


LINC01410 Knockdown Suppresses Cervical Cancer Growth and Invasion via Targeting miR-2467-3p/VOPPI Axis

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Background: Long noncoding RNAs have essential roles in human diseases, including cancer. Our work aims to assess the function and mechanisms of LINC01410 in cervical cancer (CC) development.

Methods: Expression analyses were performed using qRT-PCR. Proliferation was determined through CCK8 and colony formation assays. Cell migration and invasion were determined by Transwell assay. The interactions among LINC01410, miR-2467-3p and VOPPI were analyzed via luciferase reporter assay.

Results: LINC01410 was upregulated in CC tissues and cell lines. LINC01410 upregulation correlated with poor prognosis. LINC01410 silencing suppressed proliferation, migration and invasion of CC cells. LINC01410 was the sponge for miR-2467. And LINC01410 promoted VOPPI expression through inhibiting miR-2467.

Conclusion: Our findings demonstrated that LINC01410 contributed to CC progression through regulating miR-2467/VOPPI axis and suggested that LINC01410/miR-2467/VOPPI cascade may be a potential therapeutic target.

Keywords: LINC01410, miR-2467-3p, VOPPI, cervical cancer, progression

Introduction

Cervical cancer (CC) is one of the most malignant cancers in females and become a leading cause of tumor-related deaths worldwide.^{1,2} Although CC at the early stage could be cured via surgery, most patients are diagnosed at advanced or metastatic stages.^{3,4} Treatment by surgery, chemotherapy and radiotherapy achieves unsatisfactory outcomes in these advanced patients. And the five-year survival rate of CC patients remains very low.^{5,6} Consequently, it is urgent to understand the mechanism of CC progression.

Long noncoding RNA (lncRNA) is characterized by over 200 nucleotides in length and lack of protein-coding ability.^{7,8} LncRNA has been shown to exert various biological functions through diverse mechanisms, such as epigenetic regulation and microRNA sponging.^{9,10} Increasing reports indicate that lncRNA regulates the development and progression of human cancers.^{11–13} LncRNAs may regulate proliferation, invasiveness and differentiation of tumor cells.¹⁴ For example, HOXC-AS2 promotes metastasis of glioma cells by promoting ZEB1 expression.¹⁵ LncRNA ZFAS1 initiates thyroid cancer development via inhibiting miR-590.¹⁶ Additionally, IDH1-AS1 overexpression contributes to prostate cancer cell proliferation and invasion through modulating autophagy.¹⁷ The importance of

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lncRNA in CC has been widely acknowledged. Several important lncRNAs have been identified in CC, such as SNHG20 and XLOC_008466.^{18,19} Thus, it is still critical to reveal the correlation between lncRNA and CC progression in depth.

LINC01410 has been found to promote gastric cancer development, enhance colon cancer growth and regulate thyroid cancer apoptosis.^{20–22} However, the role of LINC01410 in CC remains undetermined. Here we found that LINC01410 was upregulated in CC samples. LINC01410 silencing represses the growth and invasion of CC via sponging miR-2467 and upregulating VOPP1. Summarily, our work illustrated that LINC01410/miR-2467-3p/VOPP1 axis plays a critical role in CC progression and may be a novel therapeutic target.

Materials and Methods

Clinical Sample

51 CC tissues and normal controls were collected from Affiliated Hangzhou First People's Hospital. All samples were frozen in liquid nitrogen. This study was approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital. All patients provided written informed consents. All experiments were conducted in accordance with the Declaration of Helsinki.

Cell Culture and Transfection

CC cell lines and the normal cervical cell line (Ect1/E6E7) were from Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured using RPMI-1640 medium containing 10% FBS and maintained in a sterilized incubator with 5% CO₂ at 37 °C. siRNAs targeting LINC01410 or VOPP1, miR-2467 mimics, miR-2467 inhibitors and corresponding negative controls were bought from RiboBio (Guangzhou, China). Transfection was conducted using Lipofectamine 2000 (Invitrogen, Carlsbad, USA) according to the manufacturer's protocol.

qRT-PCR

RNAs were isolated from tissues or cell lines using Trizol reagent (Invitrogen, Carlsbad, USA). Then, cDNA was synthesized using PrimeScript RT Master Mix kit (Takara, Dalian, China). And qPCR was carried out using SYBR Green Master Mix kit (Takara). GAPDH or U6 was the internal control. Relative expression was calculated according to the $2^{-\Delta\Delta Ct}$ method.

CCK8 Assay

CCK8 (Dojindo, Kumamoto, Japan) assay was performed to test proliferation following the manufacturer's protocol. Briefly, cells were planted into the 96-well plate and incubated for indicated days. Then, CCK8 solution was added and incubated for 2 h. The absorbance at 450nm was determined using a microplate reader (Bio-Rad, CA, USA).

Colony Formation Assay

Cells were seeded into the 6-well plate and cultured for 2 weeks. Then, cells were fixed with formaldehyde and stained using crystal violet. Colony numbers were counted using a light microscope (Olympus, Tokyo, Japan).

Cell Migration and Invasion

Cell migration and invasion were examined using Transwell assay. In brief, for migration assay, cells were seeded into the upper chamber (8- μ m pore size; Corning Costar, New York, USA) with serum-free medium. Twenty-four hours later, migrated cells were fixed and stained using crystal violet. Cell numbers were counted under a light microscope (Olympus). For invasion assay, the chambers were coated with Matrigel and other steps were the same as migration assay.

Luciferase Reporter Assay

Bioinformatics prediction was carried out using miRDB and TargetScan7 tools. Then, LINC01410 or VOPP1 fragment containing wild-type or mutant miR-2467-binding site was inserted into the pMIR-Report plasmid (Promega, Madison, USA) to generate luciferase reporter for luciferase reporter assay. Luciferase activities were measured through the Dual-Luciferase Reporter Assay System (Promega) following the Kit's instruction.

Statistical Analysis

All results were from at least three independent experiments and expressed as mean \pm standard deviation. Student's *t*-test or One-way ANOVA was used for Statistical analysis by using GraphPad Prism 6 (GraphPad Software, La Jolla, USA). The *P* value for statistical significance was set at <0.05.

Results

LINC01410 Was Upregulated in CC

LINC01410 expression in CC was analyzed. LINC01410 was unregulated in CC tissues (Figure 1A). Notably, LINC01410 expression was positively correlated with clinical stage

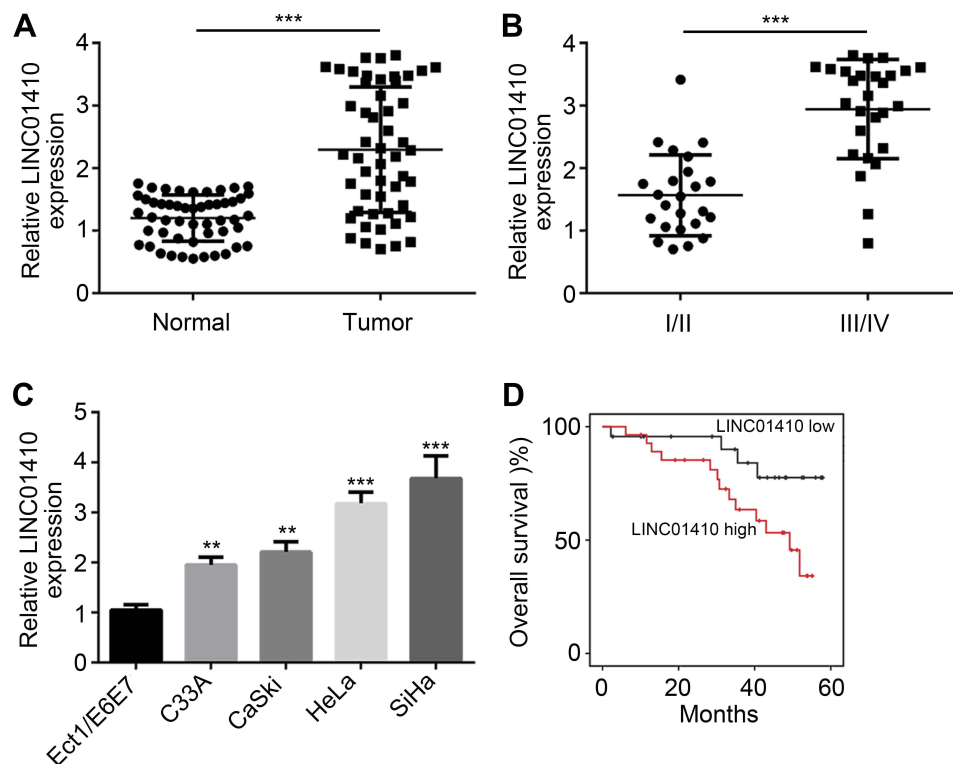


Figure 1 LINC01410 was upregulated in CC. **(A)** LINC01410 expression in 51 CC tissues and their adjacent normal controls was measured. **(B)** LINC01410 expression was increased in CC tissues with advanced stages. **(C)** LINC01410 level was upregulated in CC cell lines. **(D)** Kaplan-Meier analysis was conducted to illustrate the correlation between LINC01410 expression and patients' survival. ** $P < 0.01$ and *** $P < 0.001$.

(Figure 1B). Similarly, we found that LINC01410 level was also upregulated in CC cell lines (Figure 1C). Then, the CC tissues were divided into LINC01410 low and high expression groups, followed by Kaplan-Meier analysis. Results showed that LINC01410 high expression was correlated with low survival rate (Figure 1D). Thus, LINC01410 may regulate CC progression.

LINC01410 Depletion Suppressed Proliferation, Migration and Invasion

LINC01410 expression was the highest in HeLa and SiHa cells among all measured cell lines. Thus, we chose HeLa and SiHa cells for the following investigations. LINC01410 was silenced in HeLa and SiHa cells (Figure 2A). Through CCK8 assay, LINC01410 knockdown suppressed proliferation (Figure 2B), which was validated through colony formation assay (Figure 2C). To determine the correlation between LINC01410 and metastasis, we performed transwell assay. We found that LINC01410 knockdown significantly decreased the cell numbers of migration and invasion (Figure 2D and E). Therefore, LINC01410 is an oncogenic lncRNA in CC.

LINC01410 Regulated miR-2467-3p/VOPPI Axis

To explore the mechanism, we performed bioinformatics analysis. We found that LINC01410 might be the sponge for miR-2467 and identified their potential binding elements (Figure 3A). We then confirmed the transfection efficiency of miR-2467 mimics and inhibitors (Figure 3B). miR-2467 mimic suppressed the activity of LINC01410-WT reporter and vice versa (Figure 3C). Moreover, LINC01410 knockdown promoted miR-2467 expression and vice versa (Figure 3D). We then further analyzed the target of miR-2467 and identified a potential candidate VOPPI (Figure 3E). Similarly, we constructed VOPPI luciferase reporters (Figure 3E). VOPPI-WT reporter activity was suppressed by miR-2467 mimics and vice versa (Figure 3F). Moreover, miR-2467 suppressed the expression of VOPPI (Figure 3G). Interestingly, LINC01410 knockdown also suppressed VOPPI expression (Figure 3H). And this suppression was abrogated by miR-2467 inhibitors (Figure 3H). Hence, LINC01410 promoted VOPPI expression via sponging miR-2467.

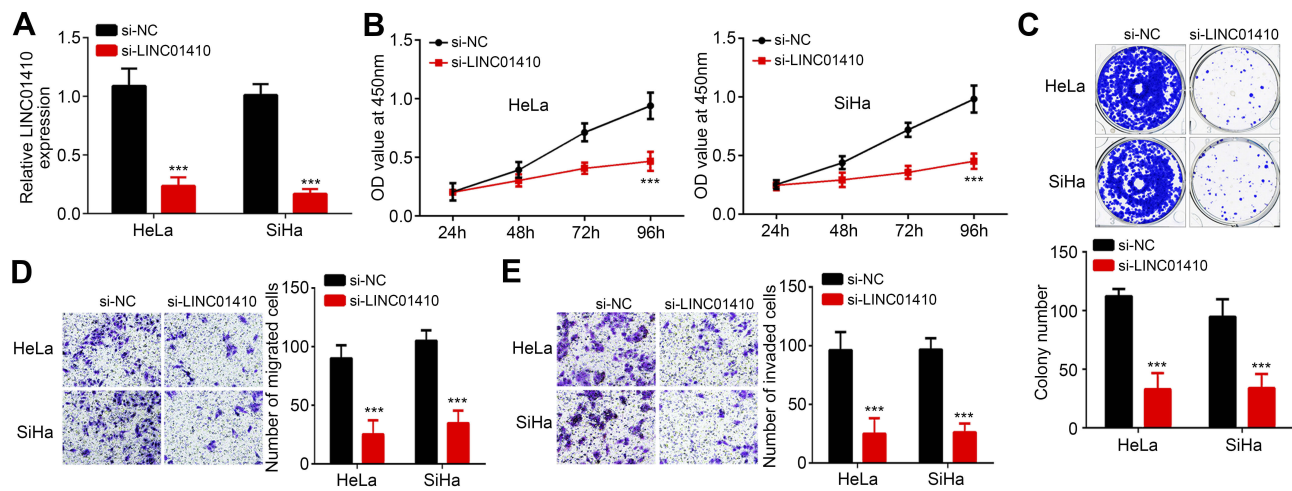


Figure 2 LINC01410 depletion suppressed proliferation, migration and invasion. **(A)** Expression detection of LINC01410 in HeLa and SiHa cells. **(B and C)** CCK8 and colony formation assays were carried out to test the effects of LINC01410 silencing on proliferation. **(D and E)** Transwell assay was conducted to analyze migration and invasion. *** $P < 0.001$.

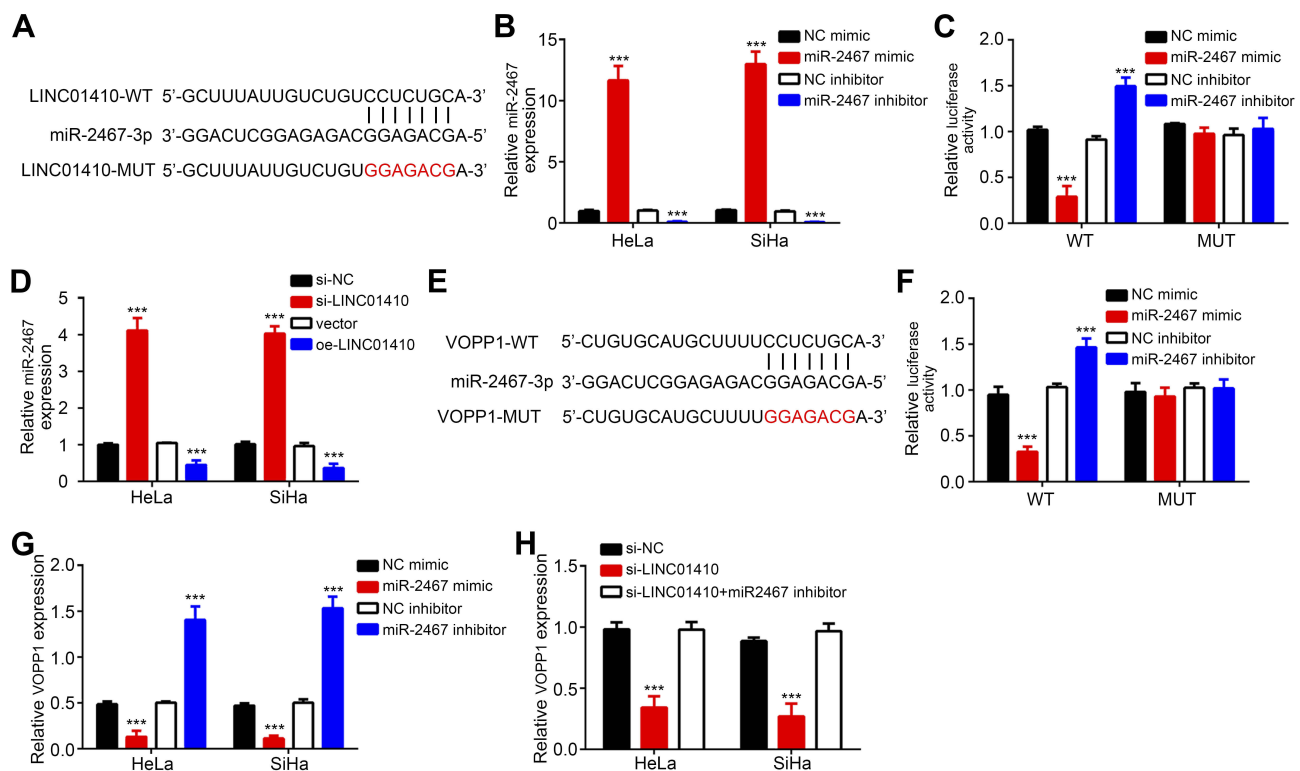


Figure 3 LINC01410 regulated miR-2467-3p/VOPPI axis. **(A)** miRDB predicted the complementary sequence between LINC01410 and miR-2467. **(B)** Expression analysis of miR-2467 after transfection with miR-2467 mimics, miR-2467 inhibitors or negative controls. **(C)** Luciferase reporter assay was performed to analyze the activity of LINC01410-WT or MUT reporter in HeLa cells. **(D)** miR-2467 expression was analyzed after transfection with indicated vectors. **(E)** TargetScan7 predicted the complementary sequence between VOPPI-3'UTR and miR-2467. **(F)** Luciferase reporter assay was performed to analyze the activity of VOPPI-WT or MUT reporter in HeLa cells. **(G)** VOPPI expression was inhibited by miR-2467. **(H)** LINC01410 knockdown inhibited the expression of VOPPI. *** $P < 0.001$.

LINC01410 promoted CC progression through miR-2467-3p/VOPPI axis

We also found that VOPPI was upregulated in CC tissues (Figure 4A), suggesting a potential oncogenic role. To determine whether LINC01410 promotes CC progression via

miR-2467/VOPPI axis, we carried out rescue assays. We found that miR-2467 inhibitors reversed the effects of LINC01410 knockdown on proliferation, migration and invasion (Figure 4B–D). Moreover, VOPPI silencing further suppressed the proliferation, migration and invasion of CC

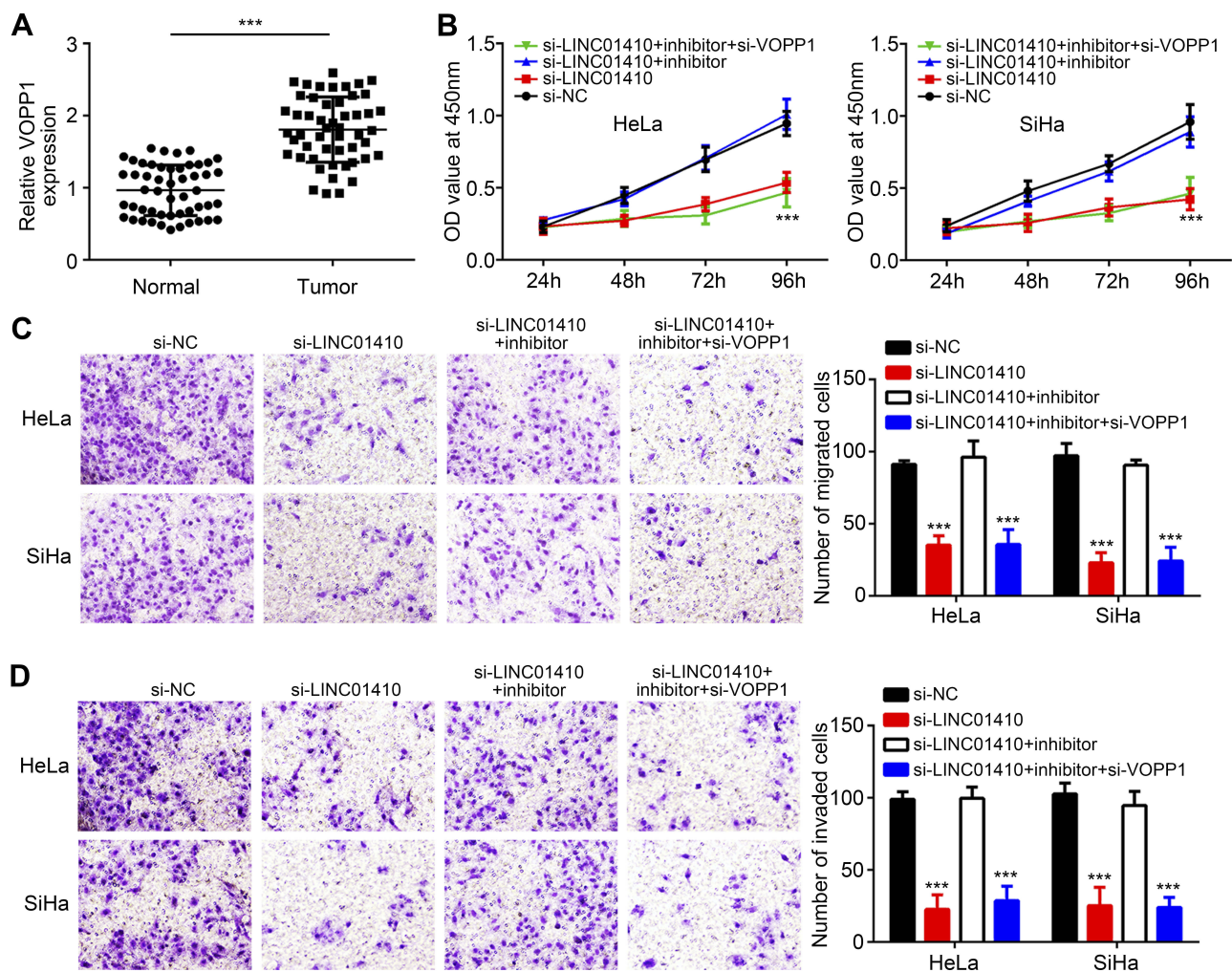


Figure 4 LINC01410 promoted CC progression through miR-2467-3p/VOPPI axis. (A) Relative expression of VOPPI in CC tissues. (B) CCK8 assay was performed after transfection with indicated plasmids. (C and D) Transwell assay was conducted to analyze migration and invasion. *** $P < 0.001$.

cells (Figure 4B–D). In conclusion, LINC01410 contributes to CC progression through miR-2467/VOPPI axis.

Discussion

Uncovering the molecular mechanism of CC progression is urgently required, which is quite important for the development of novel therapeutic strategies.²³ In this study, we researched the relationship between lncRNA expression and CC progression. We identified that LINC01410 was highly expressed in CC tissues and correlated with the clinical stage. Moreover, LINC01410 high expression indicated a low survival rate in CC patients. Functionally, we showed that LINC01410 knockdown suppressed the proliferation, migration and invasion of CC cells. Thus, our study revealed a novel oncogenic lncRNA.

LncRNAs, as tumor suppressors or oncogenes, are critical regulators in CC, which has been proven by

growing references.^{24,25} For instance, LncRNA-CTS accelerates growth and invasion of CC via regulating miR-505/ZEB2 signaling.²⁶ LncRNA GAS5-AS1 inhibits proliferation and migration of CC through stabilizing GAS5.²⁷ Linc00483 promotes CC growth and invasion via targeting miR-508-3p/RGS17 axis.²⁸ At first, LINC01410 was reported to enhance gastric cancer metastasis.²⁰ Afterwards, a study shows that LINC01410 increases growth and invasiveness of colon cancer cells through sponging miR-3128.²¹ Recently, a work reveals a close correlation between LINC01410 expression and thyroid cancer development.²² However, whether LINC01410 affects CC progression remains unclear. In our study, we firstly showed that LINC01410 was upregulated in CC tissues and cell lines. Moreover, our data suggested that LINC01410 may be a prognostic biomarker for CC patients. Through functional experiments, we

demonstrated that LINC01410 depletion markedly inhibited the proliferation, migration and invasion of CC cells. Therefore, our findings proved that LINC01410 is a novel important oncogene in CC.

Working as the sponge for microRNAs to play roles is the most common manner of lncRNA functioning.^{15,20} For example, lncRNA MIAT sponges miR-212 to regulate thyroid cancer development.²⁹ FLVCR1-AS1 sponges miR-485-5p to enhance the growth and metastasis of cholangiocarcinoma.³⁰ LINC01410 has also been shown to sponge several miRNAs, such as miR-532 and miR-3619-5p.^{20,22} Therefore, we analyzed the potential miRNAs of LINC01410 in CC. We identified a novel target, namely miR-2467. Through luciferase reporter assay, we demonstrated their direct interaction and found that LINC01410 inhibited the miR-2467 level. The miR-2467 function is rarely studied. A recent study shows that miR-2467 inhibits colorectal cancer development.³¹ Whether miR-2467 regulates CC remains unclear. In our study, our results showed that miR-2467 inhibited proliferation, migration and invasion of CC cells, suggesting miR-2467 is a tumor suppressor.

miRNAs are a class of small non-coding RNAs that act as epigenetic modulators.³² These molecules exert their effect via targeting a variety of biological processes such as angiogenesis, growth, and differentiation. It has been indicated deregulation of miRNAs are associated with several diseases such as cancer, cardiovascular diseases and CNS-related disorders.^{33,34} We then analyzed the downstream target of miR-2467. Through bioinformatics analysis, we identified miR-2467 directly targeted VOPPI. Several kinds of research indicate that VOPPI may be an essential oncogene. VOPPI downregulation promotes apoptosis of squamous carcinoma cells.³⁵ Another study reveals that VOPPI acts as a potential oncogene in gastric cancer.³⁶ Recently, Bonin et al indicated that VOPPI contributes to breast cancer progression.³⁷ Its role in CC is largely unknown. In our study, we found that VOPPI was upregulated in CC tissues. And its expression was upregulated by LINC01410 through sponging miR-2467. Moreover, a series of rescue experiments demonstrated that VOPPI silencing suppressed CC growth and metastasis. Thus, VOPPI also promotes CC tumorigenesis.

Taken together, our results revealed that LINC01410/miR-2467/VOPPI regulatory loop contributes to CC progression and may be a promising therapeutic target.

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Disclosure

Both authors declare no conflict of interest.

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