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LncRNA LOXL1-AS1 inhibited cell proliferation, migration and invasion as well as induced apoptosis in breast cancer *via* regulating miR-143-3p

G.-H. LI[1], J.-H. YU[2], B. YANG[1], F.-C. GONG[1], K.-W. ZHANG[1]

[1]Department of Thoracic Surgery, First Hospital of Jilin University, Changchun, China
[2]Department of Gastrointestinal Surgery, First Hospital of Jilin University, Changchun, China

Guanghu Li and *Jinhai Yu* contributed equally to this work

Abstract. – OBJECTIVE: In recent years, studies have shown that lncRNA plays an essential regulatory role in biological life activities. In disease and cancer research, the function of lncRNA is closely related to inflammatory response, tumor formation and cellular metabolism. Breast cancer is one of the most common malignant tumors in women. The research on the pathogenesis of breast cancer is the focus of current research. Although the regulatory mechanisms of some lncRNAs have been proven, the complexity of cancer regulation has led to incomplete research.

MATERIALS AND METHODS: The expression of LOXL1-AS1 and miR-143-3p was measured using qRT-PCR. Western blot was used to detect CDK, Cyclin D1, MMP-2, MMP-9, Bcl-2, Bax and Cleaved caspase-3 protein expression. MTT assay and transwell assay were applied to analyze cell proliferation, migration and invasion, respectively. Cell apoptosis rate of transfected cells was measured with flow cytometry. Luciferase reporter assay was applied to verify the relationship between LOXL1-AS1 and miR-143-3p.

RESULTS: In this study, we found that LOXL1-AS1 expression was induced while miR-142-3p expression was decreased in breast cancer tissues and cells, implying that LOXL1-AS1 and miR-143-3p play an important role in cell progression of breast cancer. Further investigation showed that silencing LOXL1-AS1 inhibited proliferation, promoted cell apoptosis and decreased the capacity of cell migrated and invasive in breast cancer cells. The analysis of luciferase reporter assay determined that LOXL1-AS1 directly targeted miR-143-3p in breast cancer cells. The rescue experiments further proved that miR-143-3p reversed the inhibited effects of si- LOXL1-AS1 on breast cancer cells.

CONCLUSIONS: In this study, we verified that LncRNA LOXL1-AS1 inhibited cell proliferation, migration and invasion as well as induced apoptosis in breast cancer via regulating miR-143-3p, providing a novel therapeutic target and improving understanding of the regulatory mechanism of cell progression in breast cancer.

Key Words:
Breast cancer, LOXL1-AS1, MiR-143-3p, Cell progression.

Introduction

Breast cancer is one of the most common malignancies in women worldwide. In recent years, the incidence of breast cancer has increased. Due to the complexity of its carcinogenic causes, the research and treatment of breast cancer are very difficult[1]. Although surgery and some adjuvant treatments, such as chemotherapy and radiation therapy, can effectively improve the patient's life, the emergence of drug resistance will have certain limitations. Therefore, the prevention and diagnosis of breast cancer, as well as related pathogenesis, still need to be further explored.

lncRNA is a non-coding RNA of ~200 nt in length and plays an essential role in human diseases, especially in cancers[2-4]. lncRNAs are widely involved in the formation, development and development of various cancers[5-8]. Moreover, lncRNA has been shown to affect cell proliferation, invasion, metastasis and apoptosis in cell progression[7,9,10]. Moreover, lncRNA is also involved in the regulation of cancer resistance mechanisms, including breast cancer, colorectal cancer and ovarian cancer[11-13]. Han et al[14] reported that lncRNA CRNDE enhanced cell proliferation

Corresponding Authors: Fangchao Gong, MD; e-mail: sanlinsi20021111sg@yeah.net
Kewei Zhang, MD; e-mail: guigong1967921@yeah.net

and chemoresistance through miR-181a-5p-mediated regulation of Wnt/β-catenin signaling in colorectal cancer. However, studies on the function and mechanism of lncRNA in breast cancer have not been fully elucidated.

In this paper, we found that lncRNA LOXL1-AS1 is abnormally highly expressed in breast cancer cells and tissues, suggesting that LOXL1-AS1 may be involved in the regulation of breast cancer. Further functional studies confirm our prediction. Studies have shown that lncRNA has been reported as a ceRNA involved in regulating the downstream miRNAs that play a role in tumor cell metabolism[15,16]. Therefore, we predicted that miR-143-3p was the target miRNA of LOXL1-AS1. Finally, our experimental results indicated that LOXL1-AS1 affected proliferation, apoptosis, migration and invasion of breast cancer cells by modulating miR-143-3p.

Patients and Methods

Patients and Tissues

Breast cancer tissues and adjacent tissues were obtained from 97 breast cancer patients at the First Hospital of Jilin University. All patients had not received chemotherapy or medication after diagnosis. This study has been approved by the First Hospital of Jilin University Ethics Committee and has obtained written informed consent from all patients.

Cell Culture and Transfection

Human breast epithelial normal cells (HBL-100) and breast cancer cell lines (MCF-7, MDA-MB-231, BT549 and SKBR-3) were purchased from the Chinese Academy of Sciences Cell Bank. All cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium (Life Technologies, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS), 1% penicillin–streptomycin at 37°C in humid air containing 5% CO_2.

Scrambled siRNA of LOXL1-AS1(si- LOXL1-AS1), pcDNA-LOXL1-AS1, miR-143-3p inhibitor (anti-miR-143-3p) and their negative control (si-con pcDNA and anti-miR-con) were purchased from GenePharma (Shanghai, China). These fragments and oligos were transfected into MCF-7 and MDA-MB-231 cell using the Lipofectamine 2000 Reagents (Invitrogen Co., Carlsbad, CA, USA).

qRT-PCR

Total RNA from cells was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). For qPCR, RNA was reversely transcribed into cDNA with a PrimeScript RT Reagent Kit (TaKaRa, Otsu, Shiga, Japan). One Step SYBR PrimeScript™ RTPCR Kit (TaKaRa, Otsu, Shiga, Japan) and TaqMan miRNA assays (Applied Biosystems, Foster City, CA, USA) was used to analyze LOXL1-AS1 and miR-143-3p expression on a CFX96 TouchTM Real-Time PCR system (Bio-Rad, Hercules, CA, USA), respectively. GAPDH and U6 were used as the normalization control genes for LOXL1-AS1 and miR-143-3p, respectively. The relative expression of LOXL1-AS1 and miR-143-3p were calculated using the $2^{-\Delta\Delta Ct}$ method.

Western Blot

The cells were lysed in RIPA buffer (Sigma-Aldrich, St. Louis, MO, USA). The BCA Protein assay kit (Beyotime, Shanghai, China) was used to quantify the protein concentration. The equivalent of protein (20 μg) was added into sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred onto a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). After blocked with nonfat dried milk and washed in TBST, the membranes were incubated with primary antibodies CDK, Cyclin D1, MMP-2, MMP-9, Bcl-2, Bax, Cleaved caspase-3 and β-actin (1:1000 dilution; Abcam, Cambridge, MA, USA) at 4°C overnight. After washed with TBST, the membrane was further incubated with horseradish peroxidase (HRP)-conjugated secondary antibody anti-mouse IgG (1:1000 dilution; Abcam, Cambridge, MA, USA) for 1 h at 37°C. The protein blots were caught via the Clarity Western ECL substrate (Bio-Rad, Hercules, CA, USA).

Cell Proliferation and Cell Apoptosis

Cell proliferation was detected by MTT assay. Transfected cells were seeded into 96-well plates and cultured for 24, 48 and 72 h. Then, 20 μl MTT (Sigma-Aldrich, St. Louis, MO, USA) and 150 μl dimethylsulfoxide (DMSO; Sigma-Aldrich) was added into each well to dissolve formazan and stained cells. The SpectraMax 360 pc microplate reader (Molecular Devices, LLC, Sunnyvale, CA, USA) was applied to detect the relative absorbance of cell proliferation at a wavelength of 490 nm.

Cell apoptosis was measured via flow cytometry. Briefly, transfected cells were trypsinized and stained with Annexin V-fluorescein isothiocyanate (FITC)/propidum iodide (PI) Apoptosis Detection Kit (Beyotime, Shanghai, China). Cell apoptotic rate was analyzed using a MoFlo XDP Cell Sorter (Beckman Coulter, Brea, CA, USA).

Cell Migration and Invasion

Cell migration and invasion were evaluated using transwell migrated and invasive assay. Briefly, cell invasion of transfected cells was suspended in RPMI-1640 medium and then seeded into the upper chamber (8-μm pore; BD Biosciences, Franklin Lakes, NJ, USA) of the inserts of Matrigel-coated (BD Biosciences). Cell migrations were seeded into the upper chamber without Matrigel-coated. Medium supplemented with FBS as the chemoattractant was added to the lower chamber. After incubation for 22 h, the cells of upper chambers were removed off gently, and methanol and crystal violet were added into lower chambers to fix and stained cells. The stained cells of invaded and migrated were calculated through counting five random views under the microscope.

Luciferase Reporter Assay

The fragments of LOXL1-AS1 containing wild-type or mutated of miR-143-3p binding sites were synthesized and then inserted into Dual-luciferase Vector pRL-TK (Promega, Madison, WI, USA) to name LOXL1-AS1-WT and LOXL1-AS1-MUT. Then the LOXL1-AS1-WT or LOXL1-AS1-MUT and miR-143-3p or miR-con were cotransfected into MCF-7 and MDA-MB-231 cell using Lipofectamine 2000 reagent (Invitrogen, Carlsbad, CA, USA). After 48 h post-transfection, luciferase activities of collected cells were measured using the Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA).

Statistical Analysis

All data are presented as the mean ± SD, Student's *t*-test (unpaired, two-tailed) was used to analyze differences among groups. The correlations between LOXL1-AS1 and miR-143-3p were analyzed using Spearman's rank test. The results were displayed using GraphPad Prism 7.0. (La Jolla, CA, USA). $p < 0.05$ was considered statistically significant. Each experiment was repeated at least three times.

Results

LncRNA LOXL1-AS1 Expression was Induced While miR-142-3p Expression was Decreased in Breast Cancer Tissues and Cells

To further investigate the effect of LOXL-AS1 and miR-142-3p on breast cancer, the expression of LOXL-AS1 and miR-142-3p was measured using qRT-PCR in breast cancer tissues and cells. As shown in Figure 1A and 1B, we found that LOXL-AS1 expression in tumor tissues was significantly higher than that in adjacent tissues while miR-142-3p expression in tumor tissues was remarkable lower than that in adjacent tissues. More than that, miR-142-3p expression was negatively correlated with LOXL-AS1 expression in breast cancer tissues (Figure 1C). Additionally, their expression was detected in human normal cell line (HBL-100) and breast cancer cell lines (MCF-7, MDA-MB-231, BT549 and SKBR-3), and the results showed that LOXL-AS1 was upregulated and miR-142-3p was downregulated in breast cancer cells compared with that in normal cells. Thus, LOXL-AS1 and miR-142-3p might play an essential role in the progression of breast cancer.

Silencing LOXL1-AS1 Inhibited Proliferation of Breast Cancer Cells

To further explore the effect of LOXL-AS1 on breast cancer cell proliferation, we selected breast cancer cell lines MCF-7 and MDA-MB-231 with a high expression of LOXL-AS1 for subsequent studies. LOXL-AS1 was knocked out and transfected into the MCF-7 and MDA-MB-231 cell lines, and the expression of LOXL-AS1 was stably reduced (Figure 2A and 2B). The results of MTT showed that si-LOXL-AS1 significantly inhibited the proliferation of breast cancer cells. Moreover, analysis by western blot showed that decreased expression of LOXL-AS1 reduced the protein expression of CDK4 and Cyclin D1 in MCF-7 and MDA-MB-231 cells. Therefore, these results reflected that inhibition of LOXL-AS1 promoted to prevent the proliferation of breast cancer cells.

Silencing LOXL1-AS1 Promoted Cell Apoptosis in Breast Cancer Cells

Apoptosis is an important process in the process of cells. Notably, in this experiment, we found that the inhibited expression of LOXL1-AS1 significantly promoted apoptosis in MCF-7 and MDA-MB-231 cells (Figure 3A to3D).

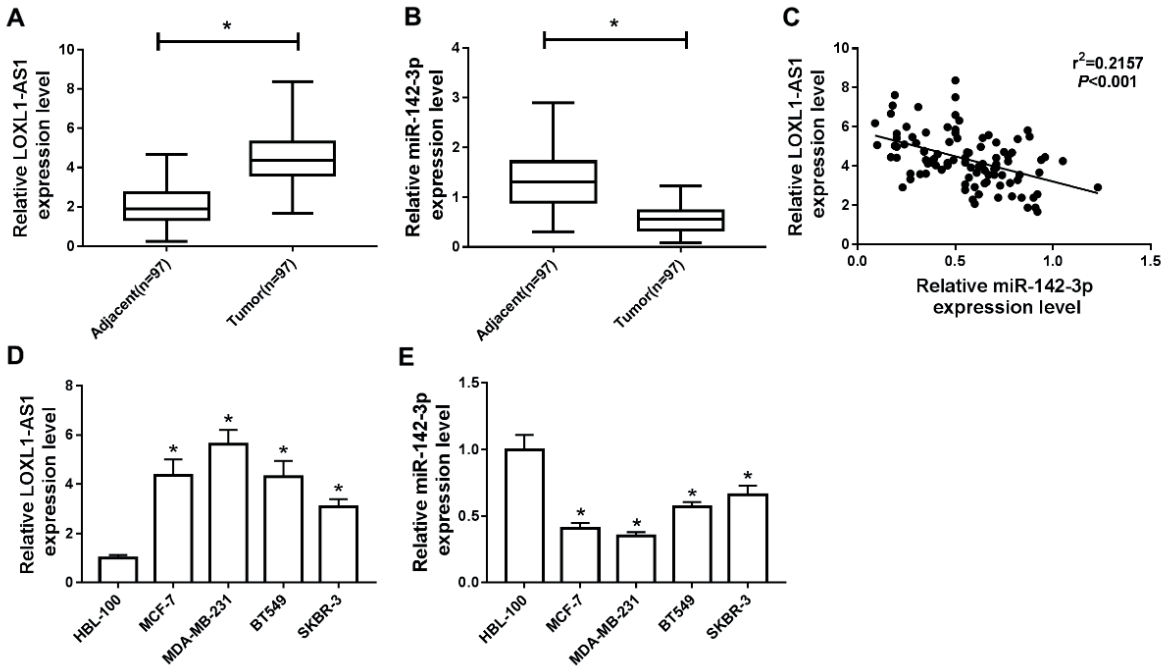

Figure 1. LncRNA LOXL1-AS1 expression was induced while miR-142-3p expression was decreased in breast cancer tissues and cells. **A-B,** QRT-PCR was used to detect the expression of LOXL1-AS1 and miR-143-3p in tumor tissues and adjacent tissues compared with the adjacent group. **C,** LOXL1-AS1 and miR-143-3p expression correlation in tumor tissues with Spearman's rank test. **D-E,** Expressions of LOXL1-AS1 and miR-143-3p were detect in breast cancer cell lines (MCF-7, MDA-MB-231, BT549 and SKBR-3) compared with that in human normal cell line (HBL-100). *p<0.05.

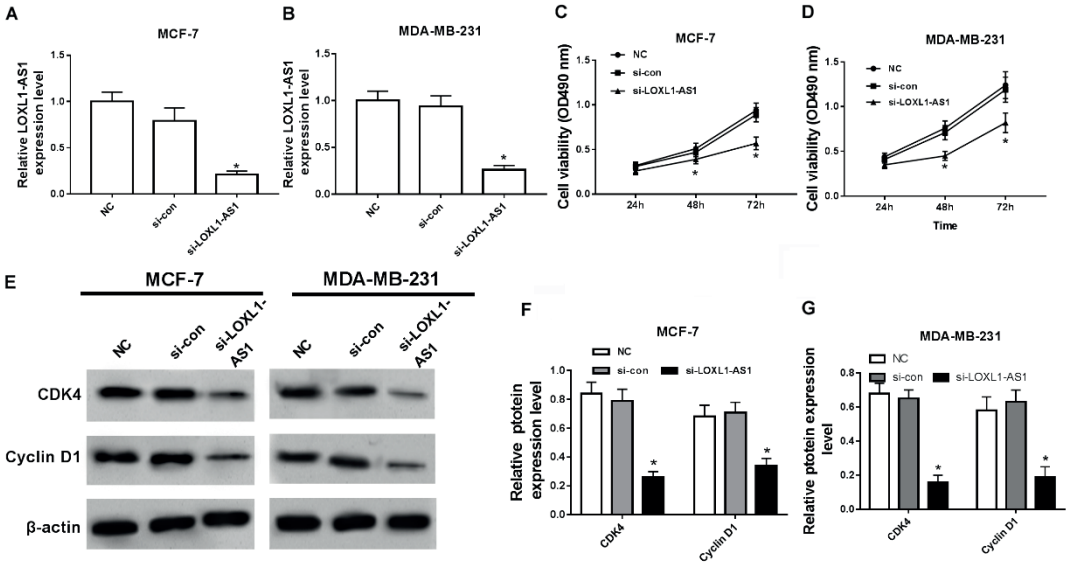

Figure 2. Silencing LOXL1-AS1 inhibited proliferation of breast cancer cells. **A-B,** Detection of LOXL1-AS1 expression in MCF-7 and MDA-MB-231 cells transfected with si-LOXL-AS1 and si-con using qRT-PCR. **C-D,** MTT assay was used to detect cell activity of MCF-7 and MDA-MB-231 cells transfected with si-LOXL-AS1 and si-con. **E-G,** Western blot was used to detect the protein expression of CDK4 and CyclinD1 in MCF-7 and MDA-MB-231 cells transfected with si-LOXL-AS1 and si-con. *p<0.05.

Further, compared with NC and si-con groups, Bcl-2 protein expression was significantly reduced whereas Bax and Cleaved caspase-3 protein expression was rapidly increased in si-LOXL1-AS1 group of MCF-7 and MDA-MB-231 cells (Figure 3E to 3F). Therefore, apoptosis of breast cancer cells was induced by si-LOXL1-AS1.

Inhibition of LOXL1-AS1 Suppressed Cell Migration and Invasion in Breast Cancer

Moreover, we also detect the capacity of cell migrated and invasive in MCF-7 and MDA-MB-231 cells transfected with si-LOXL1-AS1. As shown in Figure 3A to 3D, cell migration and invasion in si-LOXL1-AS1 groups was significantly lower than that in NC and si-con groups in MCF-7 and MDA-MB-231 cells. In addition, the MMP-2 and MMP-9 protein expression was dramatically decreased by silencing LOXL1-AS1 expression (Figure 4E to 4G).

LOXL1-AS1 Directly Targeted miR-143-3p in Breast Cancer

lncRNAs have been verified to bind their target miRNA to participate in cell progression of various cancers. In this study, we used Diana tool to predict the target miRNA of LOXL1-AS1 and the results showed that miR-143-3p has binding sites with LOXL1-AS1 (Figure 5A). Therefore, we constructed fluorescent reporters LOXL1-AS1-WT and LOXL1-AS1-MUT, which were co-transfected with MCR-7 and MDA-MB-231 cells and with miR-con and miR-143-3p. Analysis of the luciferase reporter assay showed that when miR-143-3p binds to LOXL1-AS1-WT instead of LOXL1-AS1-MUT, luciferase activities are significantly reduced in MCF-7 and MDA-MB-231 cells (Figure 5B and 5C). This result indicated that miR-143-3p was the target miRNA of LOXL1-AS1. In addition, we also found that decreasing or increasing the expression of LOXL1-AS1 significantly promoted or inhibited the expression of miR-143-3p in MCF-

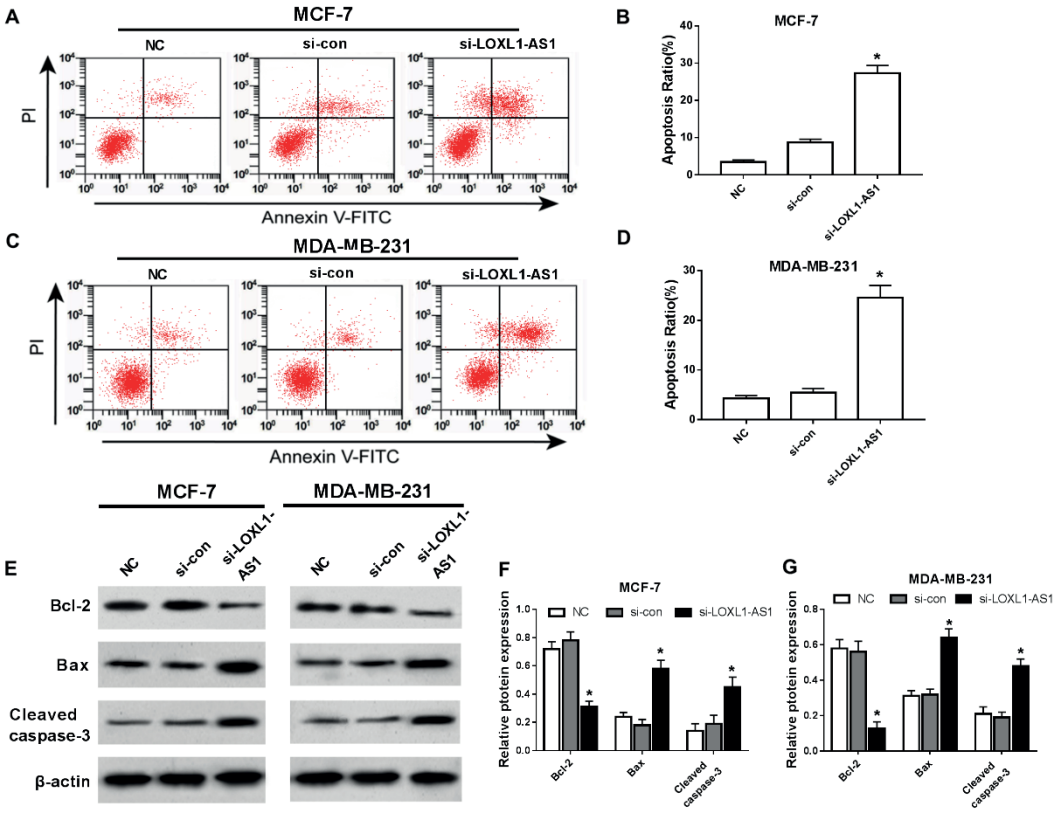

Figure 3. Silencing LOXL1-AS1 promoted cell apoptosis in breast cancer cells. **A-D,** Flow cytometry was used to detect the cell apoptosis of MCF-7 and MDA-MB-231 cell transfected with si-LOXL-AS1 and si-con. **E** and **F,** Western blot was used to detect the protein expression of Cleaved caspase-3, Bcl-2 and Bax in MCF-7 and MDA-MB-231 cells transfected with si-LOXL-AS1 and si-con. *p<0.05.

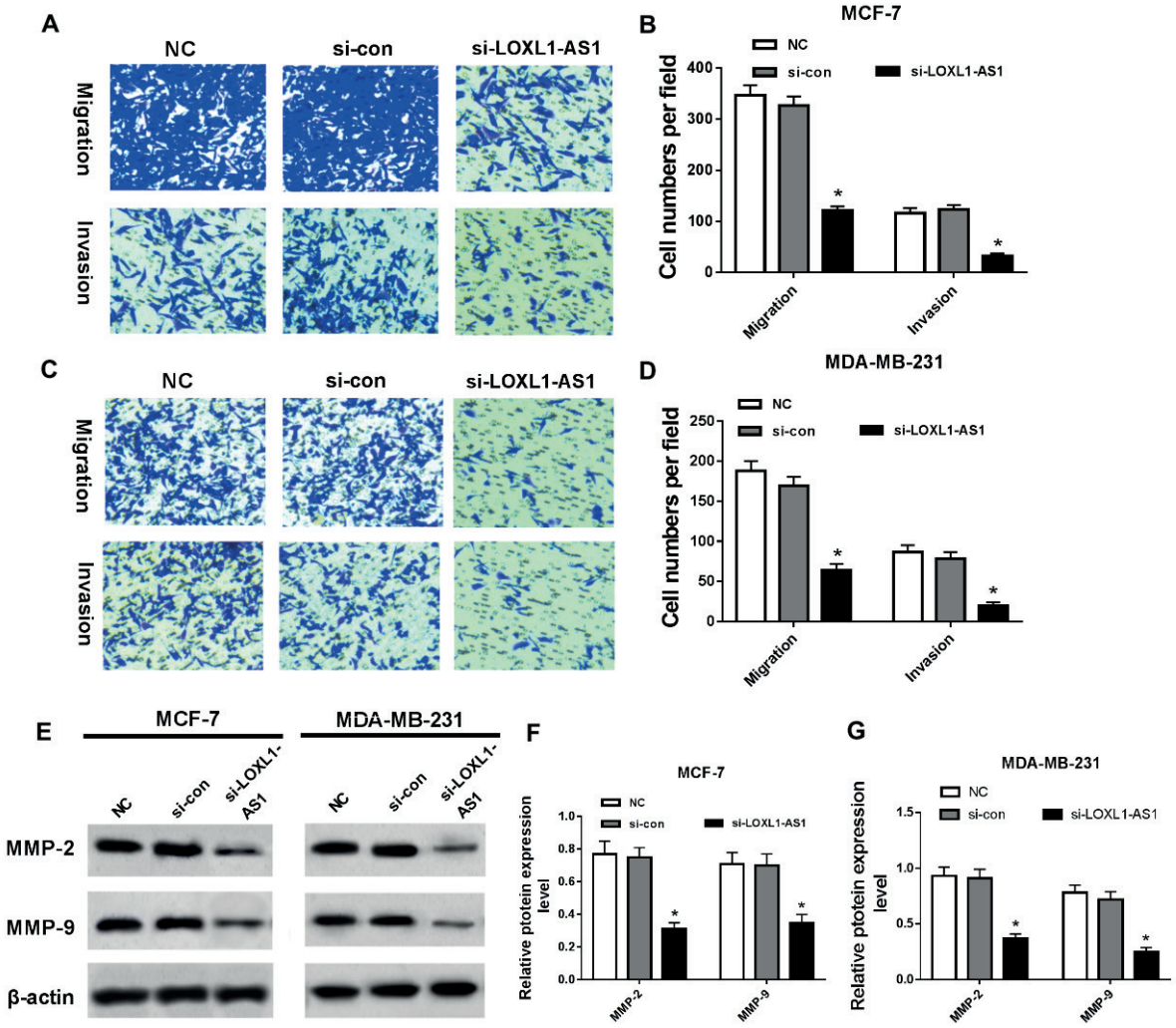

Figure 4. Inhibition of LOXL1-AS1 suppressed cell migration and invasion in breast cancer. **A-D,** Transwell was applied to measure cell migration and invasion of b MCF-7 and MDA-MB-231 cells transfected with si-LOXL-AS1 and si-con. **E-G,** Western blot was used to detect MMP-2 and MMP-9 protein expression MCF-7 and MDA-MB-231 cells transfected with si-LOXL-AS1 and si-con. *p<0.05.

7 and MDA-MB-231 cells (Figure 5D and 5E). These results determine that LOXL1-AS1 directly targeted miR-143-3p in breast cancer.

miR-143-3p Reversed the Inhibited Effects of si- LOXL1-AS1 on Breast Cancer Cells

To further clarify the regulatory mechanisms of LOXL1-AS1 and miR-143-3p in breast cancer, the rescued experiment was used and the results indicated that si-LOXL1-AS1 increased the expression of miR-143-3p; however, this phenomenon was inhibited through decreasing miR-143-3p expression in MCF-7 and MDA-MB-231 cells (Figure 6A and 6B). In addition, si-LOXL1-AS1 transfection significantly inhibited cell proliferation, migration and metastasis, which was attenuated by reducing miR-143-3p expression (Figure 6C to 6F). Inhibition of LOXL1-AS1 increased the apoptotic rate of breast cancer cells; this effect was reversed by anti-miR-143-3p transfection. Similarly, proteins associated with cell cycle have also been significantly affected. Protein expression of CDK, Cyclin D1, MMP-2 and MMP-9 was inhibited by si-LOXL1-AS1, which was improved by inhibition of miR-143-3p (Figure 6I to 6K). Moreover, the effect of si-LOXL1-AS1 on Bcl-2, Bax and Cleaved caspase-3 was reversed through downregulating miR-143-3p expression in MCF-7 and MDA-MB-231 cells (Figure 6L

to 6N). These results indicated that LOXL1-AS1 was involved in cell progression by modulating miR-143-3p in breast cancer.

Discussion

A variety of studies have shown that lncRNA is involved in cell progression in a variety of tumors, including colorectal cancer, laryngeal squamous cell cancer, non-small cell lung cancer and breast cancer[17-20]. Therefore, the study of lncRNA can provide new therapeutic targets and ideas for cancer treatment and diagnosis. lncRNA, as an important regulatory factor, is widely involved in the process of tumor formation and development, and is closely related to cell proliferation, metastasis and invasion in breast cancer[21-23]. lncRNA UCA1 expressed high in breast tissues, which significantly promoted cell growth and epithelial-mesenchymal transition (EMT) via enhancing Wnt/beta-catenin signaling pathway[24]. On the other hand, lncRNA is used as a biomarker for the diagnosis and treatment of breast cancer, improving the diagnostic efficiency of cancer and the precise treatment of breast cancer[25-27]. In this study, we found that lncRNA XLOX1-AS1 was highly expressed in breast cancer cells and may play an important regulatory role in breast cancer formation.

Accumulating studies have shown that LOXL1-AS1 is relatively high expressed in a variety of cancers, indicating a poor prognosis. Thus, reducing its expression can inhibit cancer cell proliferation, migration, invasion, and proliferative drug sensitivity as well as induce apoptosis[28-31]. Therefore, the role of LOXL1-AS1 in breast cancer cannot be ignored. Functional experiments showed that in breast cancer cells, decreased expression of LOXL1-AS1 inhibited cell proliferation, reduced migration and proliferation, and promoted apoptosis, suggesting that LOXL1-AS1 definitely affects breast cancer cell growth and die.

Many studies have been reported that miRNAs are also involved in breast cellular processes, including cell migration, invasion and metastasis[32,33]. Besides, miRNAs always modulate the chemoresistance and radioresistance in the treatment of breast cancer, including miR-142-3p, miR-574-3p and miR-221/222[34-36]. In this paper, we observed the regulation mechanism of LOXL1-AS1 and predicted that miR-143-3p is the target gene for LOXL1-AS1 using Diana tool. Interestingly, microRNA-143-3p has been reported to be a tumor suppressor in various cancers, inhibiting proliferation and metastasis of various cancer

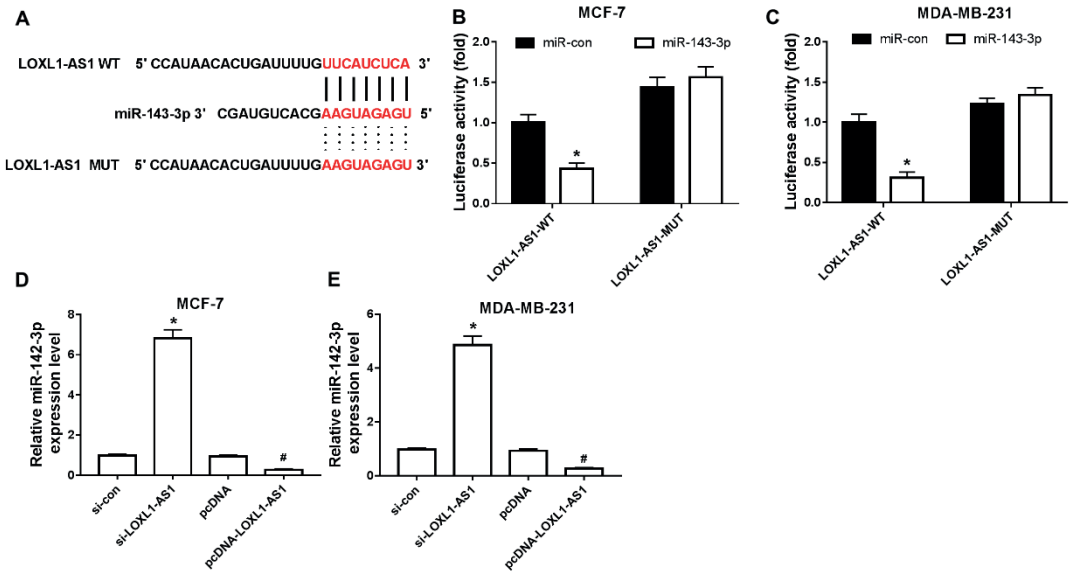

Figure 5. LOXL1-AS1 directly targeted miR-143-3p in breast cancer. **A,** Targeted complementary sequences of LOXL1-AS1 and miR-143-3p using Diana. **B-C,** luciferase activities were measured using luciferase reporter assay to determine the relationship between LOXL1-AS1 and miR-143-3p compared with miR-con group. **D-E,** The expression of miR-143-3p in si-LOXL1-AS1 and pcDNA-LOXL1-AS1 group of MCF-7 and MDA-MB-231 was compared with that of si-con group, *p<0.05; compared with pcDNA group, *p<0.05.

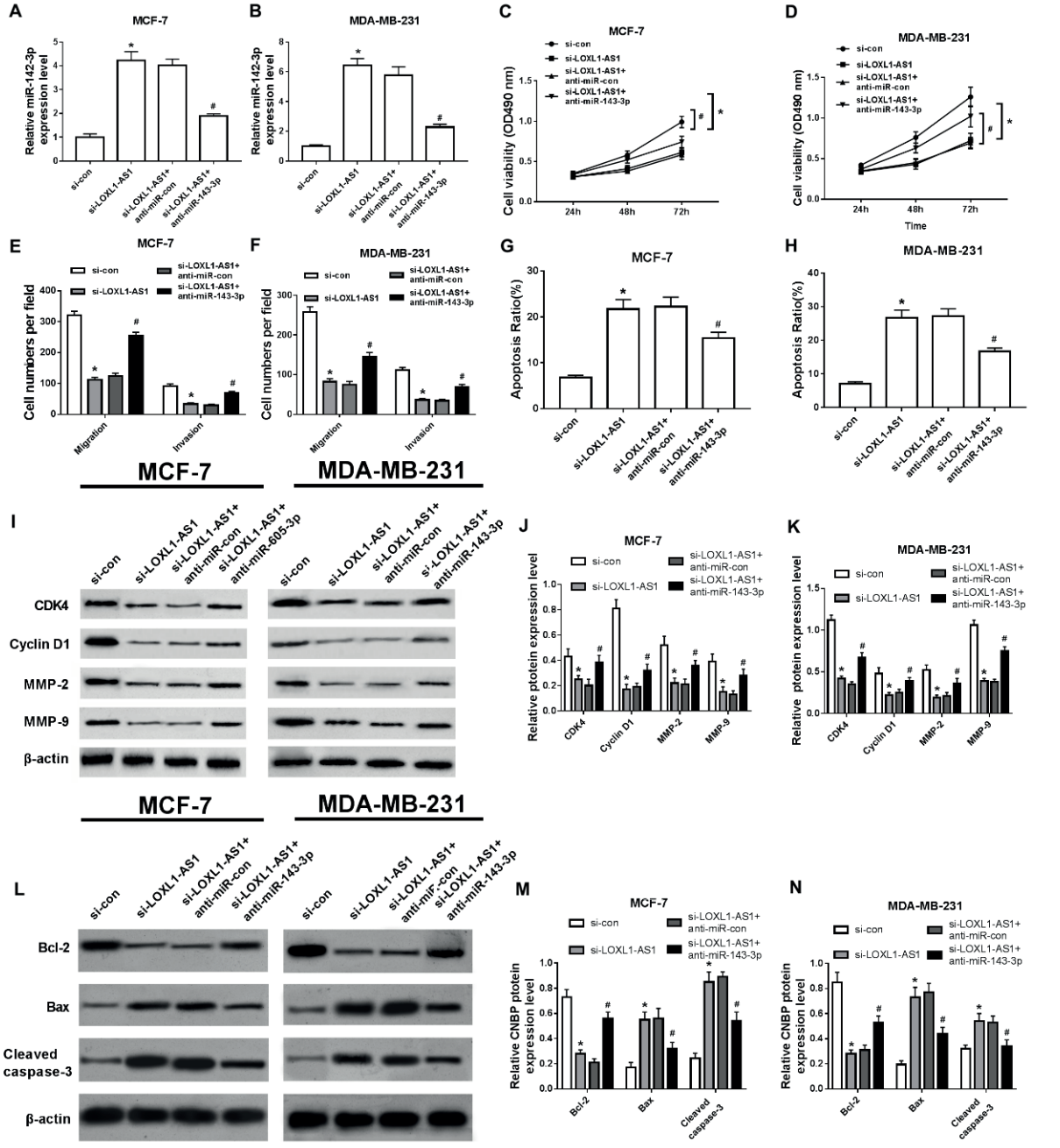

Figure 6. miR-143-3p reversed the inhibited effects of si- LOXL1-AS1 on breast cancer cells. **A-B,** The expression of miR-143-3p in MCF-7 and MDA-MB-231 transfected with si-con, si-LOXL1-AS1, si-LOXL1-AS1+anti-miR-con and si-LOXL1-AS1+anti-miR-143-3p was detected via qRT-PCR. **C-D,** Cell proliferation of MCF-7 and MDA-MB-231 cells transfected with si-con, si-LOXL1-AS1, si-LOXL1-AS1+anti-miR-con and si-LOXL1-AS1+anti-miR-143-3p was detected via MTT assay. **E-F,** Cell migration and invasion in MCF-7 and MDA-MB-231 transfected with si-con, si-LOXL1-AS1, si-LOXL1-AS1+anti-miR-con and si-LOXL1-AS1+anti-miR-143-3p was measured with transwell assay. **G-H,** Cell apoptosis in MCF-7 and MDA-MB-231 transfected with si-con, si-LOXL1-AS1, si-LOXL1-AS1+anti-miR-con and si-LOXL1-AS1+anti-miR-143-3p was measured with flow cytometry. (I-K) CDK, Cyclin D1, MMP-2 and MMP-9 protein expression was detected with Western blot in si-con, si-LOXL1-AS1, si-LOXL1-AS1+anti-miR-con and si-LOXL1-AS1+anti-miR-143-3p groups of MCF-7 and MDA-MB-231 cells. (L-N) Bcl-2, Bax and Cleaved caspase-3 protein expression was detected with Western blot in si-con, si-LOXL1-AS1, si-LOXL1-AS1+anti-miR-con and si-LOXL1-AS1+anti-miR-143-3p groups of MCF-7 and MDA-MB-231 cells. *p<0.05.

cells[37-40]. Xia et al[41] indicated that miR-143-3p acts as a tumor suppressor miRNA and regulates the tumorigenicity, invasiveness and migration of human breast cancer by targeting MAPK7 expression. In addition, miR-143-3p attenuates the characteristics of breast cancer stem cells and reduces drug resistance *in vitro*. Therefore, we speculated that miR-143-3p might be related to cell progression in breast cancer. The results of the rescue experiments demonstrated that LOXL1-AS1 affects the progression and apoptosis of breast cancer cells by modulating miR-143-3p, indicating that LOXL1-AS1/miR-143-3p axis plays an essential regulatory role in the formation and development of breast cancer.

Conclusions

We verified that LncRNA LOXL1-AS1 inhibited cell proliferation, migration and invasion as well as induced apoptosis in breast cancer via regulating miR-143-3p, providing a novel therapeutic target and improving understanding of the regulatory mechanism of cell progression in breast cancer. The regulatory mechanism of LncRNA LOXL1-AS1 in breast cancer can improve the knowledge of the pathogenesis of breast cancer and help to expand the treatment of breast cancer.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Stagl JM, Bouchard LC, Lechner SC, Blomberg BB, Gudenkauf LM, Jutagir DR, Glück S, Derhagopian RP, Carver CS, Antoni MH. Long term psychological benefits of cognitive-behavioral stress management for women with breast cancer: 11-year follow-up of a randomized controlled trial. Cancer 2015; 121: 1873-1881.
2) Ransohoff JD, Wei Y, Khavari PA. The functions and unique features of long intergenic non-coding RNA. Nat Rev Mol Cell Biol 2018; 19:143-157.
3) Fan C, Tang Y, Wang J, Xiong F, Guo C, Wang Y, Zhang S, Gong Z, Wei F, Yang L, He Y, Zhou M, Li X, Li G, Xiong W, Zeng Z. Role of long non-coding RNAs in glucose metabolism in cancer. Mol Cancer 2017; 16: 130.
4) Eades G, Zhang Y, Li Q, Xia J, Yao Y, Zhou Q. Long non-coding RNAs in stem cells and cancer. World J Clin Oncol 2014; 5: 134-141.
5) Gutschner T, Hämmerle M, Eissmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Gross M, Zörnig M, MacLeod AR, Spector DL, Diederichs S. The Noncoding RNA MALAT1 Is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res 2013; 73: 1180-1189.
6) Lei H, Gao Y, Xu X. LncRNA TUG1 influences papillary thyroid cancer cell proliferation, migration and EMT formation through targeting miR-145. Acta Biochim Biophys Sin (Shanghai) 2017; 49: 588-597.
7) Hu Y, Ma Z, He Y, Liu W, Su Y, Tang Z. LncRNA-SNHG1 contributes to gastric cancer cell proliferation by regulating DNMT1. Biochem Biophys Res Commun 2017; 491: 926-931.
8) Lin XC, Zhu Y, Chen WB, Lin LW, Chen DH, Huang JR, Pan K, Lin Y, Wu BT, Dai Y, Tu ZG. Integrated analysis of long non-coding RNAs and mRNA expression profiles reveals the potential role of lncRNAs in gastric cancer pathogenesis. Int J Oncol 2014; 45: 619-628.
9) Gao Y, Meng H, Liu S, Hu J, Zhang Y, Jiao T, Liu Y, Ou J, Wang D, Yao L, Liu S, Hui N. LncRNA-HOST2 regulates cell biological behaviors in epithelial ovarian cancer through a mechanism involving microRNA let-7b. Hum Mol Genet 2015; 24: 841-852.
10) Hu JJ, Song W, Zhang SD, Shen XH, Qiu XM, Wu HZ, Gong PH, Lu S, Zhao ZJ, He ML, Fan H. HBx-upregulated lncRNA UCA1 promotes cell growth and tumorigenesis by recruiting EZH2 and repressing p27Kip1/CDK2 signaling. Sci Rep 2016; 6: 23521.
11) Si X, Zang R, Zhang E, Liu Y, Shi X, Zhang E, Shao L, Li A, Yang N, Han X, Pan B, Zhang Z, Sun L, Sun Y. LncRNA H19 confers chemoresistance in ER-positive breast cancer through epigenetic silencing of the pro-apoptotic gene BIK. Oncotarget 2016; 7: 81452-81462.
12) Li Y, Huang S, Li Y, Zhang W, He K, Zhao M, Lin H, Li D, Zhang H, Zheng Z, Huang C. Decreased expression of LncRNA SLC25A25-AS1 promotes proliferation, chemoresistance, and EMT in colorectal cancer cells. Tumour Biol 2016; 37: 14205-14215.
13) Xu J, Wu J, Fu C, Teng F, Liu S, Dai C, Shen R, Jia X. Multidrug resistant lncRNA profile in chemotherapeutic sensitive and resistant ovarian cancer cells. J Cell Physiol 2018; 233: 5034-5043.
14) Han P, Li JW, Zhang BM, Lv JC, Li YM, Gu XY, Yu ZW, Jia YH, Bai XF, Li L, Liu YL, Cui BB. The lncRNA CRNDE promotes colorectal cancer cell proliferation and chemoresistance via miR-181a-5p-mediated regulation of Wnt/β-catenin signaling. Mol Cancer 2017; 16: 9.
15) Tu CF, Wu MH, Li GY. The Interaction between lncRNA and microRNA Contributes to Tumor. Chinese J Biochem Mol Biol 2013; 11: 1029-1034.
16) Jiang H, Ma R, Zou S, Wang Y, Li Z, Li W. Reconstruction and analysis of the lncRNA–

miRNA–mRNA network based on competitive endogenous RNA reveal functional lncRNAs in rheumatoid arthritis. Mol Biosyst 2017; 13: 1182-1192.

17) Song W, Mei JZ, Zhang M. Long noncoding RNA PlncRNA-1 promotes colorectal cancer cell progression by regulating the PI3K/Akt signaling Pathway. Oncol Res 2018; 26: 261-268.

18) Wu T, Qu L, He G, Tian L, Li L, Zhou H, Jin Q, Ren J, Wang Y, Wang J, Kan X, Liu M, Shen J, Guo M, Sun Y. Regulation of laryngeal squamous cell cancer progression by the lncRNA H19/miR-148a-3p/DNMT1 axis. Oncotarget 2016; 7: 11553-11566.

19) Cui Y, Zhang F, Zhu C, Geng L, Tian T, Liu H. Upregulated lncRNA SNHG1 contributes to progression of non-small cell lung cancer through inhibition of miR-101-3p and activation of Wnt/β-catenin signaling pathway. Oncotarget 2017; 8: 17785-17794.

20) Shi SJ, Wang LJ, Yu B, Li YH, Jin Y, Bai XZ. LncRNA-ATB promotes trastuzumab resistance and invasion-metastasis cascade in breast cancer. Oncotarget 2015; 6: 11652-11663.

21) Xu F, Li H, Hu C. LIFR-AS1 modulates Sufu to inhibit cell proliferation and migration by miR-197-3p in breast cancer. Biosci Rep 2019; 39(7). pii: BSR20180551.

22) Zhang M, Wu WB, Wang ZW, Wang XH. lncRNA NEAT1 is closely related with progression of breast cancer via promoting proliferation and EMT. Eur Rev Med Pharmacol Sci 2017; 21: 1020-1026.

23) Xu S, Kong D, Chen Q, Ping Y, Pang D. Oncogenic long noncoding RNA landscape in breast cancer. Mol Cancer 2017; 16: 129.

24) Xiao C, Wu CH, Hu HZ. LncRNA UCA1 promotes epithelial-mesenchymal transition (EMT) of breast cancer cells via enhancing Wnt/beta-catenin signaling pathway. Eur Rev Med Pharmacol Sci 2016; 20: 2819-2824.

25) Li X, Wang S, Li Z, Long X, Guo Z, Zhang G, Zu J, Chen Y, Wen L. The lncRNA NEAT1 facilitates cell growth and invasion via the miR-211/HMGA2 axis in breast cancer. Int J Biol Macromol 2017; 105: 346-353.

26) Zhang XF, Liu T, Li Y, Li S. Overexpression of long non-coding RNA CCAT1 is a novel biomarker of poor prognosis in patients with breast cancer. Int J Clin Exp Pathol 2015; 8: 9440-9445.

27) Zhang K, Luo Z, Zhang Y, Zhang L, Wu L, Liu L, Yang J, Song X, Liu J. Circulating lncRNA H19 in plasma as a novel biomarker for breast cancer. Cancer Biomark 2016; 17: 187-194.

28) Chen S, Li W, Guo A. LOXL1-AS1 predicts poor prognosis and promotes cell proliferation, migration and invasion in osteosarcoma. Biosci Rep 2019; 39(4). pii: BSR20190447.

29) Gao R, Zhang R, Zhang C, Liang Y, Tang W. LncRNA LOXL1-AS1 promotes the proliferation and metastasis of medulloblastoma by activating the PI3K/AKT pathway. Anal Cell Pathol (Amst) 2018; 2018: 9275685.

30) Long B, Li N, Xu XX, Li XX, Xu XJ, Liu JY, Wu ZH. Long noncoding RNA LOXL1-AS1 regulates prostate cancer cell proliferation and cell cycle progression through miR-541-3p and CCND1. Biochem Biophys Res Commun 2018; 505: 561-568.

31) Wang H, Li L, Yin L. Silencing LncRNA LOXL1-AS1 attenuates mesenchymal characteristics of glioblastoma via NF-κB pathway. Biochem Biophys Res Commun 2018; 500: 518-524.

32) Harouail J, Benzina S, Robichaud GA. MicroRNAs and breast cancer malignancy: an overview of miRNA-regulated cancer processes leading to metastasis. Cancer Biomark 2012; 11: 269-280.

33) Luo D, Wilson JM, Harvel N, Liu J, Pei L, Huang S, Hawthorn L, Shi H. A systematic evaluation of miRNA:mRNA interactions involved in the migration and invasion of breast cancer cells. J Transl Med 2013; 11: 57.

34) Ujihira T, Ikeda K, Suzuki T, Yamaga R, Sato W, Horieinoue K, Shigekawa T, Osaki A, Saeki T, Okamoto K. MicroRNA-574-3p, identified by microRNA library-based functional screening, modulates tamoxifen response in breast cancer. Sci Rep 2015; 5: 7641.

35) Troschel FM, Böhly N, Borrmann K, Braun T, Schwickert A, Kiesel L, Eich HT, Götte M, Greve B. miR-142-3p attenuates breast cancer stem cell characteristics and decreases radioresistance in vitro. Tumour Biol 2018; 40: 1010428318791887.

36) Miller TE, Ghoshal K, Ramaswamy B, Roy S, Datta J, Shapiro CL, Jacob S, Majumder S. MicroRNA-221/222 confers tamoxifen resistance in breast cancer by targeting p27Kip1. J Biol Chem 2008; 283: 29897-29903.

37) Mu S, Kang B, Zeng W, Sun Y, Yang F. MicroRNA-143-3p inhibits hyperplastic scar formation by targeting connective tissue growth factor CTGF/CCN2 via the Akt/mTOR pathway. Mol Cell Biochem 2016; 416: 99-108.

38) Wang F, Liu J, Zou Y, Jiao Y, Huang Y, Fan L, Li X, Yu H, He C, Wei W, Wang H, Sun G. MicroRNA-143-3p, up-regulated in H. pylori -positive gastric cancer, suppresses tumor growth, migration and invasion by directly targeting AKT2. Oncotarget 2017; 8: 28711-28724.

39) Chen L, Yao H, Wang K, Liu X. Long non-coding RNA MALAT1 regulates ZEB1 expression by sponging miR-143-3p and promotes hepatocellular carcinoma progression. J Cell Biochem 2017; 118: 4836-4843.

40) Li D, Hu J, Song H, Xu H, Wu C, Zhao B, Xie D, Wu T, Zhao J, Fang L. miR-143-3p targeting LIM domain kinase 1 suppresses the progression of triple-negative breast cancer cells. Am J Transl Res 2017; 9: 2276-2285.

41) Xia C, Yang Y, Kong F, Kong Q, Shan C. MiR-143-3p inhibits the proliferation, cell migration and invasion of human breast cancer cells by modulating the expression of MAPK7. Biochimie 2018; 147: 98-104.