC group (\( P < .05 \), Figure 2C,D). This meant when IncOGFRP1 was silenced, the proliferation of cells was inhibited. Further, the migration of cells also was hindered when IncOGFRP1 level was reduced (\( P < .05 \), Figure 2E,F). These results suggest that IncOGFRP1 level is related to the biological function in the CC cells.

#### 3.3 Depletion of IncOGFRP1 induces apoptosis and blocks cell cycle

We further examined the effect of IncOGFRP1 depletion on cell apoptosis and cycle. After depleting IncOGFRP1, the proportion of apoptosis cells in C33A (3.71 ± 0.38% VS 11.98 ± 1.26%, \( P < .05 \)) and SiHa (0.69 ± 0.06% VS 11.06 ± 1.03%, \( P < .05 \)) cells increased significantly (Figure 3A,B). And there was no significant difference in the cell number of G1 phase, while the cell number in S phase increased, and those in G2/M phase decreased, indicating cell cycle was arrested in S phase (Figure 3D,E). The depletion of IncOGFRP1 resulted in the upregulation of apoptosis-related protein Bax, p53, caspase3, and cell cycle-related protein p21<sub>CIP1</sub> and the downregulation of Bcl-2, cyclinA1, CDK2, and PCNA (Figure 4A to C).
Depletion of lncOGFRP1 inhibits the EMT

Epithelial-mesenchymal transition (EMT) is a phenomenon characterized by the loss of epithelial characteristics of epithelial cells and the acquisition of mesenchymal characteristics, which enables cancer cells to invade, to resist apoptosis, and to metastasize. In the context of cancer, EMT causes the development of chemically resistant cells that can undergo immune escape and have stem cell properties. As shown in Figure 4D to F, the depletion of lncOGFRP1 inhibited the expression of β-catenin, Vimentin, N-cadherin, and SNAIL and promoted the expression of E-cadherin.

DISCUSSION

Prognosis and progression

Three recent meta-analysis conclude that IncRNAs may serve as novel predictor for prognosis of cervical, and high expression of HOTAIR is associated with the occurrence and development of CC. Several IncRNAs have been found to be abnormally expressed of CC. In particular, HOTAIR is significantly increased and associates with FIGO stage, lymph node metastasis, depth of cervical invasion, and tumour size in CC. The overall survival and disease-free survival of patients with high expression are lower than those with low expression. Later, Li et al find that the serum HOTAIR level of patients with CC is upregulated. In addition, elevated serum HOTAIR was implicated in late stage tumours, adenocarcinomas, lymphatic vessel infiltration, and lymph node metastasis. And high HOTAIR serum level was significantly associated with tumour recurrence and overall survival. In contrast, GASS is downregulated in CC tissues, which is significantly associated with advanced cancer progression and has been identified as an independent biomarker of clinical status in patients with CC. In addition, TUSC8, SPRY4-IT1, and IncRNA-LET are also considered as promising markers for CC. In this study, lncOGFRP1 was first found to be highly expression in CC, but it was not associated with the patient’s prognosis. This result may be related to the small sample size. However, this conclusion also requires the certification of clinical trials.

Proliferation, apoptosis, and cell cycle

As far as we know, only a few studies have shown that IncRNAs are involved in the proliferation and apoptosis of CC cells, including high level of MEG3 inhibits cell proliferation and induces G2/M cell cycle arrest in human CC cell lines. CCHE1 promotes the proliferation of CC cells by promoting the expression of PCNA. And CCAT2 knockout in HeLa, CaSkri, and SiHa CC cells, inducing G1 arrest, inhibiting cell proliferation, and triggering apoptosis. Finally, MALAT1 induces apoptosis by regulating the expression of caspase3, caspase8, Bcl-2, Bax, Bcl-XL in CC cell lines. In this study, the expression of lncOGFRP1 in C33A and SiHa cells was depleted. And we were surprised to find that this inhibited cell proliferation through the induction of apoptosis and S-phase cell cycle arrest.

In the early stage of apoptosis, the pro-apoptosis protein Bax translocates from the cytoplasm to the mitochondria, either by forming pores directly in the mitochondria, leading to the efflux of cytochrome C, or by bringing to Bcl-2 to antagonizing its antiapoptotic effect. Destruction of p53 is a common event in CC. P53 acts as a transcriptional activator, activating the Bcl-2 family of pro-apoptotic proteins and inhibiting the Bcl-2 family of anti-apoptotic proteins to initiate apoptosis. In this study, we found that by depleting the expression of IncOGFRP1 in CC cell lines, the cells upregulated the expression of p53, Bax, and caspase3 and downregulated the expression of Bcl-2. In summary, we speculate that depletion of IncOGFRP1 induces the mitochondrial pathway in CC cell lines.

CDK2 binds to CyclinA1 to form a complex that controls the S phase of the cell cycle. CyclinA1 is induced in the later stages of the
cell cycle and is required for cells to pass through the S phase. PCNA is an accessory protein of DNA polymerase δ and ε, which is considered to be the key to coordinating the synthesis of leading and lagging DNA strands. In addition to its involvement in DNA synthesis and repair pathways, PCNA also interacts with the proteins required to control the cell cycle. PCNA mRNA is present at all stages of the cell cycle and increases two to three times during S phase. P21CIP1 is a downstream target of p53 and an important inhibitor of cell cycle. Similarly, we found that CDK2, Cyclin A1, and PCNA expression were downregulated, and p21CIP1 expression was upregulated when the expression of lncOGFRP1 was depleted in CC cell lines. We suggest that lncOGFRP1 regulates cell cycle progression by modulating p53/CDK2/CyclinA1/PCNA/p21CIP1 axle in CC cell lines.

### 4.3 Migration and Metastasis

Migration and metastasis are the main causes of poor clinical outcome and high recurrence rates in tumour patients, with which IncRNAs have been shown to be associated. Sun et al discover an EZH2-binding lncRNA (lncRNA-EBIC) can enhance the cells invasion ability, subsequently downregulate the expression of E-cadherin through the association with EZH2 in CC. Li et al suggest that MALAT1 can accelerate the EMT process causing the promotion of invasion and metastasis of CC by upregulating the expression of Snail. In addition, GAS5 and HOTAIR described above are also closely related to the invasion and metastasis of CC cells.

Some biomarkers have been used to prove EMT, including membrane proteins like E-cadherin show reduced expression or are converted to N-cadherin. The expression of Vimentin not only marks the EMT on tumour cells, but also lead to changes in morphology, motor ability, and adhesion ability: all of these are favourable for metastasis. And the Snail family can reduce the expression of E-cadherin, cytokeratins, and increase the expression of mesenchyme. In this study, we found that the depletion of lncOGFRP1 hindered the migration of CC cell, and inhibited the expression of β-catenin, Vimentin, N-cadherin and SNAIL, and promoted the
expression of E-cadherin. In summary, we reveal that the depletion of lncOGFRP1 hinder the migration of CC cell lines by inhibiting the EMT pathway.

4.4 | Conclusion

We first found that lncOGFRP1 was highly expressed in CC. Depletion of lncOGFRP1 inhibited the proliferation of CC cell lines through the induction of cell cycle arrest at S phase and mitochondrial apoptosis pathway and impeded the migration by inhibiting the EMT. However, the exact molecular mechanism and clinical application of lncOGFRP1 in CC remains unclear, and further exploration and validation are needed.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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