The long noncoding RNA FTH1P3 promotes the proliferation and metastasis of cervical cancer through microRNA-145

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Abstract. Emerging evidence has revealed that long noncoding RNAs (lncRNAs) play crucial roles in the development and progression of tumors. The present study aimed to examine the roles and illustrate the underlying mechanisms of lncRNA ferritin heavy chain 1 pseudogene 3 (FTH1P3) in cervical cancer. The expression of lncRNA FTH1P3 and microRNA-145 (miRNA-145 or miR-145) in human cervical cancer samples and cervical cancer cell lines was detected by qRT-PCR (reverse transcription-quantitative polymerase chain reaction). FTH1P3 overexpression, siRNA plasmid, hsa-miR-145 mimic or hsa-miR-145 inhibitor were transfected. The target of FTH1P3 was predicted by bioinformatics analysis and validated by luciferase assay. Statistical significance analysis was performed by SPSS software. The results revealed that FTH1P3 was significantly upregulated in cervical cancer tissues compared with normal tissues. Increased expression of FTH1P3 was revealed in human cervical cancer cell lines compared with cervical normal epithelial cells. Downregulation of FTH1P3 inhibited cell proliferation, invasion and migration, and promoted apoptosis in cervical cancer cells. miR-145 was predicted and validated as a direct target of FTH1P3. Moreover, FTH1P3 siRNA partially attenuated the effects of the miR-145 inhibitor on cell viability and mobility in cervical cancer cells. The present results demonstrated that lncRNA FTH1P3 functioned as a promoting factor in cervical cancer by targeting miR-145.

Introduction

Cervical cancer ranks as the 4th most common female malignancy and the 2nd most common cancer in developing countries, which affects women globally (1-3). Surgery or a combination of chemotherapy and radiotherapy are the routine treatments for cervical cancer patients (4-7). However, the malignancy is largely incurable for the patient. The early stage of cervical cancer is predisposed to develop progressively into an advanced stage. Therefore, early detection and prognosis are crucial. It is critical to understand the molecular mechanisms of cervical cancer development and identify novel biomarkers for the early detection and treatment of cervical cancer.

Long non-coding RNAs (lncRNAs) emerged as important molecules involved in normal development and in tumorigenesis (8). Growing evidence has revealed that lncRNAs are involved in the aberrant pathological development of cervical cancer (9). For example, reduced lncRNA MEG3 (maternally expressed 3) is associated with increased cervical cancer cell proliferation (10). LncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) markedly increased after HPV infection in cervical cancer (11). FTH1P3 belongs to long non-coding RNAs, and is a member of the ferritin heavy chain (FHC) gene family located at chromosome 2p23.3 (12). Zhang et al revealed that FTH1P3 is a promoting factor in the growth and progression of OSCC by stimulating cell proliferation, migration, and invasion (13). However, the role of FTH1P3 in cervical cancer has not yet been elaborated.

MicroRNAs (miRNAs or miRs), ~18-25 nucleotides, are another component of the noncoding RNA family. They participate and regulate gene expression through a post-transcriptional pattern (14-16). miRNAs are aberrantly expressed in various types of malignancies and function either as oncogenes or as tumor suppressors (17-19). Accumulating evidence has demonstrated that miRNAs regulated various carcinogenesis processes, including cell maturation, cell proliferation, migration, invasion, autophagy, apoptosis, and metastasis (20-26). Therefore, miRNAs have a large potential to serve as promising markers in the diagnosis, prognosis, and personalized targeted therapies (22-26). miR-145 plays a tumor-suppressive role in several types of cancer, such as gastric (27), hepatic (28), breast (29), non-small cell lung (30), and cervical cancer (31). Zhou et al reported that miRNA-145...
functions and associations between FTH1P3 and miR-145 in cervical cancer. In the present study, the study aimed to determine whether FTH1P3 can regulate miR-145 in cervical cancer cells and tissues were demonstrated. The present findings may further provide a therapeutic target for the treatment and diagnosis of cervical cancer patients.

Materials and methods

Patients and materials. Fifty-two cervical cancer tissues (all females, 44-69 years, 55.7±5.5 years) were collected from patients who underwent surgery at our hospital from March 2015 to March 2017. The samples of patients with other major diseases were excluded. Normal cervix healthy tissues were used as a normal control. The disected patient surgical specimen was immediately transferred to the surgical laboratory. Written consent was signed from each patient. The implemented protocol was approved by the Human Ethics Committee of Gansu Provincial Cancer Hospital. All of the tissues were either fixed in 4% PFA (paraformaldehyde) or were snap-frozen in liquid nitrogen for later use. Cervical cancer patients (52) were divided into high-and low-expression groups according to the median values of FTH1P3 (fold change=4.32) and miR-145 (fold change=0.41) expression.

Cell culture. Human cervical cancer cell lines (SiHa, HeLa, CaSki, and C4-1) and normal cervical epithelial cells (Ect1/E6E7) were purchased from Cell Bank of the Chinese Academy of Sciences (Shanghai, China). The cells were cultured in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with 10% heat-inactivated fetal bovine serum (Hi-FBS) and 100 U/ml penicillin-streptomycin (10,000 U/ml; all from Thermo Fisher Scientific, Inc.). Cells were maintained at 37°C, and 5% CO2 in a humidified incubator.

Bioinformatics analysis. The binding candidates of FTH1P3 were predicted using miRcode software (http://www.mircode.org/). All parameters were default.

Quantitative real-time reverse transcription-PCR (qRT-PCR). Total RNA was extracted using TRIzol™ reagent (Thermo Fisher Scientific, Inc.). RNA concentrations were measured using an ND-1000 UV-Vis Spectrophotometer (Thermo Fisher Scientific, Inc.), and the quality was monitored by an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.). qRT-PCR was carried out using a TaqMan miRNA Assay according to the manufacturer's protocol (Applied Biosystems; Thermo Fisher Scientific, Inc.). The amplification conditions were: 40 cycles of 15 sec at 95°C and 1 min at 60°C. The expression levels of miR-145 and FTH1P3 were normalized by U6.

Cell transfection. The hsa-miRNA-145 mimic/miRNA-145 scramble (negative-control for miRNA-145 mimic) and hsa-miRNA-145 inhibitor/miRNA-145 scramble (negative-control for miRNA-145 inhibitor) were designed and synthesized from Shanghai GeneChem Co., Ltd. The FTH1P3 siRNAs were synthesized by Invitrogen; Thermo Fisher Scientific, Inc. FTH1P3 siRNA (targeted region) sequences were: siRNA_1, CGCCUGUAUCCAGCCUCA; siRNA_2, AUAGCGUAACUUCCUCUAA; siRNA_3, CGUAACUUCUCUCAAGCACAACC. pcDNA-3.1(+) -FTH1P3 (IncRNA-FTH1P3). The overexpression plasmid of FTH1P3 was purchased from Shanghai GeneChem Co., Ltd. A transfection assay was conducted using a Lipofectamine 3000 kit (Thermo Fisher Scientific, Inc.). The sequence of miRNA-145 mimic, miRNA-145 inhibitor or respective control were as follows: miRNA-145 mimic: 5'-UCCCUAGGACCCUUUUGACUG-3' (sense) 3'-AGG GAUUCUGGGGAAAUCUGAC-5' (antisense); miRNA-145 scramble (negative-control for miRNA-145 mimic): 5'-CUA UCCCAGGUGCUUGACC-3' (sense) 3'-GAUAGG UGGUCAAAGCAGUGG-5' (antisense); miRNA-145 inhibitor: 5'-CAGGUAAAAGGGCUUAGGGA-3'; miRNA-145 scramble (negative-control for miRNA-145 inhibitor): 5'-GUCCAGAGAAAUCUCUGAAGG-3'.

CCK-8 analysis. Cell Counting Kit-8 (CCK-8) was used to determine the cell viability in cell proliferation and cytotoxicity. Briefly, human cervical cancer cells were seeded in a 96-well plate (5x10^3 cells/well) overnight. After cell confluence reached 70-80%, the miR-145 mimic or FTH1P3 siRNA was transfected into the cells using Lipofectamine 3000 kit (Thermo Fisher Scientific, Inc.). After 2 days, the CCK-8 reagent (5 mg/ml) was directly loaded into each well and incubated in the dark for 2 h at 37°C followed by measurement of the absorbance at OD 490 nm. Each measurement was repeated in triplicate.

Flow cytometric analysis. After transfection with the desired plasmid or negative control in 6-well plates, the cells were cultured for 48 h. Annexin V-FITC (3 µg/ml) and propidium iodide (5 µg/ml) were incubated with cells for 30 min at RT shielded from the light. Then the cells were collected, filtered and subjected to a BD FACS Aria Fusion Cell Sorter (BD Biosciences) with Cytomics FC 500 with CXP Software (Beckman Coulter, Inc.). The data were quantified with FlowJo software v10.6.1 (FlowJo LLC).

Invasion and migration assays. For the invasion assay, 2x10^4 HeLa cells in FBS-free DMEM were placed in the upper chamber of an insert (8-µm pores; Merck KGaA). Matrigel (Merck KGaA) was employed to pre-coat the membrane of the Transwell chambers. The lower chambers were incubated in culture medium supplemented with 10% FBS for 24 h. Then, the HeLa cells on the upper surface were scraped and washed away. Subsequently, the cells on the lower surface were fixed and stained with Diff-Quik staining kit (Sysmex Corp.) at RT for 2 h. The invaded cells in the lower surface of membrane
were also fixed and stained with Diff-Quik kit (Sysmex Corp.). The invaded cells were imaged and counted under a BX43 Upright Microscope (Olympus Corp.) at a magnification of x200 from 10 random fields in each well. For the migration assay, 1.5x10⁶ cells/well were seeded in 6-well plate for overnight culture until the cells reached an ~90% confluence. The scratch was generated using a 200-µl sterile pipet tip in the hood. After aspiration and washing, fresh complete medium was added. Then the cells were cultured for another 24 h. Cell migration was monitored under a BX43 Upright Microscope (Olympus Corporation) and images were captured at 0 and 24 h.

Luciferase reporter assays. The fragments of the 3'-UTR of FTH1P3 were amplified with Phusion® High-Fidelity DNA Polymerase (NEB, Inc.) from human genomic DNA. After gel extraction, the PCR product was cloned into the multiple cloning sites located downstream of the firefly luciferase coding region of the pGL3 Luciferase Reporter Vectors (Promega, USA). The recombinant vector was named pMIR-FTH1P3-wild-type. The mutations in the miR-145 binding sites were introduced using Site-Directed Mutagenesis (Thermo Fisher Scientific, Inc.). The mutation sequence was confirmed by sequencing (Shengong Bio Company). The resulting vector was designated as pMIR-BCYRN-mutant. pMIR-FTH1P3 or pMIR-FTH1P3-mut vector and miR-145 mimic or miR-145 inhibitor were co-transfected into a 24-well plate according to the Lipofectamine 3000 kit (Thermo Fisher Scientific, Inc.). After 36 h, the cells were harvested and lysed (lysis buffer; Promega Corporation). The luciferase reporter gene assay was detected by the GloMax® 20/20 Luminometer (Promega Corporation) according to the instructions.

Statistical analysis. Statistical analysis was performed using SPSS 13.0 (Pearson). All data were expressed as the mean ± standard deviation (SD). Correlation between FTH1P3 and miR-145 expression was determined using Spearman’s correlation analysis. Differences were assessed by two-sample t-test or chi-square test or one-way ANOVA and Fisher’s LSD post hoc tests. P<0.05 was considered to indicate a statistically significant difference.

Results

**FTH1P3 expression is upregulated in cervical cancer tissues and cell lines.** To investigate the expression of lncRNA FTH1P3 in cervical cancer tissues, total RNA was extracted from 52 cervical cancer tissues and paired adjacent non-cancerous normal tissues. qRT-PCR was carried out to detect FTH1P3 mRNA expression level. As revealed in Fig. 1A, FTH1P3 expression was significantly upregulated in cervical cancer tissues compared to paired adjacent non-cancerous normal tissues (P<0.01). Furthermore, the correlation between FTH1P3 expression and pathological parameters of cervical cancer patients were evaluated. The results of Table I revealed that FTH1P3 upregulation in cervical cancer tissues was significantly correlated with crucial clinicopathological factors, including tumor size (P=0.014), lymph node metastasis (P=0.005) and FIGO stage (P=0.002). However, there was no significant difference between FTH1P3 expression and other clinicopathological factors, such as age, menopause, depth of invasion and CEA level. Next, the expression of FTH1P3 in cervical normal epithelial cells (ECT1/E6E7) was further investigated. As revealed in Fig. 1B, it was determined that FTH1P3 expression was significantly increased in cervical cancer cell lines (HeLa, SiHa, CaSki and C4-1) compared to cervical normal epithelial cells (ECT1/E6E7). Notably, higher expression of FTH1P3 was observed in the HeLa and SiHa cell lines. Therefore, HeLa and SiHa cells were selected for further studies.

**FTH1P3 silencing inhibits cell viability and motility in cervical cancer cell lines.** To determine the roles of FTH1P3 in cervical cancer, siRNA of FTH1P3 was constructed and transfected into HeLa and SiHa cells. As revealed in Fig. 2A, siRNA of FTH1P3 significantly suppressed the expression of FTH1P3 in both HeLa and SiHa cells (P<0.01). Furthermore, downregulation of FTH1P3 by siRNA induced significant apoptosis in HeLa and SiHa cells (Fig. 2B and C; P<0.01). CCK-8 assay also revealed that FTH1P3 downregulation significantly inhibited the proliferation of HeLa and SiHa cells (Fig. 2D; P<0.01). In addition, the effects of FTH1P3 on cell motility were examined by Transwell and wound-healing assays. The results revealed that the number of invasive cells...
was significantly reduced after transfection with FTH1P3 siRNA (P<0.01; Fig. 3A and B). Similarly, a significantly decreased closure rate of scratch wounds was observed in the FTH1P3 siRNA group compared with the siRNA scramble group in HeLa and SiHa cells (P<0.05; Fig. 3C and D).

**FTH1P3 is identified as a potential target of miR-145.** Bioinformatics analysis with miRcode software was performed and it was revealed that human miR-145 (hsa-miR-145) was a potential binding candidate of FTH1P3 (Fig. 4A). As revealed in Fig. 4B, FTH1P3 overexpression plasmid significantly increased the expression of FTH1P3 in both HeLa and SiHa cells compared with the negative control (P<0.01). After transfection of human miR-145 mimic, a significant increase of miR-145 expression in HeLa and SiHa cells was observed (Fig. 4C; P<0.01). The overexpression of FTH1P3 by plasmid transfection could significantly reduce the expression of miR-145, while miR-145 expression was inversely increased due to the downregulation of FTH1P3 (Fig. 4C and D; P<0.05). In addition, a luciferase reporter assay revealed that miR-145 mimic significantly suppressed the luciferase activities of FTH1P3-WT reporter vector. Conversely, after transfection with FTH1P3-MUT and the miRNA-145 mimic, the luciferase activities between these two cells were nearly comparable with that in the control cells (Fig. 4E; P<0.01). These data indicated that FTH1P3 was a potential target of miR-145.

**miRNA-145 is downregulated in cervical cancer.** To investigate the role of miR-145 in cervical cancer progression, miR-145 expression in cervical cancer tissues and non-malignant tissues was detected by qRT-PCR. As revealed in Fig. 5A, miR-145 expression in cervical cancer tissues was significantly downregulated compared with the non-malignant tissues (P<0.01). Consistently, the expression of miR-145 in five assessed cervical cancer cell lines were all significantly lower than that in normal cervical epithelial cells (Ect1/E6E7) (P<0.01; Fig. 5B). Moreover, the downregulated expression of miR-145 demonstrated a significant association with tumor size (P=0.035), lymph node metastasis (P=0.011) and FIGO stage (P=0.017). Spearman's correlation analysis revealed that miR-145 expression was inversely associated with FTH1P3 expression in cervical cancer tissues (Table II, r= -0.265, P=0.002), indicating that upregulated FTH1P3 expression in cervical cancer was correlated with downregulated miR-145 expression.

**Effects of miR-145 inhibitor on the cell proliferation, invasion, and migration in cervical cancer cells.** As illustrated in Fig. 6A, the transfection of miR-145 inhibitor caused a
significant reduction of miR-145 in cervical cancer cells (P<0.01). Moreover, downregulation of FTH1P3 significantly inhibited the proliferation, invasion and migration abilities and promoted apoptosis in HeLa and SiHa cells (Figs. 6 and 7). Notably, the miRNA-145 inhibitor could enhance the cell proliferation, invasion and migration in cervical cancer cells compared to the RNA scramble group, while FTH1P3 siRNA revealed a significant bucking effect for miRNA-145 inhibitor in HeLa and SiHa cells compared to cells transfected with FTH1P3 siRNA+ RNA scramble group (Figs. 6 and 7).

Discussion

The present study revealed that FTH1P3 was highly expressed in malignant cervical cancer tissues and cell lines. Downregulation of FTH1P3 significantly inhibited cell proliferation, invasion and migration, and promoted apoptosis in cervical cancer cells. The FTH1P3 and miR-145 axis was demonstrated, to have reciprocal repression functionally. These results demonstrated that lncRNA FTH1P3 functioned as a promoting factor in cervical cancer by targeting miR-145.

FTH1P3 expression was revealed to be enhanced in uveal melanoma cell lines and tissues, and FTH1P3 upregulation promoted cell proliferation, the cell cycle and migration in uveal melanoma by targeting miR-224-5p (34). FTH1P3 was abundantly expressed in paclitaxel-resistant breast cancer tissue and cells (35). FTH1P3 was revealed to play a role as a competing endogenous RNA (ceRNA) to sponge miR-206 and increase ABCB1 (ATP-binding cassette subfamily B member 1) protein expression (35). FTH1P3 was overexpressed in oral squamous cell carcinoma (OSCC) tissues (13). Overexpression of FTH1P3 significantly promoted OSCC cell growth, while the cell growth was inhibited after knockout of FTH1P3 (13). In the present study, it was also revealed that FTH1P3 was highly expressed in malignant cervical cancer tissues and
Figure 3. Downregulation of FTH1P3 inhibits the cell invasion and migration in cervical cancer cell lines. (A and B) The invasive capability of cervical cancer cells was detected by Transwell assay. (C and D) The migration of cervical cancer cells was measured by wound-healing assays. *P<0.05 and **P<0.01 compared to the FTH1P3 scramble group. FTH1P3, ferritin heavy chain 1 pseudogene 3.

Figure 4. miR-145 is identified as a potential target of FTH1P3. (A) Alignment of potential FTH1P3 base pairing with miR-145 as identified by miRcode. (B) Cervical cancer cells were transfected with the overexpression plasmid of FTH1P3 [pcDNA-3.1(+)-FTH1P3] or negative control. Expression of lncRNA FTH1P3 was measured by qRT-PCR. (C and D) Cervical cancer cells were transfected with lncRNA FTH1P3 or siRNA FTH1P3 combined with miR-145 mimic or mimic control. Expression of miR-145 was assessed by qRT-PCR. (E) Wild-type (lncR-FTH1P3-WT) or mutant (lncR-FTH1P3-Mut) luciferase reporter and/or miR-145 mimic were co-transfected into cervical cancer cells to determine the luciferase activity. Data are presented as the means ± SD of three independent experiments. *P<0.05 and **P<0.01 compared with lncRNA-FTH1P3 WT group. MicroRNA-145, miR-145; FTH1P3, ferritin heavy chain 1 pseudogene 3.
human cervical cancer cell lines (SiHa, HeLa, CaSki and C4-1) (Fig. 1). Collectively, these studies indicated that FTH1P3 may function as an oncogene and be favorable to tumorigenesis and progression of various cancers.
Table II. Correlation between FTH1P3 expression and miR-145 expression in cervical cancer patients.

| FTH1P3 expression | n   | Low (n, %) | High (n, %) | r_s | χ²   | P-value |
|-------------------|-----|------------|-------------|-----|------|---------|
| Low (n, %)        | 26  | 8          | 18          | -0.265 | 9.102 | 0.002   |
| High (n, %)       | 26  | 18         | 8           |       |      |         |

FTH1P3, ferritin heavy chain 1 pseudogene 3.

Figure 7. Effects of miR-145 inhibitor on cell invasion and migration in FTH1P3-siRNA-treated cervical cancer cells. (A and B) Cell invasion was detected using Transwell assay. (C and D) Cell motility was detected using wound healing assay. *P<0.05 and **P<0.01 compared to the corresponding group. MicroRNA-145, miR-145; FTH1P3, ferritin heavy chain 1 pseudogene 3.
Emerging studies have indicated that miR-145 is implicated in a number of cancers, such as breast and cervical cancer, chondrosarcoma, colorectal and endometrial cancer, esophageal squamous cell carcinoma as well as gallbladder carcinoma (32,36,37), and its downregulation inhibited tumor proliferation, migration, invasion, metastasis, progression, and angiogenesis via distinct signaling pathways. For instance, miR-145 downregulation inhibited invasion of bladder cancer cells by targeting PARK1 (38). Hsa-mir-145 downregulation was closely associated with aggressive progression and poor prognosis in human cervical cancer (31). miR-145 directly targeted p70S6K1 in cancer cells to inhibit colon cancer tumor growth and angiogenesis (39), miR-145 suppressed cell migration and invasion by targeting paxillin in human colorectal cancer cells (40). In endometrioid carcinomas, miR-145 and miR-143 were downregulated and associated with DNA methyltransferase 3B overexpression and worse prognosis (41). In the present study, miRNA-145 was predicted as a potential binding candidate of FTH1P3. Through in vitro transfection with IncRNA FTH1P3 or siRNA FTH1P3 combined with miR-145 mimic and mutant (IncRNA-FTH1P3-Mut) luciferase reporter, the association between FTH1P3 and miR-145 was further confirmed.

Moreover, it was revealed that miRNA-145 inhibitor could enhance cell proliferation, invasion, and migration in cervical cancer cells, while FTH1P3 siRNA exhibited a significant bucking effect for miRNA-145 inhibitor in HeLa and SiHa cells. FTH1P3 siRNA partially attenuated the effects of the miR-145 inhibitor on cell viability and mobility in cervical cancer cells, indicating that the FTH1P3-miR-145 axis functioned inversely in the cervical tumor.

It is worth noting that this study is limited by the small sample size. In addition, only in vitro cell experiments were performed. Future studies with a larger sample size and animal model experiments should be included to further confirm the conclusions.

In conclusion, the present study demonstrated the FTH1P3-miR-145 axis was involved in cell proliferation, invasion, migration, apoptosis, viability, and mobility in cervical cancer cells. These results may provide a potential therapeutic target and strategy to impede the progression of cervical cancer.

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Availability of data and materials
The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions
RL designed and conceived this study and performed the experiments and analysis of the data and wrote and supervised the manuscript. QZW performed the research and manuscript revision. Both authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate
The present study was approved by the Ethics Committee of Gansu Provincial Cancer Hospital. All patients and healthy volunteers provided written informed consent prior to their inclusion in the study.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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