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Long non-coding RNA 00152 promotes cell proliferation in cervical cancer via regulating miR-216b-5p/HOXA1 axis

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Abstract. – OBJECTIVE: Several studies demonstrated that aberrant lncRNA expression contributes to cervical cancer (CC) development and progression. LINC00152, a novel lncRNA, has been identified as an oncogene involved in various cancers. In the present study, we aim to investigate the expression pattern, clinical significance, potential functional roles, and regulatory mechanism of LINC00152 in CC.

PATIENTS AND METHODS: The transcription levels of LINC00152, miR-216b-5p, and HOXA1 in CC tissues and cell lines were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). LINC00152 knockdown in CC cells was conducted by transfecting the LINC00152-specific siRNA. The cell proliferation ability was evaluated by the Cell Counting Kit-8 (CCK-8) assay. Cell cycle and apoptosis analysis were assessed by flow cytometry. The target relation among LINC00152, miR-216b-5p, and HOXA1 were measured using the dual-luciferase reporter assay. The protein levels of HOXA1 in CC cells were determined by Western blot.

RESULTS: LINC00152 was up-regulated in CC tissues and cell lines. The high expression level of LINC00152 was positively correlated with poor prognosis and histologic grade in CC. The silence of LINC00152 could inhibit the proliferation of CC cells through inducing the cell cycle arrest at G0/G1 phase and promote apoptosis *in vitro*. Mechanically, we demonstrated that LINC00152 could modulate the proliferation of CC cells through elevating HOXA1 expression level via sponging miR-216b-5p based on bioinformatics analysis and experimental validation.

CONCLUSIONS: Our findings revealed a novel molecular mechanism underlying LINC00152 modulating CC progression through the miR-216b-5p/HOXA1 pathway, suggesting that LINC00152 might potentially act as an effective diagnostic marker and therapeutic target for cervical cancer.

Key Words:
LINC00152, Cervical cancer, Cell proliferation, MiR-216b-5p, HOXA1.

Introduction

Cervical cancer (CC) is one of the most common malignant carcinomas in the female reproductive system, causing a large proportion of cancer-related mortality worldwide, especially in low- and middle- income countries[1]. Despite great advancements have been made in diagnostic and therapeutic approaches including the Pap test for early screening, surgery excision, radiotherapy, as well as chemotherapy, the prognosis of patients with CC remains poor due to recurrence and metastasis[2]. Therefore, there is an urgent need to elucidate the molecular mechanisms underlying the development and progression of CC to identify and provide effective diagnostic biomarkers and therapeutic targets for therapy or early detection of CC.

Long non-coding RNAs (lncRNAs) represent a class of transcriptional RNA molecules that are longer than 200 nucleotides without significant protein-coding capacity and can be localized in both the nucleus and the cytoplasm[3]. LncRNA, as critical regulator, has been found to exert important roles in various cancers through affecting diverse cellular processes, modulating gene expression at the epigenetic, transcriptional, and posttranscriptional levels[4]. For cervical cancer, accumulating evidence has shown that dozens of lncRNAs are dysregulated in CC and implicated in multiple tumor biological behaviors involving growth, invasion, and metastasis through complicated mechanisms such as forming the lncRNA-microRNA-mRNA competing endogenous RNA (ceRNA) network[5]. For instance, a recent study[6] demonstrated that HCP5, an up-regulated lncRNA in CC, could promote cell proliferation by competitive binding with miR-15a as a molecular sponge to elevate the expression of MACC1, a modulator of tyrosine kinase-de-

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pendent signaling pathways. LINC00152 (also known as CYTOR), an intergenic lncRNA located at chromosome region 2p11.2, was transcribed from the intronic region of RMND5A that a coding gene[7]. In recent years, a number of studies have demonstrated that LINC00152, as an oncogene, was significantly up-regulated in multiple cancer types and associated with poor prognosis, as well as tumor progression[8]. For example, in liver cancer, LINC00152 could promote cell proliferation via the miR-193a/b-3p/CCND1 axis and mTOR signaling pathway[9]; in lung cancer, LINC00152 could promote cell proliferation, invasion, and migration via EGFR/PI3K/AKT pathway[10]; in gastric cancer, LINC00152 could promote cell proliferation and migration via miR-193a-3p/MCL1 and miR-139-5p/PRKAA1 axis[11,12]; in glioma, LINC00152 promotes the proliferation, invasion, and migration of glioma stem cells through miR-103a-3p/FEZF1/CDC25A pathway[13]. However, the expression and functional roles of LINC00152 in cervical cancer remain unknown. In the current study, we aimed to reveal the expression pattern and clinical significance, as well as potential functional roles and regulatory mechanism of LINC00152 in cervical cancer. Our results showed that LINC00152 was up-regulated in CC and associated with poor prognosis. In addition, we demonstrated that knockdown of LINC00152 could inhibit CC cell proliferation through affecting cell cycle progression while promoting apoptosis via modulating miR-216b-5p/HOXA1 pathway.

Patients and Methods

Human Clinical Samples

A total of 20 cervical cancer tissues and their adjacent nontumor tissues were collected from Baoji Central Hospital (Baoji, Shaanxi Province, China). All samples were not subjected to radiotherapy or chemotherapy before collection and frozen into liquid nitrogen as soon as dissected. This study was approved by the Ethics Committee of Baoji Central Hospital. Each patient involved provided written informed consent.

Cell Culture

Human cervical cancer cells (HeLa, CaSki, SiHa, C-33A, SW756) and normal human epidermal cell (HaCaT) were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured in Dulbecco's Modified Eagle's medium (DMEM; Invitrogen, Carlsbad, CA, USA) supplemented with 10% of fetal bovine serum (FBS) and 100 mg/ml penicillin-streptomycin (Invitrogen, Carlsbad, CA, USA). All cells were grown at 37°C in cell incubator with a humidified atmosphere containing 5% CO_2.

Quantitative Real Time-PCR (qRT-PCR)

Total RNA was isolated using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). cDNA for lncRNA/mRNA detection was synthesized with the PrimeScript™ RT Master Mix (Perfect Real Time; TaKaRa, Dalian, China) and cDNA for microRNA detection was synthesized with Mir-X™ miRNA First-Strand Synthesis Kit (Clontech, Mountain View, CA, USA) using total RNA according to the manufacturer's instructions. QRT-PCR reactions were performed using TB Green Premix Ex Taq II (TaKaRa, Dalian, China). The relative fold change in expression was calculated by the $2^{-\Delta\Delta Ct}$ method. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 were used as an endogenous control for lncRNA/mRNA and microRNA detection, respectively. Primers were as follows: LINC00152, 5'-CTGGATGGTCGCTGCTTTTT-3' (forward), 5'-TACATTACGGACTGCCAGGA-3' (reverse); miR-216b-5p, 5'-CTCTGCAGGCAAATGTGAA-3' (forward); HOXA1, 5'- TCCTGGAATACCCCATACTTAGC-3' (forward), 5'- GCACGACTGGAAAGTTGTAATCC-3' (reverse); GAPDH, 5'-CGACTTATACATGGCCTTA-3' (forward), 5'-TTCCGATCACTGTTGGAAT-3'(reverse); U6, 5'-CTCGCTTCGGCAGCACATATACT-3' (forward), 5'-ACGCTTCACGAATTTGCGTGTC (reverse).

siRNAs and Plasmid Transfection

Small interfering RNAs (siRNA) targeting LINC00152, HOXA1 and negative control (NC) were synthesized by Genepharma (Shanghai, China) as the following sequence: si-LINC00152, 5'-UCUAUGUGUCUUAAUCCCUUGUCCU-3'; si-HOXA1, 5'-CAACAAGUACCUUACACGA-3; si-NC, 5'-GACACGCGACUUGUACCAC-3'. MiR-216b-5p mimics/inhibitors and negative control (NC) were purchased from Genepharma (Shanghai, China). The overexpression vector of LINC00152 (pCDNA3.1-LINC00152) and pCDNA3.1 empty vector was also purchased from Genepharma (Shanghai, China). All nucleotides and plasmid mentioned above were transfected into cells using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA).

Cell-Counting Kit-8 (CCK-8) Assay

The CCK-8 assay was performed to evaluate the cell proliferation ability. Briefly, cells (5×10^3 cells/well) were seeded into 96-well plates and cultured with CCK-8 reagent (Dojindo, Kumamoto, Japan) at 37°C and the viability was analyzed at 450 nm using microplate reader.

Cell Cycle and Apoptosis Analysis by Flow Cytometry

For the cell cycle, cells were harvested and fixed with 70% of ethanol at 4°C overnight and stained with propidium iodide (PI) containing Ribonuclease A (Beyotime Biotechnology, Shanghai, China) for 30 min at room temperature and the cell cycle distribution was then analyzed by flow cytometry (BD Biosciences, Franklin Lakes, NJ, USA). For apoptosis, cells were harvested and detected using the Annexin V-FITC Apoptosis Detection Kit (Dojindo, Kumamoto, Japan) by flow cytometry (BD Biosciences, Franklin Lakes, NJ, USA) according to the manufacturer's instructions. The data were analyzed using the FlowJo software (Tree Star, Ashland, OR, USA).

Luciferase Reporter Assay

LINC00152 or HOXA1 sequence containing wild-type (Wt) or Mutant (Mut) miR-216b-5p binding sites was inserted into the pmirGLO reporter vector (Promega, Madison, WI, USA) by Genepharma (Shanghai, China). For luciferase reporter assay, HEK293 cells were co-transfected with the reporter plasmid and miR-216b-5p mimics or pCDNA3.1-LINC00152 vector using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). Luciferase activity was detected using the dual-luciferase reporter assay system (Promega, Madison, WI, USA) after transfection and was normalized to *Renilla* luciferase activity.

Western Blot

Total proteins were extracted by radioimmunoprecipitation assay (RIPA) Lysis and Extraction Buffer (Thermo Fisher Scientific, Waltham, MA, USA). 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed to separate cell lysate proteins and then transferred onto 0.22 μm polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). The membrane was blocked with 5% fat-free milk in Tris-Buffered Saline and Tween 20 (TBST) for 2 h at room temperature and incubated with the primary antibodies at 4°C overnight. Following the incubation with horseradish peroxidase (HRP) labeled the secondary antibodies for 2 h at room temperature, signals were detected by exposure to films with Immobilon Western Chemiluminescent HRP Substrate (Millipore, Billerica, MA, USA). GAPDH was used as an internal control. The antibodies used for Western blot were as follows: anti-HOXA1 (13513-1-AP, Proteintech, Rosemont, IL, USA), anti-GAPDH (ab181602, Abcam, Cambridge, MA, USA), HRP-conjugated Goat Anti-Rabbit IgG (H+L) (SA00001-2, Proteintech, Rosemont, IL, USA).

Statistical Analysis

All data were obtained from three independent experiments and data was expressed by mean ± standard deviation (SD). Data were analyzed with GraphPad Prism software (GraphPad, La Jolla, CA, USA) and Statistical Product and Service Solutions (SPSS) software using Student's *t*-test, one-way ANOVA with Tukey's post-hoc test or Spearman's correlation analysis. Differences were considered statistically significant at $p < 0.05$.

Results

Up-regulated LINC00152 is Associated with Poor Prognosis in Cervical Cancer

To explore the expression status of LINC00152 and its clinical significance in CC, we first evaluated the correlation between the expression level of LINC00152 and prognosis, as well as histologic grade in CC based on TCGA data using online tools including GEPIA (http://gepia.cancer-pku.cn/), OncoLnc (http://www.oncolnc.org), and TANRIC (http://ibl.mdanderson.org/tanric/_design/basic/index.html). GEPIA results showed LINC00152 was significantly up-regulated in cervical squamous cell carcinoma (CESC) (Figure 1A); the survival analysis by OncoLnc indicated that the up-regulation of LINC00152 was closely associated with shorter overall survival in CC patients (Figure 1B); TANRIC results indicated that the expression level of LINC00152 was significantly and positively correlated with the histologic grade (Figure 1C). Next, the up-regulation of LINC00152 was validated in 20 pairs of CC and adjacent non-tumor tissues, as well as five CC cell lines by qRT-PCR. As expected, LINC00152 expression was significantly up-regulated in CC tissue compared to adjacent normal tissues (Figure 1D). Consistently, we found that LINC00152 expression was elevated in all five detected CC

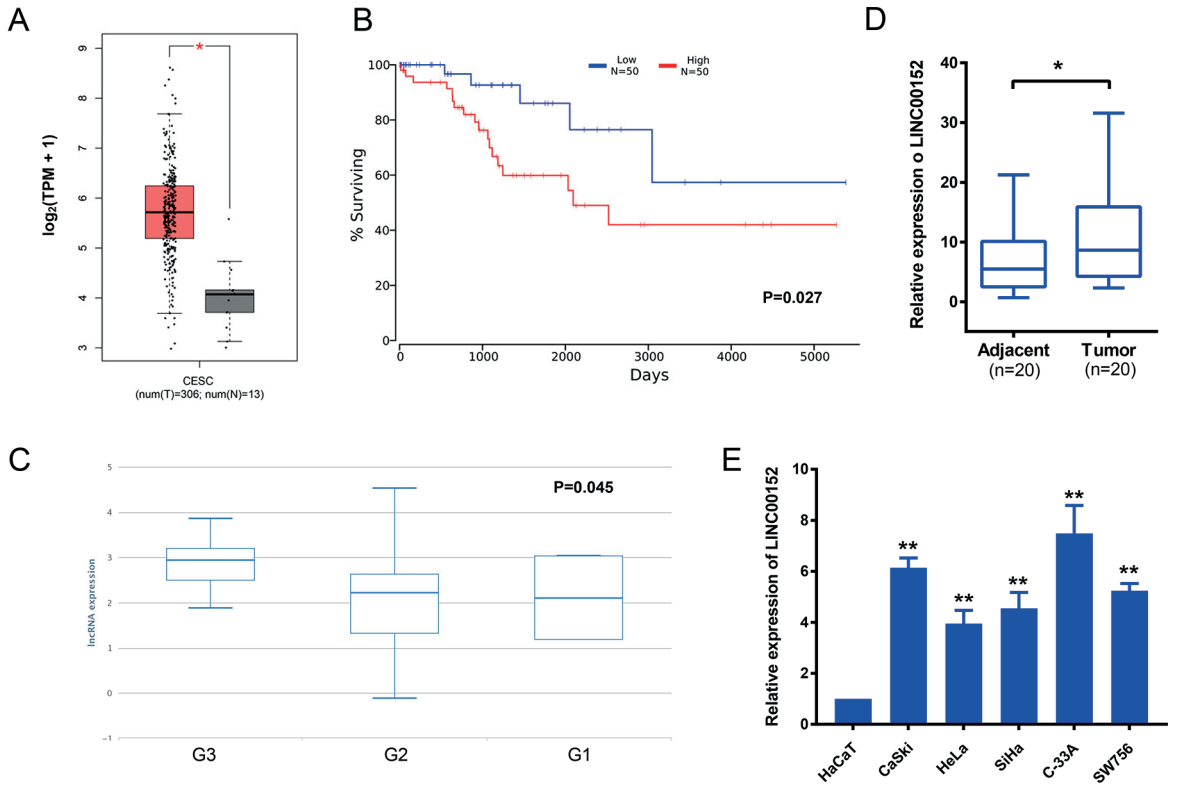

Figure 1. Up-regulated LINC00152 is associated with poor prognosis in cervical cancer (CC). ***A,*** LINC00152 expression in CC (n=306) and non-cancerous (n=13) tissues was analyzed by GEPIA. ***B,*** Association between LINC00152 expression with overall survival was evaluated by OncoLnc. ***C,*** Association between LINC00152 expression with histologic grade was evaluated by TANRIC; G1, G2, and G3 represent the low, intermediate and high grade, respectively. ***D,*** Expression level of LINC00152 was detected in human CC tissues and matched adjacent normal tissues (n = 20) by qRT-PCR. ***E,*** Expression level of LINC00152 in five CC cell lines and an immortalized human epithelial cell line (HaCat) were detected by qRT-PCR. *$p < 0.05$, ** $p < 0.01$.

cell lines, including HeLa, CaSki, SiHa, C-33A, SW756 cells, compared to HaCaT cells, a normal human epidermal cell line (Figure 1E).

Knockdown of LINC00152 Inhibits Cell Proliferation Through Inducing Cell Cycle Arrest at G0/G1 Phase and Promote Apoptosis

To investigate the role of LINC00152 in CC cells, we performed the loss-of-function experiment in CaSki and C-33A cells which express a high level of LINC00152 using siRNA to observe the effects of LINC00152 knockdown on cell proliferation, cell cycle, and apoptosis *in vitro*. QRT-PCR results showed that LINC00152 expression level was significantly silenced both in CaSki and C-33A cells upon the transfection of si-LINC00152 (Figure 2A). The CCK-8 proliferative assay indicated that LINC00152 knockdown could suppress the proliferation ability of CaSki and C-33A cells (Figure 2B). To further explore whether the alteration of the cell cycle progression and apoptosis contribute to the effect of LINC00152 knockdown on cell viability, flow cytometric analysis was used to examine cell cycle and apoptosis after cells were stained with PI or/and Annexin V. We observed that LINC00152 knockdown could arrest cell cycle at G0/G1 phase (Figure 2C) and induce apoptosis (Figure 2D) in both CaSki and C-33A cells. These results suggested that the knockdown of LINC00152 could inhibit the proliferation of cervical cancer cells through the induction of cell cycle arrest at G0/G1 phase and promote apoptosis.

LINC00152 Serves as a Sponge for miR-216-5p in Cervical Cancer Cells

LINC00152 has been demonstrated to contribute to tumor progression and metastasis as a competing endogenous RNA (ceRNA) to regulate the

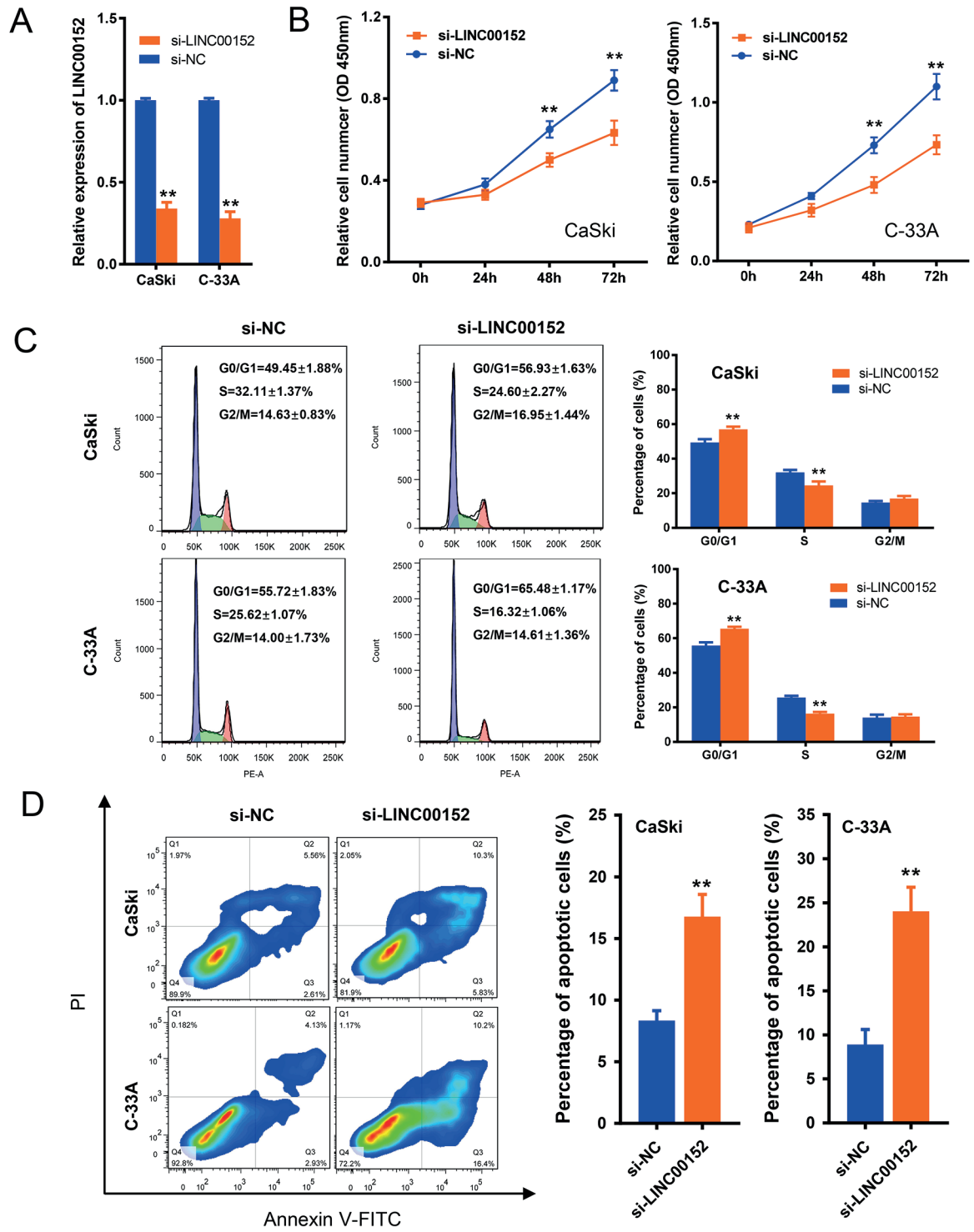

Figure 2. LINC00152 knockdown inhibits the proliferation of CC cells. ***A,*** Efficiency of LINC00152 knockdown in CasKI and C-33A cells was determined by qRT-PCR. ***B,*** Effect of LINC00152 knockdown on cell proliferation was evaluated by CCK-8 assay. ***C-D,*** Effect of LINC00152 knockdown on cell cycle distribution (PI staining) and apoptosis (Annexin V-PI staining) was detected by flow cytometry. si-LINC00152, knockdown group; si-NC, negative control group; *$p < 0.05$, ** $p < 0.01$.

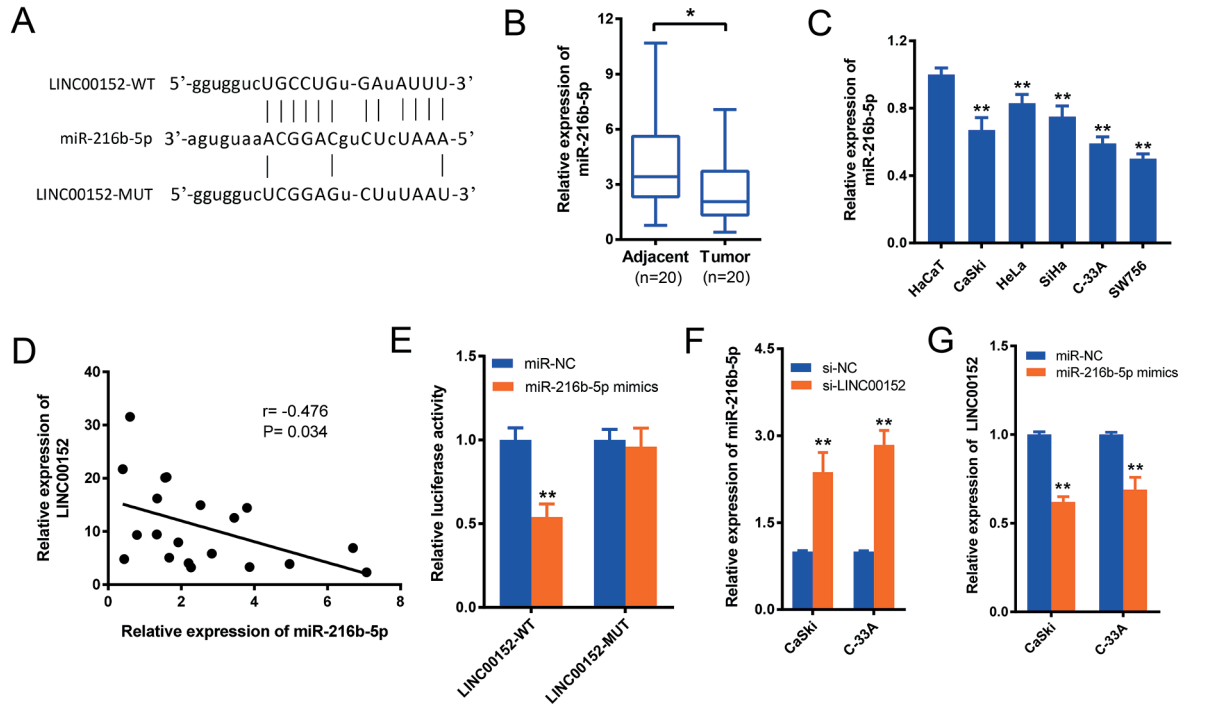

Figure 3. LINC00152 sponged miR-216b-5p in CC cells. ***A,*** Bioinformatics analysis showed the predicted binding sites between LINC00152 wild type (LINC00152-WT) and miR-216b-5p, LINC00152-mutant (MUT) means mutation of binding sites in LINC00152. ***B,*** Expression status of miR-216b-5p in human CC tissues and matched adjacent normal tissues (n = 20). ***C,*** Expression status of miR-216b-5p in CC cell lines and immortalized human epithelial cell line (HaCat). ***D,*** Relevance between the expression of LINC00152 and miR-216b-5p was evaluated with Spearman's correlation analysis. ***E,*** Dual-luciferase reporter assays were used to confirm the combination between LINC00152 and miR-216b-5p. ***F,*** Effect of LINC00152 knockdown on the expression level of miR-216b-5p in CC cells. ***G,*** Effect of overexpression of miR-216b-5p on the expression level of LINC00152 in CC cells. *$p < 0.05$, ** $p < 0.01$.

expression of target genes by sponging microRNA (miRNA) in several types of cancer[9,13]. Thus, we speculated that LINC00152 could modulate the cell proliferation of CC through the ceRNA mechanism that regulates CC related miRNAs and their target genes. Using online miRNA target search software (http://www.mircode.org), we predicted that LINC00152 could be targeted by many miRNAs, including several experimentally validated miRNAs such as miR-193a/b-3p[9,11], miR-16/497[14], miR-139-5p[12], miR-103a/107[13]. Here, we particularly focused on miR-216b-5p due to its down-regulation and negative effect on cell proliferation in CC[15]. The predicted binding site of miR-216b-5p in the LINC00152 sequence was illustrated in Figure 3A. As expected, we observed that miR-216b-5p was down-regulated in CC tissues and cell lines (Figure 3B and C), and exhibited an inverse correlation with LINC00152 expression in CC tissues (Figure 3D). Dual-luciferase reporter assays revealed that miR-216b-5p could significantly inhibit the reporter activities of LINC00152-WT but not in the mutant type (Figure 3E). Moreover, we found that the miR-216b-5p expression level could be enhanced by LINC00152 knockdown (Figure 3F), while LINC00152 expression could be down-regulated by miR-216b-5p mimics (Figure 3G). All the above results suggested that LINC00152 could directly bind to miR-216b-5p as a miRNA sponge in CC cells.

LINC00152 Modulates the Proliferation of Cervical Cancer Cells through Up-regulating HOXA1 via Sponging miR-216b-5p.

To further investigate the molecular mechanism underlying the regulation of CC cell proliferation by LINC00152 via sponging miR-216b-5p, we tried to identify the potential downstream target of miR-216b-5p. We found that HOXA1 has a potential complementary binding site with

miR-216b-5p, using TargetScan (http://www.targetscan.org/vert_72/), a miRNA target prediction tool (Figure 4A). QRT-PCR results showed that HOXA1 expression was significantly elevated in CC tissue and cell lines (Figure 4B and C), and there was a positive correlation between the expression of HOXA1 and LINC00152 in CC tissues (Figure 4D). Dual-luciferase reporter assays revealed that the luciferase activities of HOXA1-WT reporter, but not the mutant type, could be significantly suppressed by miR-216b-5p mimics and could be recovered by the overexpression of

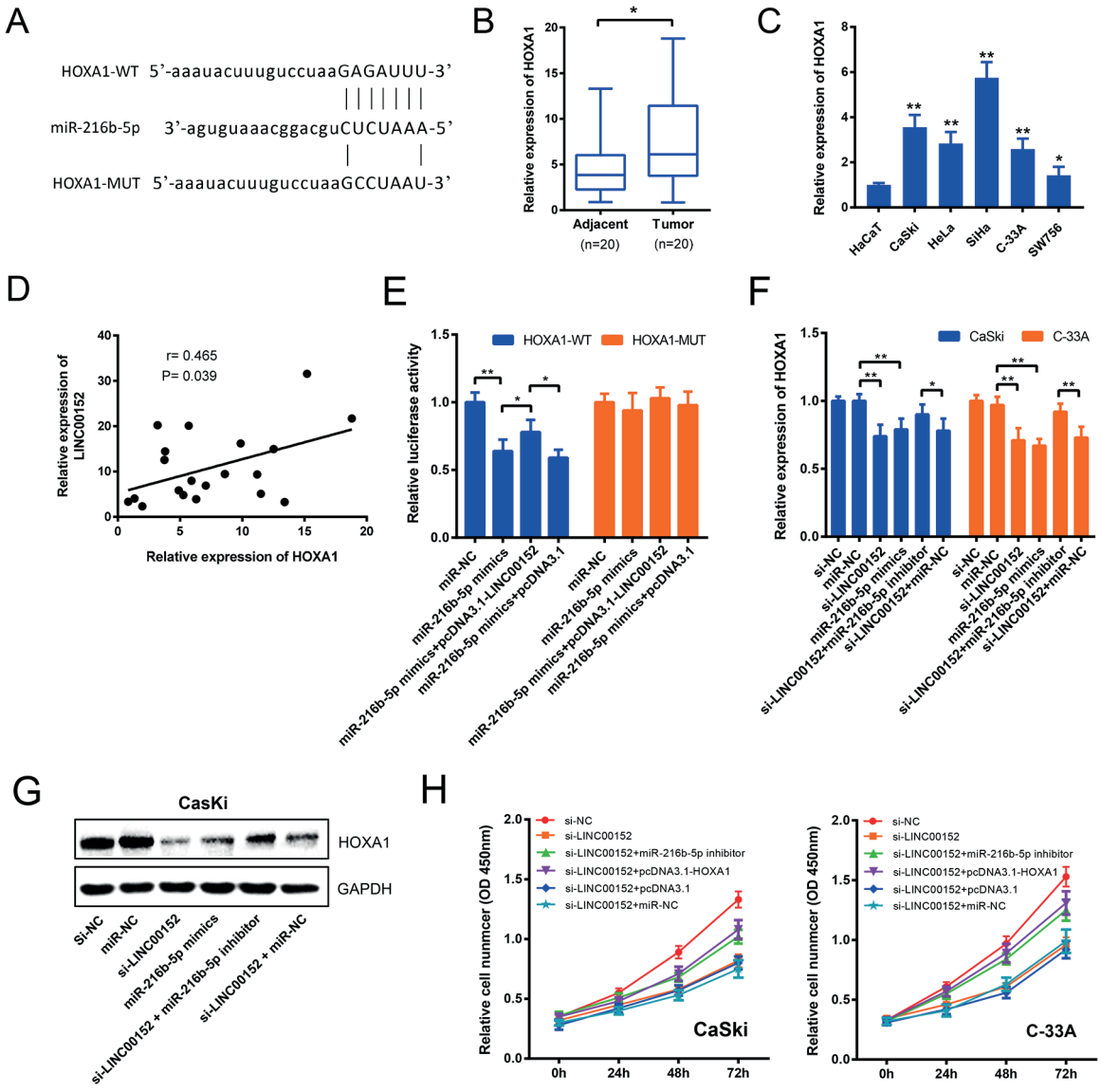

Figure 4. LINC00152 modulates the proliferation of CC cells through regulation of miR-216b-5p/HOXA1 pathway. ***A,*** Bioinformatics analysis showed the predicted binding sites between HOXA1 wild type (HOXA1-WT) and miR-216b-5p, HOXA1-mutant (MUT) means mutation of binding sites in 3' UTR of HOXA1. ***B,*** Expression level of HOXA1 in human CC tissues and matched adjacent normal tissues (n=20) was detected by qRT-PCR. ***C,*** Expression level of HOXA1 in CC cell lines and immortalized human epithelial cell line (HaCat) were detected by qRT-PCR. ***D,*** Relevance between LINC00152 and HOXA1 was evaluated with Spearman's correlation analysis. ***E,*** Dual-luciferase reporter assays were used to confirm the binding of HOXA1 and miR-216b-5p and observe the effect of overexpression of LINC00152 on bindings. ***F,*** QRT-PCR results showed HOXA1 mRNA level could be regulated by LINC00152 via miR-216b-5p in CasKi and C-33A cells. ***G,*** Western blot result showed HOXA1 protein level could be regulated by LINC00152 via miR-216b-5p in CasKi cells. ***H,*** CCK-8 rescue assays indicated that LINC00152 knockdown could suppress the CC cell proliferation through miR-216b-5p/HOXA1 axis. *$p < 0.05$, ** $p < 0.01$.

LINC00152, indicating that LINC00152, miR-216b-5p, and HOXA1 could form a ceRNA network (Figure 4E). Subsequently, we first evaluated the regulatory effect of LINC00152 and miR-216b-5p on the expression of HOXA at mRNA level using qRT-PCR. The results showed that the individual knockdown of LINC00152 or overexpression of miR-216b-5p could down-regulate the HOXA1 expression level in both CaSki and C-33A cells, and the down-regulation of HOXA1 caused by LINC00152 knockdown could be rescued by miR-216b-5p inhibition via transfecting the miR-216b-5p inhibitor (Figure 4F). Next, we validated the regulatory effect of LINC00152 and miR-216b-5p on the expression of HOXA at protein level in CaSki cells using Western blot and found that the results were coincident with that of mRNA level (Figure 4G). In addition, we found that miR-216b-5p inhibition or HOXA1 overexpression could restore the suppression of cell proliferation caused by LINC00152 knockdown in both CaSki and C-33A cells (Figure 4H). Taken together, these findings indicate that LINC00152 could modulate the proliferation of cervical cancer cells through the up-regulation of HOXA1 via sponging miR-216b-5p.

Discussion

Evidence demonstrated that lncRNAs represent a novel class of regulators for gene expression and play critical roles in the progression and development of various cancers, including CC[16]. To date, numerous dysregulated lncRNAs have been identified to be involved in CC as either tumor suppressors or oncogenes, including some well-known lncRNAs such as HOTAIR, NEAT1, XIST, PVT1, GAS5, MEG3, H19, etc[5,17]. In recent years, LINC00152, a lncRNA located at the 2p11.2 region, has been identified to be up-regulated in many cancer types and contribute to tumor progression, i.e., liver cancer, lung cancer, gastric cancer thyroid cancer and so on[8]. In the current study, we aim to explore the expression status and biological function of LINC00152 in the CC progression.

First, we revealed that LINC00152 was strongly expressed in CC tissues and cell lines and the up-regulation of LINC00152 was positively associated with poor prognosis and histologic grade in CC, suggesting that LINC00152 might serve as a potential biomarker for early diagnosis and prognosis prediction of CC. Ma et al[18] from non-small-cell lung cancer (NSCLC) demonstrated that LINC00152 levels were up-regulated in NSCLC plasma samples and were significantly decreased after surgery. The ROC curve analysis showed that LINC00152 could provide high diagnostic performance to distinguish NSCLC patients from benign lung disease and healthy controls, reflect tumor dynamics and monitor the status of NSCLC patients after operation, indicating that plasma LINC00152 could be used as a promising biomarker for NSCLC diagnosis[18].

We also demonstrated that the knockdown of LINC00152 could suppress the proliferation of CC cells by inducing the cell cycle arrest at G0/G1 phase and promote apoptosis. These results observed in CC were similar to that of other cancer types. For example, in gastric cancer[19], lung adenocarcinoma[7], multiple myeloma[20], hepatocellular carcinoma[9], the knockdown of LINC00152 could cause cell proliferation suppression, enhance cell cycle G0/G1 phase arrest and trigger apoptosis, indicating that LINC00152 might, therefore, be a potential therapeutic target for cancer treatment.

We then uncovered a novel ceRNA pathway that contributes to the regulation of cell proliferation by LINC00152 in CC cells. LINC00152 could modulate the proliferation of CC cells through the up-regulation of HOXA1 via sponging miR-216b-5p (i.e. miR-216b-5p/ HOXA1 axis). Several ceRNA pathways mediated by LINC00152 have been identified by previous studies[9,13,11,12] and demonstrated to be involved in cancer development through controlling cell growth and survival, such as miR-193a/b-3p/CCND1 in liver cancer, miR-103a-3p/FEZF1/CDC25A in glioma, miR-193a-3p/MCL1 and miR-139-5p/PRKAA1 in gastric cancer. Here, we discovered that LINC00152 could directly bind to miR-216-5p as a sponge in CC cells. Previously, He et al[15] demonstrated miR-216-5p was down-regulated in CC cells/tissues, could inhibit cell proliferation by targeting FOXM1 and its expression level was related to prognosis in CC patients, indicating that miR-216-5p may serve as a tumor suppressor in CC[15]. Besides, we also found HOXA1 was a novel target of miR-216b-5p and contributed to the regulation of cell proliferation mediated by LINC00152 through the formation of the ceRNA pathway together with miR-216b-5p in CC. Several studies[21,22] demonstrated that HOXA1, as an oncogene, plays important roles in cancer progression by binding to miRNAs. For example, miR-577 could function as an anti-oncogene to suppress the migration, invasion, and epithelial-mesenchy-

mal transition (EMT) of hepatocellular carcinoma cells through direct interaction with HOXA1; miR-433 could inhibit colon cancer cell proliferation and invasion by directly targeting HOXA1. Recently, Li et al[23] found that lncRNA CCAT1 exerted an oncogenic role in multiple myeloma cells through positively regulating the HOXA1 expression via sponging miR-181a-5p. So far, there is still no experimental evidence linking HOXA1 to cervical cancer. In the current study, we demonstrated that HOXA1 was up-regulated in CC tissues and cell lines and contributed to CC cell proliferation as the downstream target of LINC00152/ miR-216-5p pathway.

Conclusions

We revealed that LINC00152, an up-regulated lncRNA in CC, was associated with poor prognosis and contributed to cervical cancer cell proliferation through cell cycle modulation and apoptosis via a novel ceRNA pathway of miR-216-5p/ HOXA1, suggesting that LINC00152 might potentially act as an effective diagnostic marker and therapeutic target for cervical cancer.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

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