Long Noncoding RNA FBXL19-AS1 Expedites Cell Growth, Migration and Invasion in Cervical Cancer by miR-193a-5p/PIN1 Signaling

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Background: Cervical cancer is one of the most prevalent malignancies in gynecology with increasing incidence in recent years. Long noncoding RNAs (lncRNAs) have been reported to regulate human cancers including cervical cancer. F-box and leucine-rich repeat protein 19 antisense RNA 1 (FBXL19-AS1) have been unmasked to exert carcinogenic functions in several cancers except cervical cancer.

Aim: Present study hammered at investigating the function and mechanism of FBXL19-AS1 in cervical cancer.

Methods: RT-qPCR was utilized to test gene expression. EdU staining, colony formation, transwell, flow cytometry and TUNEL assays were applied for measuring the impact of FBXL19-AS1 on cervical cancer cell functions. Moreover, RIP, RNA pull-down and luciferase reporter assays were utilized for detecting the correlations among FBXL19-AS1, miR-193a-5p and PIN1 (peptidylprolyl cis/trans isomerase, NIMA-interacting 1).

Results: FBXL19-AS1 exhibited elevated expression in cervical cancer tissues and cells. Silencing FBXL19-AS1 repressed cell proliferation through arresting cell cycle and stimulating apoptosis, and losing FBXL19-AS1 also restrained cell migration and invasion. Also, we discovered FBXL19-AS1 as a miR-193a-5p sponge, while miR-193a-5p was a tumor inhibitor in cervical cancer. Further, PIN1 was proved as the miR-193a-5p target, and FBXL19-AS1 augmented PIN1 expression in cervical cancer via sequestering miR-193a-5p. Of note, PIN1 accelerated the progression of cervical cancer, and its upregulation counteracted the impacts of depleted FBXL19-AS1 on cervical cancer cell functions.

Conclusion: FBXL19-AS1 contributes to malignant phenotypes in cervical cancer by sponging miR-193a-5p and regulating PIN1.

Keywords: FBXL19-AS1, miR-193a-5p, PIN1, cervical cancer

Introduction

Cervical cancer is one of the most prevalent malignancies in gynecology with serious endangerment to women’s health.1 In recent years, the incidence of cervical cancer is increasing with a younger trend.2 With the development of early screening technology and treatment, the survival rate of early patients is also increasing.3–5 However, the prognosis of those developed into advanced stages is still not good.6 Thus, developing new biomarkers for cervical cancer are urgently demanded.

As a subclass of noncoding RNAs, long noncoding RNAs (lncRNAs) possess a length with longer than 200 nucleotides. LncRNAs cannot translate into proteins, but they can modulate gene expression through diverse manners including...
post-transcriptional regulation. An increasing number of reports have indicated that IncRNAs take part in different cellular processes to regulate the development of assorted diseases, even human cancers. Dysfunctional IncRNAs are always discovered in cancers and they are considered to be associated with cancer development. For example, TUG1 was upregulated and promoted cell proliferation in epithelial ovarian cancer via modulating AURKA. A former research also indicated that upregulated PVT1 was associated with low survival rate and it could accelerate the progression of gallbladder cancer via miR-143/HK2 axis. F-box and leucine-rich repeat protein 19 antisense RNA 1 (FBXL19-ASI) is a kind of IncRNA which has been reported to regulate cancer development by some researches. For examples, FBXL19-ASI expedited oncogenic cellular behaviors via absorbing miR-346 in osteosarcoma; FBXL19-ASI facilitated cell growth and epithelial–mesenchymal transition in non-small cell lung cancer; FBXL19-ASI acted as a miR-178 sponge to accelerate breast cancer cell proliferation. Nonetheless, the specific role and mechanism of FBXL19-ASI in cervical cancer are still unclear.

In the current work, we hammered at investigating the function and latent mechanism of FBXL19-ASI in cervical cancer, which may conduce to improving cervical cancer treatment.

Materials and Methods

Human Cervical Cancer Samples

The paired tumor and non-tumor samples were surgically acquired from 100 cervical cancer patients in the Yijishan Hospital of Wannan Medical College. The patients with no any treatment before operation signed the written informed consents prior to this research. The work was supported by the Ethics Committee of Yijishan Hospital of Wannan Medical College. Specimens were all subjected to quick-frozen via liquid nitrogen and preservation at −80°C.

Cell Culture

Human normal cervical cell line (Ect1/E6E7) and cervical cancer cell lines (C-4-I, SiHa, C-33A and HeLa) were selected for our research. Ect1/E6E7, SiHa, C-33A and HeLa cells were obtained from ATCC (Manassas, VA, USA). C-4-I cell was purchased from CoBioer Biosciences Co., Ltd (Nanjing, China). Keratinocyte Serum-Free Medium (K-SFM; Gibco Laboratories, Grand Island, NY, USA) was utilized to cultivated Ect1/E6E7 cell. Eagle’s Minimum Essential Medium (EMEM) was applied for cultivating SiHa, C-33A and HeLa cells. C-4-I was cultured in DMEM medium with 10% FBS (Gibco). Each kind of culture medium was added with 10% fetal bovine serum (FBS; Gibco). All cells were cultivated under the condition with 5% CO₂ at 37°C.

Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR)

The TRIzol reagent was implemented for separating total RNA from indicated tissues or cells. Then, the reverse transcription kit (Takara, Dalian, China) was utilized for reverse transcription of RNA to cDNA. Following, RT-qPCR was conducted via the ABI7500 System (Applied Biosystems, CA, USA). Finally, gene expression relative to GAPDH/U6 was calculated via the 2−ΔΔCt method.

Cell Transfection

For inhibiting FBXL19-ASI and PIN1, specific short-hairpin RNAs (sh-RNAs) were devised and synthesized through GenePharma (Shanghai, China), with a nonsense sequence as the negative control (sh-NC). For upregulating the expression of PIN1, the sequence of PIN1 cDNA was cloned into pcDNA3.1 vector (Invitrogen, Carlsbad, CA, USA) for acquiring pcDNA3.1/PIN1, with empty vector as the negative control. Also, NC mimics/inhibitor and miR-193a-5p mimics/inhibitor were also devised and synthesized through GenePharma. Cell transfection with indicated plasmids for 48 hours was achieved by the utilization of Lipofectamine 3000 (Invitrogen).

5-Ethynyl-2′-Deoxyuridine (EdU) Assay

In accordance with the protocol of EdU labeling/detection kit (RiboBio, Guangzhou, China), EDU experiment was employed for evaluating cell proliferation capability. Cells (1×10⁴) were placed in 96-well plates, followed by the addition of 50 μM of EdU diluent for cultivating cells for 2 hours under the condition of 5% CO₂ and 37°C. After fixation by 4% paraformaldehyde and rinsing via PBS, cells were processed with Apollo 567 working solution for 2 hours. Following, DAPI was utilized to counterstain the nuclei for 5 minutes. In the end, cells were observed by fluorescent microscopy (Thermo Fisher Scientific). Bio-repeats were run in triplicate.

Colony Formation Assay

Transfected cells were planted in the 6-well plates (500 cells per well) for two-week incubation. After that, cells
were fixated with 4% paraformaldehyde and stained by 0.1% crystal violet. Finally, the number of colonies was monitored manually. Bio-repeats were run in triplicate.

**TUNEL Assay**

TUNEL assay was operated for assessing cell apoptosis with the in situ Cell Apoptosis Detection Kit (Roche, Basel, Switzerland). Simply put, 1×10⁵ cells were added into 24-well plates. After that, cells were processed consecutively with 4% paraformaldehyde, 0.2% Triton X-100, and DAPI staining solution. Subsequently, the images were captured with a light microscope (CX23, Olympus, Japan). Bio-repeats were run in triplicate.

**Flow Cytometry Analysis**

As for cell apoptosis detection, cells were subjected to double-staining via FITC-Annexin V Apoptosis Detection Kit (BD Biosciences) in accordance with protocol of supplier. With respect to cell cycle evaluation, cells were digested and fixed with 75% ethanol, followed by discard of the supernatant and cultivation with PI-contained RNA enzyme (Sigma-Aldrich). Finally, cell apoptotic rate and cell cycle distribution were both determined via flow cytometry (FACScan; BD Biosciences. Bio-repeats were run in triplicate).

**Transwell Assay**

The capabilities of C-4-I and C-33A cells to invade or migrate were measured by using the transwell chamber with or without Matrigel (Corning Incorporated, Corning, NY), respectively. 2 × 10⁴ cells in serum-free medium were seeded to the upper chamber, while the medium supplementing 10% FBS was poured into the lower chamber. After 24 hours, cells in the lower chamber were subjected to fixation by 4% paraformaldehyde and staining with crystal violet. Afterwards, we observed cells by the microscope (magnification, ×200; Olympus, Tokyo, Japan). Bio-repeats were run in triplicate.

**Fluorescent in situ Hybridization (FISH)**

Ribo™ Fluorescent in situ Hybridization Kit (Ribobio) was applied for conducting this assay based on the user guides. In short, the FBXL19-AS1 probes labeled with fluorescent dye were incubated with indicated cells. Finally, the signals of fluorescence were analyzed by a confocal laser-scanning microscope (Leica). Bio-repeats were run in triplicate.

**Subcellular Fractionation**

The nuclear or cytoplasmic Isolation Kit (Biovision, San Francisco, CA, USA) was utilized for the isolation of cytosolic and nuclear fractions in C-4-I or C-33A cells in line with the user guide. The RNA molecules in the cytoplasm and nucleus were then detected via RT-qPCR. U6 and GAPDH served as the controls. Bio-repeats were run in triplicate.

**Luciferase Reporter Assay**

The synthesized sequences of FBXL19-AS1 or PIN1 3’UTR covering wild-type (WT) or mutated-type (Mut) of miR-193a-5p interacting sites were inserted into pmirGLO vectors (Promega, Madison, WI, USA) for constructing FBXL19-AS1-WT or PIN1-WT/Mut. Then, cells were subjected to co-transfection with the constructed vectors and miR-193a-5p mimics (or NC mimics) using Lipofectamine™3000 (Invitrogen) for 48 hours. In the end, dual-luciferase reporter gene assay system (Promega) was employed for measuring the luciferase activity. Bio-repeats were run in triplicate.

**RNA Immunoprecipitation (RIP) Assay**

Magna RIPTM RNA Binding Protein Immunoprecipitation Kit (Millipore) was utilized for conducting this assay. Simply put, cells were lysed via RIP lysis buffer (Solarbio) and then the obtained lysates were cultivated for a whole night in RIP buffer with magnetic beads coating anti-Ago2 (Millipore) or anti-IgG. After that, the precipitated RNAs was isolated and analyzed through RT-qPCR. Bio-repeats were run in triplicate.

**RNA Pull-Down Assay**

The lysates acquired from C-4-I and C-33A cells via RIPA lysis buffer were cultivated for 1 hour at 4°C with biotinylated miR-193a-5p sequences with wild-type or mutated seed region (Bio-miR-193a-5p-WT/Mut), with the biotin-labelled nonsense sequence as the negative control (Bio-NC). Then, the streptavidin agarose magnetic beads were supplemented into above mixtures, and the enrichment of RNAs captured by beads were analyzed via RT-qPCR. Bio-repeats were run in triplicate.

**Statistical Analysis**

The data from all three bio-repeats were expressed as mean ± standard deviation (SD) after analysis via SPSS 22.0 software (IBM, Armonk, NY, USA). The group


Results

Knockdown of FBXL19-AS1 Restrains Cell Proliferation, Migration and Invasion in Cervical Cancer

First of all, in order to examine the function of FBXL19-AS1 in cervical cancer, we tested its expression under malignant conditions. Intriguingly, FBXL19-AS1 presented high expression in cervical cancer tissues relative to matched non-cancerous ones (Supplementary Figure 1A). Consistently, we observed that FBXL19-AS1 was highly expressed in cervical cancer cell lines (C-4-I, SiHa, C-33A and HeLa) in contrast with the normal cell line (Ect1/E6E7), especially in C-4-I and C-33A cells (Figure 1A). Then, for conducting loss-of-function assays, we interfered FBXL19-AS1 expression in C-4-I and C-33A cells using sh-FBXL19-AS1#1/2 (Figure 1B). Subsequently, we discovered that cell proliferative capability was restrained through the lack of FBXL19-AS1, because the quantity of colonies and the rate of EdU positive cells were both reduced after FBXL19-AS1 was knocked down (Figure 1C-D). After that, we measured cell migration and invasion through transwell experiments. Results displayed that the number of migrated and invaded cells was dramatically declined when FBXL19-AS1 was inhibited (Figure 1E), indicating the repressive impact of depleted FBXL19-AS1 on cervical cancer cell migration and invasion. In the end, to further uncover the in-depth influence of FBXL19-AS1 on cervical cancer cell proliferation, we then investigated its impact on cell cycle progression and cell apoptosis. It manifested that the absence of FBXL19-AS1 led to increased percent of cells at G0/G1 phase and decreased proportion of cells at S and G2/M phases (Supplementary Figure 1B), disclosing that FBXL19-AS1 inhibition induced cell cycle arrest in cervical cancer cells. Meanwhile, the outcomes of flow cytometry analysis and TUNEL experiment revealed that both the rates of apoptotic cells and TUNEL positive cells were lowered under FBXL19-AS1 deficiency (Figure 1F-G), which demonstrated that cell apoptotic ability could be expedited by FBXL19-AS1 shortage. In a word, the expression of FBXL19-AS1 is extremely high and knockdown of FBXL19-AS1 restraints cell proliferation, migration and invasion in cervical cancer.

FBXL19-AS1 Sponges miR-193a-5p and Overexpression of miR-193a-5p Inhibits the Progression of Cervical Cancer

For the sake of exploring the regulatory mechanism of FBXL19-AS1 in cervical cancer, we conducted subcellular fractionation assay and FISH experiment to figure out the distribution of FBXL19-AS1 in cervical cancer cells. The outcomes indicated the major location of FBXL19-AS1 in C-4-I and C-33A cell cytoplasm (Figure 2A-B), which signified that FBXL19-AS1 might serve as a miRNA sponge to exert its function at post-transcription level. Thus, we used the ENCORI database (http://starbase.sysu.edu.cn/index.php) to search for the latent miRNAs binding to FBXL19-AS1. On the basis of specific conditions (CLIP-Data ≥2; Degradome-Data ≥0; pan-Cancer ≥4), we found seven miRNA candidates (including miR-331-3p, miR-193a-5p, miR-378a-3p, miR-378c, miR-378d, miR-5586-5p and miR-6512-3p). Then, we implemented RT-qPCR experiments to examine the expression of the aforementioned miRNAs in cervical cancer cells. As a result, we discovered that only miR-193a-5p was lowly expressed in cervical cancer cells, while the levels of other miRNAs were relatively high (Figure 2C). Of importance, cervical cancer samples tended to possess higher miR-193a-5p level than paired controls (Supplementary Figure 1C). Hence, we selected miR-193a-5p for further experiments. Through RNA pull-down experiments, we discovered that the enrichment of FBXL19-AS1 was extremely high in biotinylated wild-type miR-193a-5p group rather than the other two groups (Figure 2D). Following, we elevated miR-193a-5p expression in these two cells (Figure 2E), and also acquired the predicted binding sites between miR-193a-5p and FBXL19-AS1 by ENCORI (Figure 2F). As expected, the results of luciferase reporter experiments displayed that overexpressed miR-193a-5p caused a notable reduction in the luciferase activity of FBXL19-AS1-WT, while the luciferase activity of FBXL19-AS1-Mut emerged no visible change (Figure 2G). Furthermore, we examined the role of miR-193a-5p in cervical cancer. Through colony formation and EdU experiments, we discovered that upregulation of miR-193a-5p inhibited cell proliferation (Figure 2H-I). In the same way, cell migration and invasion were also suppressed by miR-193a-5p overexpression according to the results of transwell experiments (Figure 2J). Further, we discovered that miR-193a-5p elevation resulted in cell cycle arrest in both the two cervical cancer cells (Supplementary Figure 1D). Nevertheless, the outcomes of flow cytometry analysis and TUNEL experiments indicated that cell apoptotic ability was
Knockdown of FBXL19-AS1 restrains cell proliferation, migration and invasion in cervical cancer. (A) The expression of FBXL19-AS1 in cervical cancer cells was tested through RT-qPCR. (B) Knockdown efficiency of FBXL19-AS1 in C-4-I and C-33A cells was detected via RT-qPCR. (C-D) Cell proliferative capability was estimated by colony formation and EdU staining experiments when FBXL19-AS1 was inhibited. (E) Transwell experiments were carried out to evaluate cell migratory and invasive capabilities after silencing FBXL19-AS1. (F-G) Flow cytometry and TUNEL experiments were adopted to evaluate the influence of knocking down FBXL19-AS1 on cell apoptosis. *P<0.05, **P<0.01.
Figure 2 FBXL19-AS1 sponges miR-193a-5p and overexpression of miR-193a-5p inhibits the progression of cervical cancer. (A-B) The subcellular fractionation and FISH experiments were utilized to detect the location of FBXL19-AS1 in C-4-I and C-33A cells. (C) The expression of possible miRNAs in cervical cancer cells was tested through RT-qPCR. (D) RNA pull-down assay was conducted to verify the interaction between miR-193a-5p and FBXL19-AS1. (E) The overexpression efficiency of miR-193a-5p was detected by RT-qPCR. (F) The binding site between miR-193a-5p and FBXL19-AS1 was predicted by ENCORI. (G) Luciferase reporter experiments were conducted to detect the correlation between miR-193a-5p and FBXL19-AS1. (H-I) Colony formation and EdU experiments were implemented to measure cell proliferation when miR-193a-5p was overexpressed. (J) Transwell assays were conducted to estimate cell migration and invasion after overexpressing miR-193a-5p. (K-L) Cell apoptosis was measured by flow cytometry analysis and TUNEL assay when miR-193a-5p was subjected to upregulation. **P<0.01.
accelerated after overexpressing miR-193a-5p (Figure 2K-L). Overall, FBXL19-AS1 sponges miR-193a-5p, a progression-repressor in cervical cancer.

**PIN1 is the Target of miR-193a-5p in Cervical Cancer**

In order to further investigate the downstream molecules, we began to find the target genes of miR-193a-5p. After searching on ENCORI database based on following conditions: CLIP-Data ≥2, Degradome-Data≥1, pan-Cancer ≥10 and programNum ≥1), we discovered 5 potential genes (CARD19, FDFT1, PIN1, INO80Eand REPIN1) targeted by miR-193a-5p. Thereafter, RT-qPCR was conducted to measure the influence of upregulated miR-193a-5p on the expression of above targets. The results presented that the expression of PIN1 (peptidylprolyl cis/trans isomerase, NIMA-interacting 1) was visibly inhibited by miR-193a-5p enhancement, while that of others almost unchanged (Figure 3A). Then, we intended to inhibit miR-193a-5p expression in the two cells by transfecting with miR-193a-5p inhibitor, and examined the interference efficiency using RT-qPCR. The results indicated that miR-193a-5p expression was evidently declined by an miR-193a-5p inhibitor (Figure 3B). Further, we discovered that the expression of PIN1 was ascended in response to miR-193a-5p deficiency (Figure 3C), but declined in face of FBXL19-AS1 knockdown (Figure 3D). In addition, it was unveiled that the expression of PIN1 was heightened in cervical cancer specimens compared to adjacent non-tumor ones (Supplementary Figure 1E), as well as in cervical cancer cells relative to normal controls (Figure 3E). Following, RIP experiments were implemented and the outcomes displayed that FBXL19-AS1, miR-193a-5p and PIN1 were co-precipitated by anti-Ago2, proving their existence in RNA-induced silencing complexes (RISCs) (Figure 3F). In Figure 3G, we displayed the binding sites between miR-193a-5p and PIN1 which were predicted by ENCORI. Furthermore, luciferase reporter experiment results showed that only the luciferase activity of PIN1 3’UTR-WT was evidently declined when miR-193a-5p was upregulated (Figure 3H). Moreover, the outcomes of RNA pull-down experiments also proved the combining relationship between miR-193a-5p and PIN1 (Figure 3I). Subsequently, we evaluated the function of PIN1 in cervical cancer cellular behaviors after validating the successful decline of PIN1 expression by sh-PIN1#1/2 (Figure 3J). As anticipated, we found that loss of PIN1 could hinder cell proliferation, migration and invasion (Figure 3K-M). In depth, knockdown of PIN1 in cervical cancer cells could induce cell cycle arrest (Supplementary Figure 1F), and boost apoptosis (Figure 3N-O). In sum, PIN1 that serves as a tumor-accelerator is the downstream of FBXL19-AS1/miR-193a-5p signaling in cervical cancer.

**FBXL19-AS1 Accelerates Cervical Cancer Progression via Regulating PIN1**

In order to examine whether FBXL19-AS1 accelerated cervical cancer progression via regulating PIN1, we conducted following rescue experiments. Firstly, we overexpressed PIN1 in C-4-1 and C-33A cells and tested the overexpression efficiency of PIN1 through RT-qPCR (Figure 4A). Then, we implemented colony formation and EdU experiments to evaluate the influence of overexpressed PIN1 on the proliferation of FBXL19-AS1-silenced cells. The outcomes indicated that cell proliferation restrained by silenced FBXL19-AS1 was then reversed by overexpression of PIN1 (Figure 4B-C). Also, transwell experiments were carried out and the outcomes demonstrated that the inhibited cell migration and invasion caused by the lack of FBXL19-AS1 could be recovered when PIN1 was upregulated (Figure 4D). Additionally, we revealed that cell cycle arrested by depleted FBXL19-AS1 was propelled under PIN1 elevation (Supplementary Figure 1G). Furthermore, it was proved that the promoting influence of FBXL19-AS1 suppression on cell apoptosis was offset when augmenting PIN1(Figure 4E-F). Taken together, FBXL19-AS1 accelerates cervical cancer progression via regulating PIN1.

**Discussion**

Cervical cancer is one of the most common gynecological malignant tumors, and it is a major hidden danger to women’s health in the world. So far, a large number of researches have confirmed that assorted cancers are associated with the maladjusted lncRNAs, which means that the variation on the expression of lncRNAs influences the process of tumor formation. Similarly, cervical cancer, as a cancer with high incidence, has been discovered to be tightly associated with lncRNAs by a crowd of scholars. For instance, GAS5 restrains the development of cervical cancer through sponging miR-196a and miR-205.16 PVT1 epigenetically silences miR-195 and regulates EMT in cervical cancer.17 Also, SNHG20 strengthens the proliferative capability of cervical cancer cells by miR-140-5p/ADAM10 axis.18 Although lots of lncRNAs have been searched in cervical cancer, the functions of many other lncRNAs in cervical cancer still need to be further
PIN1 is the target of miR-193a-5p in cervical cancer. (A) The expression of indicated genes was detected via RT-qPCR when miR-193a-5p was overexpressed. (B) Interference efficiency of miR-193a-5p was detected by RT-qPCR in C-4-I and C-33A cells. (C-D) The expression of PIN1 was tested via RT-qPCR after miR-193a-5p or FBXL19-AS1 were silenced. (E) The expression of PIN1 in cervical cancer cells was tested via RT-qPCR. (F) RIP experiment was utilized to detect the co-existence of FBXL19-AS1, miR-193a-5p and PIN1 in RISCs. (G) The binding sites between miR-193a-5p and PIN1 predicted by ENCORI. (H-I) Luciferase reporter and RNA pull-down experiments were implemented to prove the interplay between miR-193a-5p and PIN1. (J) The knockdown efficiency of PIN1 was tested via RT-qPCR. (K-L) Colony formation and EdU experiments were carried out to test cell proliferation when PIN1 was inhibited. (M) Transwell experiments were implemented to test cell migration and invasion after silencing PIN1. (N-O) Flow cytometry and TUNEL experiments were utilized to test cell apoptosis when PIN1 was subjected to inhibition. *P<0.05, **P<0.01.
FBXL19-AS1 accelerates cervical cancer progression via regulating PIN1. (A) The overexpression efficiency of PIN1 in C-4-I and C-33A cells was tested by RT-qPCR. (B-C) Colony formation and EdU experiments were implemented to evaluate the influence of silencing FBXL19-AS1 together with overexpressing PIN1 on cell proliferation. (D) Transwell experiments were utilized to measure the influence of overexpressing PIN1 on the migration and invasion of FBXL19-AS1-inhibited cells. (E-F) Flow cytometry analysis and TUNEL assay were conducted to detect cell apoptosis in different groups. \(^{**} P<0.01.\)
 unearthed. *FBXL19-ASI* has been unveiled to be highly expressed in osteosarcoma cells and to facilitate malignancy in this cancer.\(^{13}\) Nevertheless, the specific function and mechanism of *FBXL19-ASI* in cervical cancer are still in an unknown state. In our research, we discovered that the expression of *FBXL19-ASI* was singularly strong in cervical cancer tissues and cells. In recent years, lncRNAs have been reported to be regulated at transcriptional and post-transcriptional levels.\(^{19}\) Further, *FBXL19-ASI* was proved to be post-transcriptionally stabilized by LIN28A in breast cancer.\(^{20}\) Nevertheless, the mechanism whereby *FBXL19-ASI* was upregulated in cervical cancer remains unknown, and this needs to be further focused on in future studies.

Thereupon we took the functional experiments to search the influence of *FBXL19-ASI* silence on the behaviors of cervical cancer cells. Interestingly, we discovered that cervical cancer cell proliferation could be restrained by the lack of *FBXL19-ASI*, which was proved to be attributed to arrested cell cycle and accelerated cell apoptosis under the context of *FBXL19-ASI* inhibition. Meanwhile, we also elucidated that cell migration and invasion capabilities were suppressed when *FBXL19-ASI* was subjected to inhibition. Consequently, we deduced that *FBXL19-ASI* exerted a carcinogenic function in cervical cancer.

In recent years, lncRNAs have been proposed to serve as the sponge of miRNAs, so as to release the controlled mRNAs.\(^{21}\) For example, *HOXD-ASI* acts as a ceRNA for *SOX4* to accelerate the development of liver cancer.\(^{22}\) Besides, *UICLM* expedites colorectal cancer progression through serving as a sponge for *miR-215* to boost *ZEB2* expression.\(^{23}\) Importantly, whether certain lncRNA could function as a ceRNA primarily depends on its cellular position. In other words, nuclear lncRNAs always regulate pre-transcription or transcription, while cytoplasmic lncRNAs often function as a ceRNA by sponging miRNAs to indirectly regulate target mRNA expression at the post-transcriptional level. In our research, we found that the distribution of *FBXL19-ASI* was mostly in the cytoplasm of cervical cancer cells. Consequently, we conjectured that *FBXL19-ASI* worked by the ceRNA mechanism. Hence, we discovered *miR-193a-5p* as the downstream sponged by *FBXL19-ASI* in cervical cancer. Further, *miR-193a-5p* was indicated to hamper cell proliferation, migration and invasion in cervical cancer, consistently as it did in other cancer types like colon cancer,\(^{24}\) osteosarcoma,\(^{25}\) and gastric cancer.\(^{26}\)

Subsequently, we discovered that *PIN1* was the target of *miR-193a-5p*. *PIN1* has been reported to expedite the progression of hepatocellular carcinoma,\(^{27}\) esophageal squamous-cell carcinoma\(^{28}\) and prostate cancer.\(^{29}\) In our study, we proved that *PIN1* was the downstream of *FBXL19-ASI/miR-193a-5p* pathway in cervical cancer. Besides, silencing *PIN1* mitigated the oncogenic behaviors of cervical cancer cells, and the findings supporting *PIN1* as a cancer-promoter in this tumor was consistent with a former study.\(^{30}\) Moreover, rescue experiments demonstrated that overexpressing *PIN1* could reverse the influences of silenced *FBXL19-ASI* on cervical cancer cellular functions. Previously, *PIN1* has been suggested to have roles in cell cycle control,\(^{31}\) regulation of PI3K/AKT and Wnt/β-catenin pathways,\(^{32}\) or modulation of Hippo signaling.\(^{33}\) More importantly, several reports revealed that *PIN1* also affects cyclin D1 expression and Wnt/β-catenin pathway in cervical cancer,\(^{34,35}\) which might be the downstream mechanism underlying the contribution of *FBXL19-ASI/miR-193a-5p/PIN1* axis to cervical cancer development.

**Conclusions**

All in all, our research unmasked that *FBXL19-ASI* accelerates cell growth, migration and invasion in cervical cancer by sponging *miR-193a-5p* to augment *PIN1*, which provides a new direction for treating patients with cervical cancer.

**Data Sharing Statement**

Research data have been presented within this manuscript and the Additional file.

**Ethics Approval and Informed Consent**

This work was conducted under the support of the Ethics Committee of Yijishan Hospital of Wannan Medical College. All cervical cancer patients enrolled in signed the informed consents before this research.

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**Author Contributions**

Conceptualization: Su Wan  
Methodology: Guantai Ni
Disclosure

The authors declare that they have no competing interests in this work.

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