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Long non-coding RNA FGF14-AS2 represses proliferation, migration, invasion, and induces apoptosis in breast cancer by sponging miR-205-5p

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Abstract. – OBJECTIVE: The heterogeneity of breast cancer leads to its complexity and diversity in the process of evolution, which brings great difficulties to the stratification and individualized treatment of breast cancer patients. The long noncoding RNA FGF14 antisense RNA 2 (FGF14-AS2) is concerned with the progression and prognosis of breast cancer, but the underlying molecular mechanism of FGF14-AS2 in breast cancer has rarely been reported.

PATIENTS AND METHODS: The expressions of FGF14-AS2 and miR-205-5p in breast cancer tissues and cells were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The proliferation, migration, invasion, and apoptosis of breast cells were assessed by MTT or transwell or flow cytometry assay. The interaction between FGF14-AS2 and miR-205-5p were predicted by lncRNA-microRNA database DIANA-LncBase v2 and confirmed by the Dual-Luciferase Reporter Assay System.

RESULTS: FGF14-AS2 was down-regulated while miR-205-5p was up-regulated in breast cancer tissues and cells and correlated with tumor stage and size. Functionally, the overexpression of FGF14-AS2 or miR-205-5p knockdown suppressed proliferation, migration, and invasion, and induced apoptosis of breast cancer cells. Moreover, FGF14-AS2 could directly bind to miR-205-5p, and the overexpression of FGF14-AS2 undermined the miR-205-5p induced effects on proliferation, migration, invasion, and apoptosis in breast cancer cells.

CONCLUSIONS: FGF14-AS2 directly bind to miR-205-5p to repress proliferation, migration, invasion, and induce apoptosis in breast cancer. This study may provide a potential therapeutic strategy for breast cancer.

Key Words:
Breast cancer, FGF14-AS2, MiR-205-5p.

Abbreviations

lncRNA = long non-coding RNA, si-RNA = small interfering RNA, si-FGF14-AS2 = targeting FGF14-AS2, si-NC = siRNA negative control, miR-NC and anti-NC = miR-205-5p mimics or inhibitor and their corresponding negative control, FITC = V-fluorescein isothiocyanate.

Introduction

Breast cancer is one of the most common malignant tumors in females around the world, and the second leading cause of cancer-related deaths among women in the United States[1]. With the development of medical technology, breast cancer can be treated to the greatest extent through surgery, endocrine, cytotoxicity, or targeted therapy[2]. However, breast cancer is a heterogeneous disease with different clinical and therapeutic specificity[3], so there is an urgent need to provide potential biomarkers for patient stratification and personalized treatment to avoid overtreatment or insufficient treatment.

Long non-coding RNA (lncRNA), a transcript with a length of more than 200 nucleotides that

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cannot be translated into proteins, plays a vital regulatory role in human tissues physiology and disease processes[4,5]. Many studies[6-9] show that the abnormal expression of lncRNAs is related to tumorigenesis and progression. For instance, lncRNA HEIH was up-regulated in colorectal cancer tissues and cells, and positively correlated with tumor size, invasion depth, and poor prognosis[10]. Also, lncRNA LUCAT1 is positively correlated with ovarian cancer metastasis and clinical staging[11]. Therefore, understanding more about the mechanism of cancer-related lncRNAs will contribute to the development of molecular markers for prognostic assessment and gene therapy. A novel long non-coding RNA, FGF14 antisense RNA 2 (FGF14-AS2), has been reported to be prominently down-regulated in breast cancer tissues[12]. However, the molecular mechanism of FGF14-AS2 in breast cancer has rarely been reported.

In the present study, we demonstrated that FGF14-AS2 was dramatically down-regulated while miR-205-5p was up-regulated in breast cancer tissues and cells and correlated with tumor stage and size. FGF14-AS2 could directly bind to miR-205-5p to repress proliferation, migration, invasion ability, and induced apoptosis in breast cancer cells.

Patients and Methods

Human Breast Cancer Tissues Samples

Tissues samples (breast cancer tissues samples and adjacent normal tissues) were obtained from 80 patients with breast cancer who underwent surgery at the First Affiliated Hospital of Sun Yat-Sen University. All participants obtained informed consent and did not receive chemotherapy or radiotherapy before surgery. According to clinical stages, 80 cases of breast cancer were divided into two groups: TNM I+II (n=32) and TNM III+IV (n=48). In addition, 80 patients with breast cancer were divided into two groups according to the size of their tumors: ≤2 cm (n=43) and >2 cm (n=37). This study was approved by the Independent Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University.

Cell culture and Transfection

Breast cancer cells lines (MDA-MB-231 and SK-BR-3) and human epithelial breast cells (MCF-10A) were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). MDA-MB-231 and SK-BR-3 cells lines were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA) with 10% fetal bovine serum (FBS; Thermo Fisher Scientific, Waltham, MA, USA). MCF-10A cells were cultured in DMEM-F12 media containing 10% fetal bovine serum. All cell lines were maintained in a 37°C incubator with 5% CO_2.

A pcDNA (Thermo Fisher Scientific, Waltham, MA, USA) was used to construct pcDNA-FGF14-AS2 overexpression vector (FGF14-AS2). Small interfering RNA (si-RNA) targeting FGF14-AS2 (si-FGF14-AS2), siRNA negative control (si-NC), miR-205-5p mimics or inhibitor, and their corresponding negative control (miR-NC and anti-NC) were purchased from GenePharma (Shanghai, China). The Lipofectamine 2000 reagent (Thermo Fisher Scientific, Waltham, MA, USA) was used for transfection oligonucleotides or plasmids into MDA-MB-231 and SK-BR-3 as directed by the manufacturer.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

The total RNA of breast cancer tissues and cells was isolated using the TRIzol Reagent (TaKaRa, Otsu, Shiga, Japan) as directed by the manufacturer. PrimeScript™ TR reagent (TaKaRa, Otsu, Shiga, Japan) was used to reverse the cDNA. SYBR Premix Ex Taq II kit (TaKaRa, Otsu, Shiga, Japan) was used for Real Time-PCR analysis. GAPDH or U6 sRNA was used as an internal reference gene for FGF14-AS2 and miR-205-5p. The primers pairs for amplifying were listed as following: FGF14-AS2 (forward, 5'-AGTTCCAGTTACCATCTTCA-3'; reverse, 5'-AGGTTCATAGTTGCCAGAC-3') GAPDH (forward, 5'-GACTCCACTCACGGCAAATTCA-3'; reverse, 5'-TCGCTCCTGGAAGATGGTGAT-3'). The relative expression was calculated by the $2^{-\Delta\Delta Ct}$ method.

Cell Proliferation Assays

Cell proliferation ability was assayed using the MTT kit (Promega Corporation, Madison, WI, USA). Briefly, the post-transfecting cells were incubated with 20 μg of 5 mg/mL MTT solution for 4 h. Then, 150 μg of dimethyl sulfoxide (DMSO) solution was added to dissolute the formazan crystals. Finally, the Microplate Reader (Thermo Fisher Scientific, Waltham, MA, USA) was used to measure the absorbance of the solution at 570 nm.

Cell Migration and Invasion Assays

The migration and invasion ability of MDA-MB-231 and SK-BR-3 cells was determined using the transwell chamber (8 mm pore filter; BD Bioscience, Franklin Lakes, NJ, USA). 100 μg transfected cells with the density of 3×10^5/ml were added into the upper chamber containing free FBS. Meanwhile, the medium with 10% FBS was added to the lower chamber and cultured for 24 h. For the invasion assay, the upper chamber was filled with the Matrigel matrix (BD Biosciences, Franklin Lakes, NJ, USA). Then, the migrated cells at the bottom of the transwell membrane were stained using 0.1% crystal violet. At last, the migration and invasion numbers of MDA-MB-231 and SK-BR-3 cells were observed and photographed using an inverted microscope (Olympus, Tokyo, Japan).

Flow Cytometry Assays

The apoptosis rate of MDA-MB-231 and SK-BR-3 cells was detected with an annexin V-fluorescein isothiocyanate (FITC) apoptosis-detection kit (Beyotime, Shanghai, China). After transfection, the cells were collected, washed, and re-suspended in the binding solution. Subsequently, the annexin V-FITC and propidium iodide (PI) were used to stain the cells in the dark for 20 min. After incubation, the apoptotic rate of MDA-MB-231 and SK-BR-3 was assessed with a FACScan® flow cytometry (BD Biosciences, Franklin Lakes, NJ, USA).

Luciferase Reporter Assays

An online lncRNA-microRNA database DIANA-LncBase v2 (http://www.microrna.gr/LncBase) was utilized to predict the binding sites of FGF14-AS2 and miR-205-5p. The pGL3-control Luciferase reporter vectors (Promega, Madison, WI, USA) were used to construct the Luciferase reporter vectors of the wild type FGF14-AS2 (FGF14-AS2-wt) and mutant FGF14-AS2 (FGF14-AS2-mut). The Luciferase reporter vectors and miR-205-5p or miR-NC were co-transfected into MDA-MB-231 and SK-BR-3 cells using Lipofectamine 2000 transfection reagent. Finally, the Luciferase activity of Luciferase reporter vectors in MDA-MB-231 and SK-BR-3 cells was determined using the Luciferase Reporter Assay kit (Promega, Madison, WI, USA).

Statistical Analysis

Statistical analysis was evaluated using SPSS software (version 19.0, IBM Corp., Armonk, NY, USA). The Student's *t*-test was used to analyze the differences between the two groups. Pearson's correlation coefficient was utilized to determine the relationship between FGF14-AS2 and miR-205-5p. When the *p*-value is less than 0.05, it is considered to have statistical significance.

Results

The expression of FGF14-AS2 was down-regulated in breast cancer tissues and cells and correlated with tumor stage and size. To define the roles of FGF14-AS2 in breast cancer progression, qRT-PCR was utilized for the detection of the expression of FGF14-AS2 in 80 paired breast cancer tissues and adjacent normal tissues. The results presented that FGF14-AS2 was down-regulated in breast cancer tissues and cells compared with the adjacent normal tissues and MCF-10A cells (Figures 1A and 1D). Then, the clinical information on breast cancer patients was further analyzed. According to clinical stages, 80 cases of breast cancer were divided into two groups: TNM I+II (n=32) and TNM III+IV (n=48). As shown in Figure 1B, the expression of FGF14-AS2 in the TNM III+IV group was significantly lower than that in the TNM I+II group. In addition, 80 patients with breast cancer were divided into two groups according to the size of their tumors: ≤2 cm (n=43) and >2 cm (n=37). The results from qRT-PCR showed that, compared with the group with tumor size ≤2 cm, FGF14-AS2 in the >2 cm group was strikingly down-regulated (Figure 1C). Therefore, these data indicated that FGF14-AS2 was down-regulated in breast cancer tissues and cells and correlated with tumor stage and size.

Overexpression of FGF14-AS2 Repressed Proliferation, Migration, Invasion, and Induced Apoptosis in Breast Cancer Cells

To explore the biological functions of FGF14-AS2 on breast cancer progression, MDA-MB-231 and SK-BR-3 cells were transfected with FGF14-AS2 or NC. The results presented that, compared to the NC group, FGF14-AS2 expression levels in the FGF14-AS2 group were dramatically up-regulated (Figure 2A). Moreover, the MTT and transwell assays indicated that the proliferation, migration, and invasion ability of MDA-MB-231 and SK-BR-3 cells were remarkably inhibited in the FGF14-AS2 group in comparison with the NC

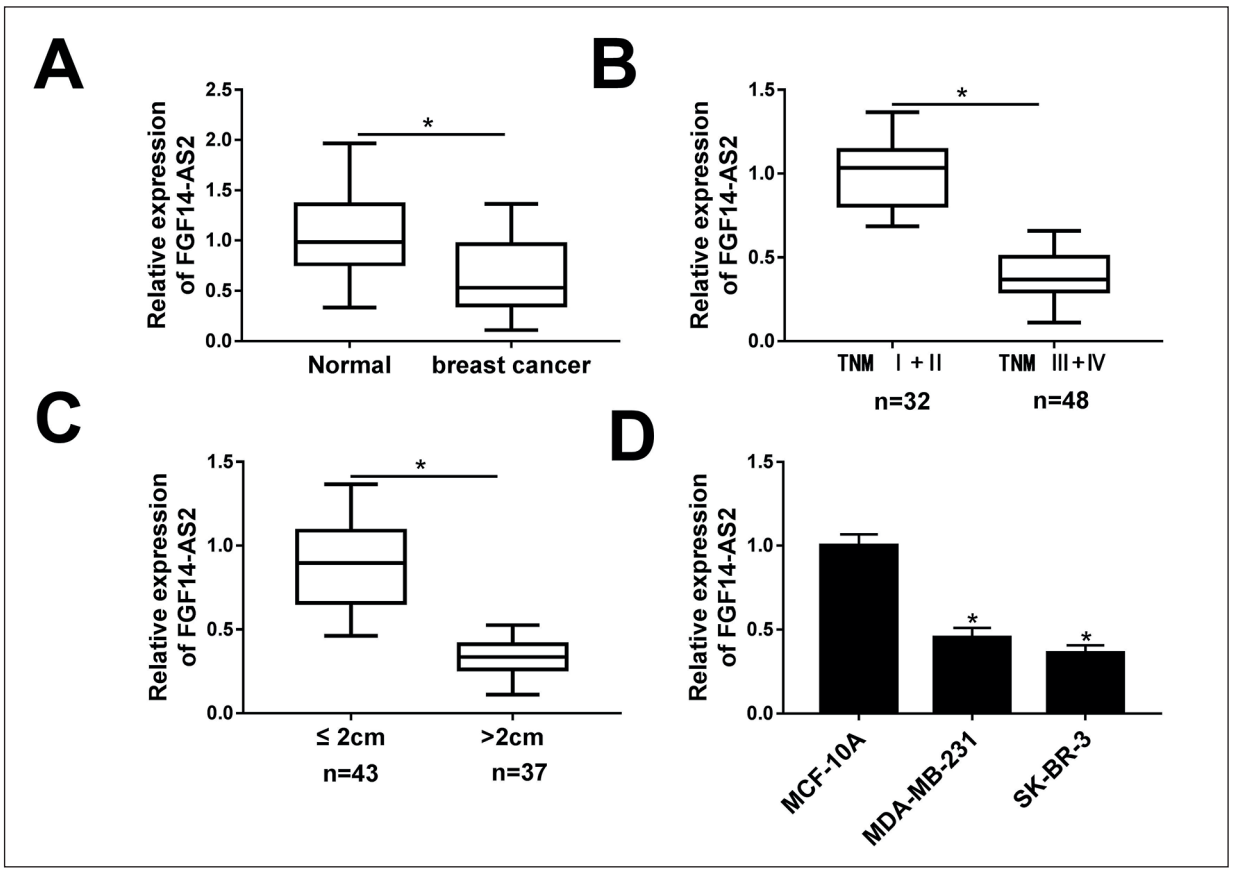

Figure 1. FGF14-AS2 was down-regulated in breast cancer tissues and cells and correlated with tumor stage and size. ***A,*** and ***D,*** FGF14-AS2 expression levels were detected by qRT-PCR in breast cancer tissues ***(A)*** and cells ***(D)***. ***B,*** The expression of FGF14-AS2 was negatively correlated with TNM stage. ***C,*** FGF14-AS2 expression was negatively correlated with tumor size. *$p<0.05$.

group (Figures 2B, 2D, and 2E). Besides, the flow cytometry analysis showed that the apoptosis rates of both MDA-MB-231 and SK-BR-3 cells were evidently enhanced in the FGF14-AS2 group than in the NC group (Figure 2C). These results indicated that the overexpression of FGF14-AS2 repressed proliferation, migration, invasion, and induced apoptosis in breast cancer cells.

MiR-205-5p Was a Target of FGF14-AS2 in Breast Cancer Cells

Based on the above results, an online lncRNA-microRNA database DIANA-LncBase v2 was used to investigate the possible molecular mechanism of FGF14-AS2 on breast cancer progression. As showed in Figure 3A, we observed that miR-205-5p had a possible binding site in FGF14-AS2. A Dual-Luciferase Reporter Assay was performed to confirm this prediction. The results presented that miR-205-5p overexpression could drastically reduce the Luciferase activity of the FGF14-AS2-wt in both MDA-MB-231 and SK-BR-3 cells, but not of FGF14-AS2-mut (Figure 3B). However, when miR-205-5p was inhibited, the Luciferase activity of the FGF14-AS2-wt was effectively increased, while FGF14-AS2-mut remained unchanged (Figure 3B). These data implied that miR-205-5p was a target of FGF14-AS2 in breast cancer cells.

MiR-205-5p Was Upregulated in Breast Cancer Tissues and Cells, and Correlated With Tumor Stage and Size

To survey the roles of miR-205-5p in breast cancer progression, we measured the expression of miR-205-5p in breast cancer tissues and adjacent normal tissues, as well as in the breast cancer cells by qRT-PCR. The results showed that miR-205-5p was markedly up-regulated in breast cancer tissues and cells (Figures 4A and F). In addition, miR-205-5p in the TNM III+IV group was significantly higher than that in the

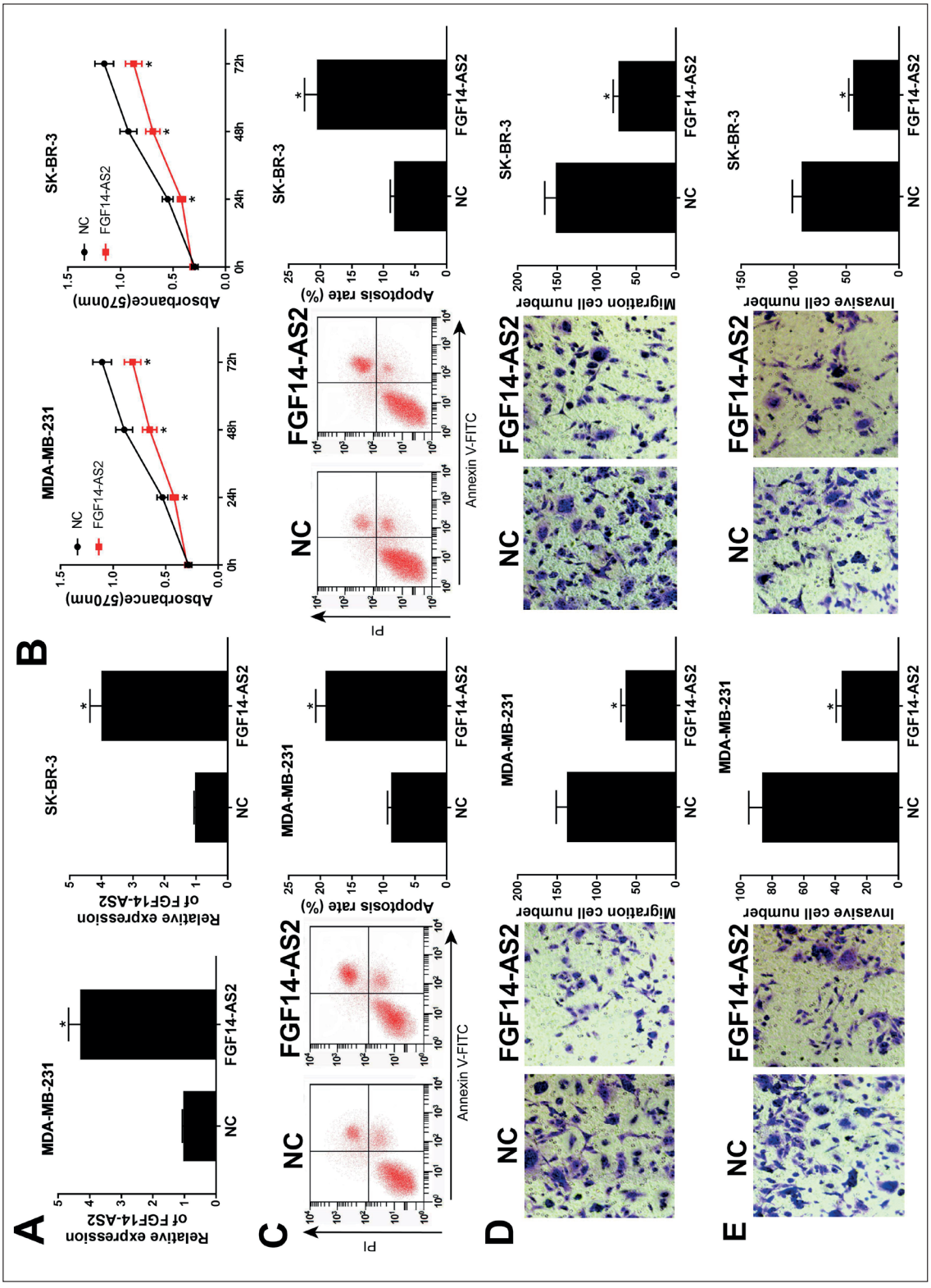

Figure 2. Overexpression of FGF14-AS2 repressed proliferation, migration, invasion, and induced apoptosis in breast cancer cells. MDA-MB-231 and SK-BR-3 cells were transfected with FGF14-AS2 or NC. ***A***, ***B***, Overexpression efficiency of FGF14-AS2 was proved by qRT-PCR in MDA-MB-231 and SK-BR-3 cells. ***B***, ***E***, The proliferation ***(B)***, migration ***(D)***, and invasion ***(E)*** ability, and apoptosis ***(C)*** rates of MDA-MB-231 and SK-BR-3 cells were determined by MTT or Transwell or flow cytometry assays. *$p<0.05$.

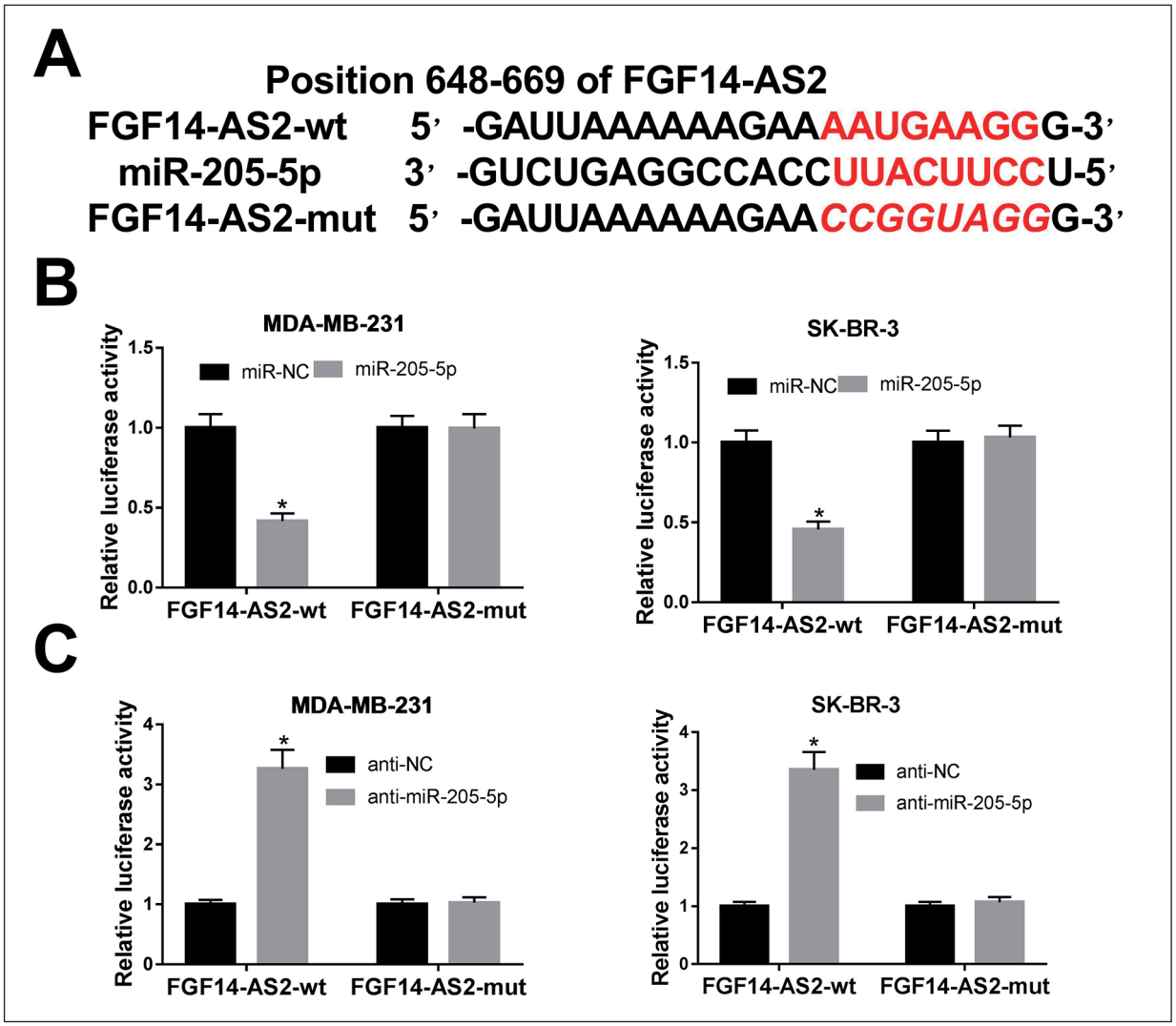

Figure 3. MiR-205-5p was a target of FGF14-AS2 in breast cancer cells. ***A,*** The predicted binding sites of miR-205-5p in FGF14-AS2 by LncBase Predicted v2. ***B, C,*** The Luciferase activity of MDA-MB-231 and SK-BR-3 cells co-transfected with miR-205-5p or miR-NC or anti-miR-205-5p or anti-NC and FGF14-AS2-wt or FGF14-AS2-mut were detected by a Dual-Luciferase Reporter Assay. *$p<0.05$.

TNM I+II group (Figure 4B). Besides, compared to the group with tumor size ≤2 cm, miR-205-5p in the >2 cm group was strikingly up-regulated (Figure 4C). Pearson's correlation coefficient indicated that between FGF14-AS2 and miR-205-5p the expression levels in breast cancer tissues were inversely correlated (Figure 4D). Moreover, the overexpression of FGF14-AS2 could inhibit the expression levels of miR-205-5p in both MDA-MB-231 and SK-BR-3 cells, and FGF14-AS2 knockdown enhanced miR-205-5p expression levels (Figure 4E). Then, miR-205-5p was up-regulated in breast cancer tissues and cells and was inversely correlated with FGF14-AS2.

Inhibition of MiR-205-5p Impeded Proliferation, Migration, Invasion, and Induced Apoptosis in Breast Cancer Cells

In consideration of the above results, MDA-MB-231 and SK-BR-3 cells were transfected with anti-miR-205-5p or anti-NC to explore the functions of miR-205-5p on breast cancer progression. First, we found that miR-205-5p was markedly down-regulated in both MDA-MB-231 and SK-BR-3 cells which were transfected with anti-miR-205-5p (Figure 5A). Besides, the proliferation, migration, and invasion ability of MDA-MB-231 and SK-BR-3 cells were transfected with anti-miR-205-5p and were remarkably inhibited

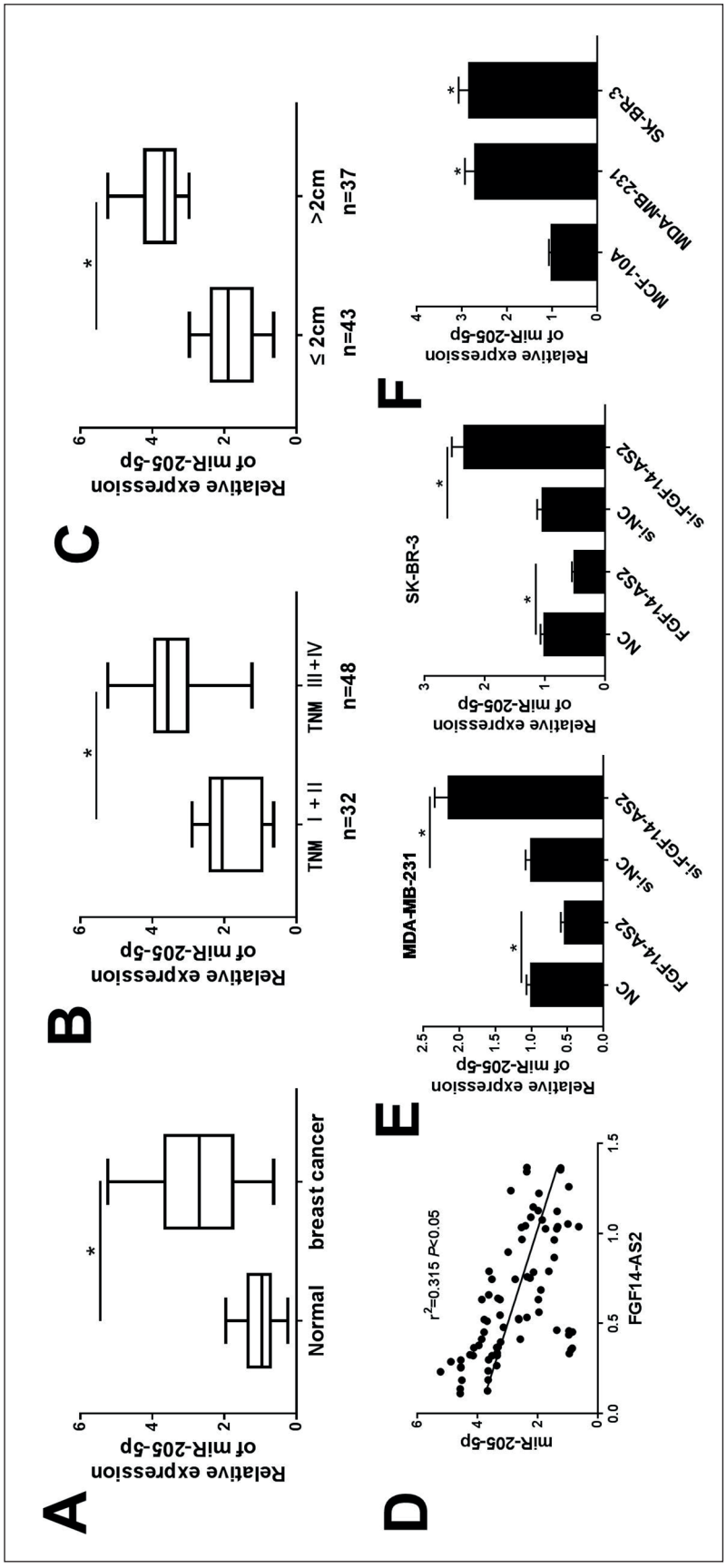

Figure 4. MiR-205-5p was up-regulated in breast cancer tissues and cells. ***A***, and ***F***, qRT-PCR assays were utilized to detect the miR-205-5p expression levels in breast cancer tissues ***(A)*** and cells ***(F)***. ***B***, The expression of miR-205-5p was positively correlated with TNM stage. ***C***, MiR-205-5p expression was positively correlated with tumor size. ***D***, The relationship between FGF14-AS2 and miR-205-5p expression levels in breast cancer tissues were analyzed by Pearson's correlation coefficient. ***E***, qRT-PCR assays were utilized to detect miR-205-5p expression in MDA-MB-231 and SK-BR-3 cells were transfected with NC, FGF14-AS2, si-NC, and si-FGF14-AS2, respectively. *$p<0.05$.

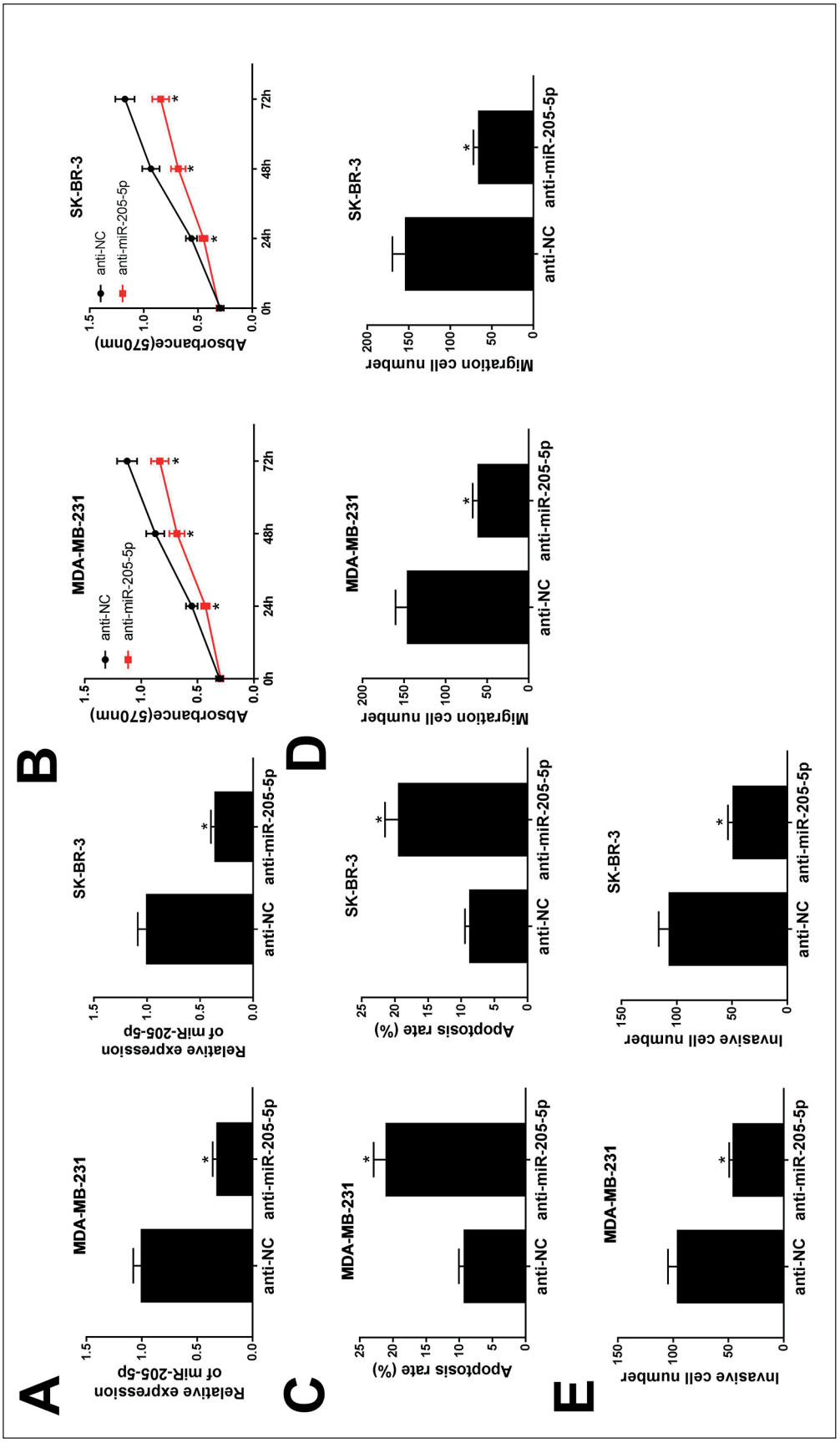

Figure 5. Inhibition of miR-205-5p impeded proliferation, migration, invasion, and induced apoptosis in breast cancer cells. MDA-MB-231 and SK-BR-3 cells were transfected with anti-NC or anti-miR-205-5p. ***A,*** Knockdown efficiency of miR-205-5p was determined by qRT-PCR in MDA-MB-231 and SK-BR-3 cells. ***B, E,*** The proliferation ***(B)***, migration ***(D)*** and invasion ***(E)*** ability, and apoptosis ***(C)*** rates of MDA-MB-231 and SK-BR-3 cells were determined by MTT or transwell or flow cytometry assays. *$p<0.05$.

(Figures 5B, D, and E). Moreover, the apoptosis rates of MDA-MB-231 and SK-BR-3 cells were transfected with anti-miR-205-5p and were remarkably enhanced (Figure 5C). In principle, the inhibition of miR-205-5p could impede proliferation, migration, invasion, and induce apoptosis in breast cancer cells.

Overexpression of FGF14-AS2 Undermined the MiR-205-5p Induced Effects on Proliferation, Migration, Invasion, and Apoptosis in Breast Cancer Cells

To determine whether FGF14-AS2 affects breast cancer cells proliferation, migration, invasion, and apoptosis by regulating miR-205-5p, the miR-NC, miR-205-5p, miR-205-5p+NC, and miR-205-5p+FGF14-AS2 were transfected into MDA-MB-231 and SK-BR-3 cells for rescue experiment. The result from qRT-PCR assay showed that miR-205-5p overexpression markedly up-regulated miR-205-5p expression in both MDA-MB-231 and SK-BR-3 cells, while the overexpression of FGF14-AS2 could reverse this trend (Figure 6A). In addition, MTT, transwell and flow cytometry assays showed that miR-205-5p overexpression strikingly facilitated proliferation, migration, and invasion, and repressed apoptosis of MDA-MB-231 and SK-BR-3 cells, while the overexpression of FGF14-AS2 could reverse miR-205-5p induced effects on proliferation, migration, invasion, and apoptosis (Figures 6B-6E).

Discussion

As in other countries, breast cancer is the most common malignant tumor in China, threatening the lives and health of the female population. Although the treatment of breast cancer has made great progress, the efficacy is still unsatisfactory. Many researches[13-15] have indicated the crucial roles of lncRNAs in the progression of diverse tumors. In this study, we aimed at exploring the expression and molecular mechanism of FGF14-AS2 in breast cancer and provide a theoretical basis for developing new strategies for diagnosis and treatment of breast cancer.

It is well documented that the abnormal expression of lncRNAs plays a vital role in the tumorigenesis and progression of breast cancer. For example, lncRNA SNHG20 and HOXA11-AS were up-regulated in breast cancer tissues and promoted proliferation and migration of breast cancer cells[16,17]. Ma et al[18] reported that lncRNA FGF13-AS1 was down-regulated in breast cancer tissues, and was associated with poor prognosis. In this study, we found that FGF14-AS2 was down-regulated in breast cancer tissues and cells and correlated with tumor stage and size. The overexpression of FGF14-AS2 could repress proliferation, migration, invasion, and induce apoptosis in breast cancer cells. Yang et al[12] pointed out that the decreased expression of FGF14-AS2 was correlated with tumor size and stage as well as lymph node metastasis, which was consistent with our study.

Tay et al[19] have demonstrated that lncRNAs function as competing endogenous RNAs, binding to specific microRNAs (miRNA) to regulate the progression of multiple diseases. MiRNAs, a kind of non-coding RNA with a length of 20-200 nucleotides, mainly regulate gene expression by targeting the 3' untranslated region of target miRNAs, and participate in diversiform biological processes such as cell differentiation, proliferation, invasion, and apoptosis[20]. It has been proven that miRNAs could act as potential biomarkers and therapeutic targets for many diseases[21-23]. MiR-205-5p was reported to be an anti-tumor gene in prostate cancer[24]. Lu et al[25] showed that miR-205-5p promoted paclitaxel resistance and progression of endometrial cancer. In this study, we utilized DIANA-LncBase v2 to predict and confirmed that FGF14-AS2 could directly bind to miR-205-5p with the Luciferase Reporter Assay. Moreover, miR-205-5p was up-regulated in breast cancer tissues and cells, and the inhibition of miR-205-5p could impede proliferation, migration, invasion, and induced apoptosis of breast cancer cells. De Cola et al[26] showed that miR-205-5p was highly expressed in breast cancer stem cells and related to drug resistance in targeted therapy. De Cola et al[27] also showed that miR-205-5p inhibition could recede metastatic of breast cancer cells. Besides, the overexpression of FGF14-AS2 undermined the miR-205-5p induced effects on proliferation, migration, invasion, and apoptosis in breast cancer cells.

Conclusions

We found that FGF14-AS2 was down-regulated while miR-205-5p was up-regulated in breast cancer tissues and cells and correlated with

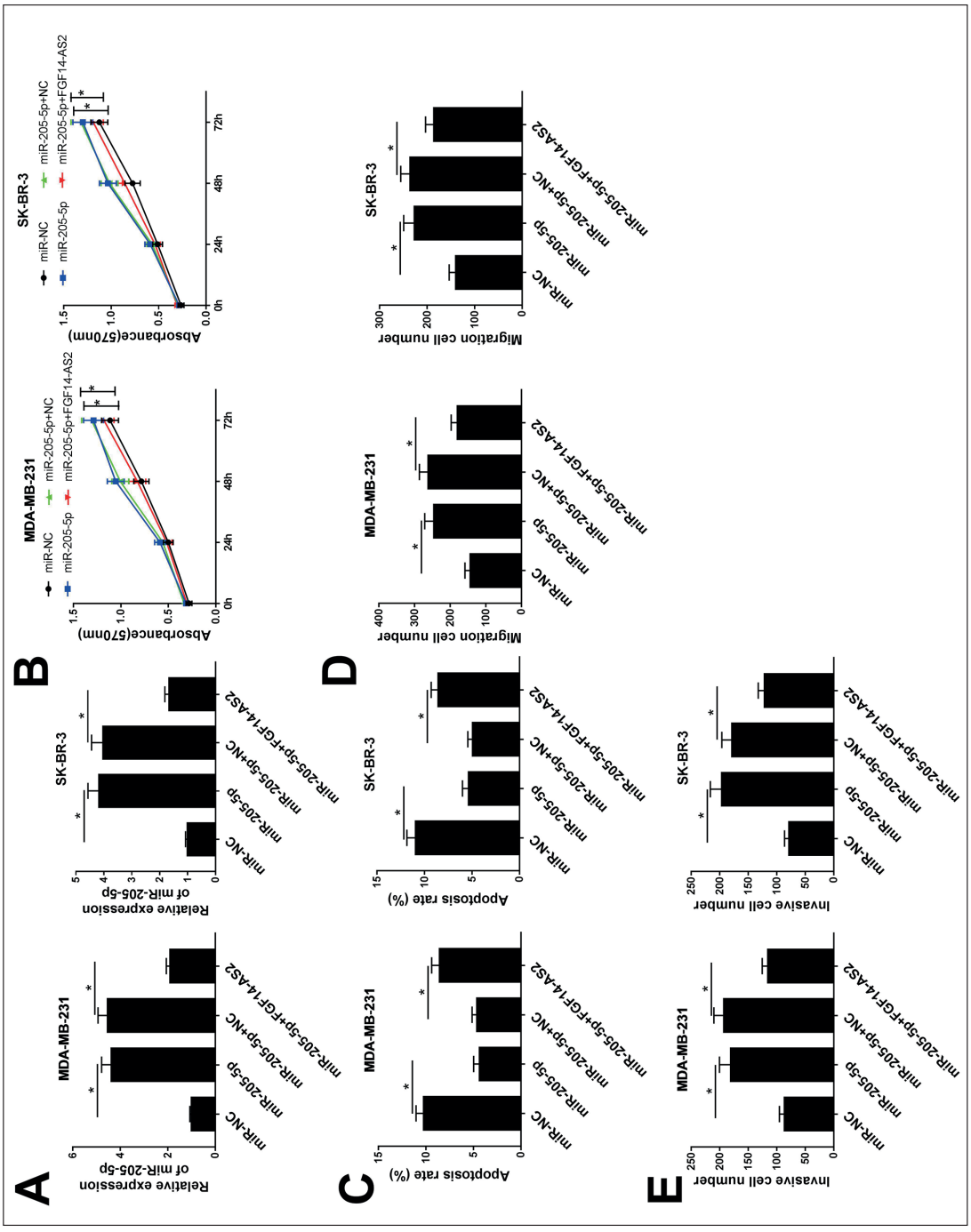

Figure 6. Overexpression of FGF14-AS2 undermined the miR-205-5p induced effects on proliferation, migration, invasion, and apoptosis in breast cancer cells. MDA-MB-231 and SK-BR-3 cells introduced with miR-NC or miR-205-5p or miR-205-5p+FGF14-AS2, respectively. ***A***, qRT-PCR assays were performed for detection miR-205-5p expression in MDA-MB-231 and SK-BR-3 cells. ***B***, ***E***, MTT, transwell, and flow cytometry assays were performed for determining the proliferation ***(B)***, migration ***(D)***, and invasion ***(E)*** ability, and apoptosis ***(C)*** rates of MDA-MB-231 and SK-BR-3. *$p<0.05$.

tumor stage and size. FGF14-AS2 could directly bind to miR-205-5p to repress proliferation, migration, invasion ability, and induced apoptosis in breast cancer cells. This study may provide a potential therapeutic strategy for breast cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA Cancer J Clin 2011; 61: 409-418.
2) Cadoo KA, Traina TA, King TA. Advances in molecular and clinical subtyping of breast cancer and their implications for therapy. Surg Oncol Clin N Am 2013; 22: 823-840.
3) Zardavas D, Irrthum A, Swanton C, Piccart M. Clinical management of breast cancer heterogeneity. Nat Rev Clin Oncol 2015; 12: 381-394.
4) Li J, Li Z, Zheng W, Li X, Wang Z, Cui Y, Jiang X. LncRNA-ATB: an indispensable cancer-related long noncoding RNA. Cell Prolif 2017; 50. doi: 10.1111/cpr.12381.
5) Li CH, Chen Y. Insight into the role of long noncoding RNA in cancer development and progression. Int Rev Cell Mol Biol 2016; 326: 33-65.
6) Jing H, Qu X, Liu L, Xia H. A novel long noncoding RNA (lncRNA), LL22NC03-N64E9.1, promotes the proliferation of lung cancer cells and is a potential prognostic molecular biomarker for lung cancer. Med Sci Monit 2018; 24: 4317-4323.
7) Misawa A, Takayama K, Urano T, Inoue S. Androgen-induced long noncoding RNA (lncRNA) SOCS2-AS1 promotes cell growth and inhibits apoptosis in prostate cancer cells. J Biol Chem 2016; 291: 17861-17880.
8) Iguchi T, Uchi R, Nambara S, Saito T, Komatsu H, Hirata H, Ueda M, Sakimura S, Takano Y, Kurashige J, Shinden Y, Eguchi H, Sugimachi K, Maehara Y, Mimori K. A long noncoding RNA, lncRNA-ATB, is involved in the progression and prognosis of colorectal cancer. Anticancer Res 2015; 35: 1385-1388.
9) Li H, Wang Y. Long noncoding RNA (lncRNA) MIR22HG suppresses gastric cancer progression through attenuating NOTCH2 signaling. Med Sci Monit 2019; 25: 656-665.
10) Cui C, Zhai D, Cai L, Duan Q, Xie L, Yu J. Long noncoding RNA HEIH promotes colorectal cancer tumorigenesis via counteracting mir-939-mediated transcriptional repression of Bcl-xL. Cancer Res Treat 2018; 50: 992-1008.
11) Yu H, Xu Y, Zhang D, Liu G. Long noncoding RNA LUCAT1 promotes malignancy of ovarian cancer through regulation of miR-612/HOXA13 pathway. Biochem Biophys Res Commun 2018; 503: 2095-2100.
12) Yang F, Liu YH, Dong SY, Ma RM, Bhandari A, Zhang XH, Wang OC. A novel long non-coding RNA FGF14-AS2 is correlated with progression and prognosis in breast cancer. Biochem Biophys Res Commun 2016; 470: 479-483.
13) Zhang JJ, Fan LP. Long non-coding RNA CRNDE enhances cervical cancer progression by suppressing PUMA expression. Biomed Pharmacother 2019; 117: 108726.
14) Niu L, Zhou Y, Zhang W, Ren Y. Long noncoding RNA LINC00473 functions as a competing endogenous RNA to regulate MAPK1 expression by sponging miR-198 in breast cancer. Pathol Res Pract 2019: 152470. doi: 10.1016/j.prp.2019.152470. [Epub ahead of print].
15) Guo J, Li Y, Duan H, Yuan L. LncRNA TUBA4B functions as a competitive endogenous RNA to inhibit gastric cancer progression by elevating PTEN via sponging miR-214 and miR-216a/b. Cancer Cell Int 2019; 19: 156.
16) Guan YX, Zhang MZ, Chen XZ, Zhang Q, Liu SZ, Zhang YL. LncRNA SNHG20 participated in proliferation, invasion, and migration of breast cancer cells via miR-495. J Cell Biochem 2018; 119: 7971-7981.
17) Su JC, Hu XF. Long noncoding RNA HOXA11AS promotes cell proliferation and metastasis in human breast cancer. Mol Med Rep 2017; 16: 4887-4894.
18) Ma F, Liu X, Zhou S, Li W, Liu C, Chadwick M, Qian C. Long non-coding RNA FGF13-AS1 inhibits glycolysis and stemness properties of breast cancer cells through FGF13-AS1/IGF2BPs/Myc feedback loop. Cancer Lett 2019; 450: 63-75.
19) Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. Nature 2014; 505: 344-352.
20) Cai Y, Yu X, Hu S, Yu J. A brief review on the mechanisms of miRNA regulation. Genomics Proteomics Bioinformatics 2009; 7: 147-154.
21) Shin VY, Chu KM. MiRNA as potential biomarkers and therapeutic targets for gastric cancer. World J Gastroenterol 2014; 20: 10432-10439.
22) McGuire A, Brown JA, Kerin MJ. Metastatic breast cancer: the potential of miRNA for diagnosis and treatment monitoring. Cancer Metastasis Rev 2015; 34: 145-155.
23) Backes C, Meese E, Keller A. Specific miRNA disease biomarkers in blood, serum and plasma: challenges and prospects. Mol Diagn Ther 2016; 20: 509-518.
24) Yamada Y, Nishikawa R, Kato M, Okato A, Arai T, Kojima S, Yamazaki K, Naya Y, Ichikawa T, Seki N. Regulation of HMGB3 by antitumor miR-205-5p inhibits cancer cell aggressiveness and is involved in prostate cancer pathogenesis. J Hum Genet 2018; 63: 195-205.

25) Lu Z, Xu Y, Yao Y, Jiang S. MiR-205-5p contributes to paclitaxel resistance and progression of endometrial cancer by downregulating FOXO1. Oncol Res 2019. doi: 10.3727/096504018X15452187888839. [Epub ahead of print].

26) De Cola A, Volpe S, Budani MC, Ferracin M, Lattanzio R, Turdo A, D'Agostino D, Capone E, Stassi G, Todaro M, Di Ilio C, Sala G, Piantelli M, Negrini M, Veronese A, De Laurenzi V. MiR-205-5p-mediated downregulation of ErbB/HER receptors in breast cancer stem cells results in targeted therapy resistance. Cell Death Dis 2015; 6: e1823.

27) De Cola A, Lamolinara A, Lanuti P, Rossi C, Iezzi M, Marchisio M, Todaro M, De Laurenzi V. MiR-205-5p inhibition by locked nucleic acids impairs metastatic potential of breast cancer cells. Cell Death Dis 2018; 9: 821.