MicroRNA-431 serves as a tumor inhibitor in breast cancer through targeting FGF9

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Abstract. Breast cancer has become an important public health problem. Moreover, the functions of microRNA-431 (miR-431) have been detected in human cancers other than breast cancer. Hence, we investigated the role of miR-431 in progression of breast cancer. RT-qPCR and Western blot analysis were performed to assess expression of miR-431 and genes. The regulatory mechanism of miR-431 was investigated using MTT, Transwell and luciferase reporter assay. Decreased miR-431 expression was identified in breast cancer, which was related to aggressive behavior. Furthermore, miR-431 restrained cell proliferation, metastasis and EMT in breast cancer. miR-431 induced apoptosis through enhancing Bax expression. In addition, miR-431 was found to directly target FGF9. Moreover, upregulation of FGF9 impaired the anti-tumor effect of miR-431 in breast cancer. miR-431 restrained cell viability and metastasis in breast cancer through targeting FGF9, indicating that miR-431 serves as a tumor inhibitor in breast cancer.

Introduction

Breast cancer has become a major public health problem. Its incidence accounts for 7-10% of all types of malignant tumors, and its incidence is often related to heredity (1). The breast is not an important organ for maintaining human life, but free cancer cells can spread throughout the body with blood or lymphs because of the loose connection between breast cancer cells (2). Furthermore, it can cause metastasis and endanger life. Metastasis and spread of cancer cells are the main cause of increased mortality in breast cancer patients (3). There are many related factors affecting the prognosis of breast cancer, among which the main factors are tumor invasion and pathological biological characteristics (4). Therefore, the best way to reduce breast cancer patient mortality is early detection and treatment.

As important regulators, microRNAs (miRNAs) regulate various biological processes by interacting with some target genes. The dysregulation of miRNAs have been reported to exert different effects in progression of breast cancer. For example, miR-144 suppressed proliferation, invasion, and migration of breast cancer cells through inhibiting CEP55 (5). Inversely, miR-221/222 targets adiponectin receptor 1 to promote epithelial-to-mesenchymal transition (EMT) in breast cancer (6). The dysregulation of microRNA-431 (miR-431) in human diseases and cancers has attracted attention. For instance, miR-431 restrained trophoblast migration and invasion via targeting ZEB1 in preeclampsia (7). Moreover, miR-431 can function as a chemosensitizer and potentiator of drug activity in adrenocortical carcinoma (8) and miR-431 was found to promote differentiation and regeneration of old skeletal muscle by targeting Smad4 (9). In human cancers, miR-431 usually acts as a tumor inhibitor through regulating target genes. Liu *et al* found that downregulation of miR-431 expression was associated with lymph node metastasis and promoted cell invasion in papillary thyroid carcinoma (10). Yang *et al* (11) demonstrated that miR-431 inhibited cell proliferation and induced cell apoptosis via targeting CDK14 in pancreatic cancer. However, the specific role of miR-431 remains blurry and needs to be illuminated in breast cancer.

The fibroblast growth factor (FGF) family containing 18 related proteins can be involved in skeletal development and homeostasis (12). As a member of FGF family, fibroblast growth factor 9 (FGF9) was associated with poor prognosis in patients with resected non-small cell lung cancer (13). Moreover, the promoting effects of FGF9 on cell proliferation and migration were identified in human hepatocellular carcinoma (14). FGF9, as a target gene, has been found to be mediated by some miRNAs. Li *et al* (15) proposed that miR-665 inhibited vascular

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smooth muscle cell proliferation via targeting FGF9. miR-140-5p suppressed tumor growth and metastasis by suppressing FGF9 expression in hepatocellular carcinoma (16). However, the interaction between miR-431 and FGF9 has not been reported in previous studies. Thus, we investigated their relationship as well as the functions of miR-431 in breast cancer progression. This study explored a novel biomarker for diagnosis of breast cancer patients.

Materials and methods

Clinical tissues. Ninety-eight breast cancer patients in Jining No. 1 People's Hospital (Jining, China) participated in the study. Informed consents were obtained from all breast cancer patients. Patients with breast cancer did not receive any treatment except for surgery. Permission for this study was acquired from the Institutional Ethics Committee of Jining No. 1 People's Hospital.

Cell culture and transfection. Human breast epithelial cell line MCF10A and breast cancer cells MDA-MB-231 were from the Cell Bank of Chinese Academy of Sciences (Shanghai, China). The growth conditions were 5% CO_2, at 37˚C and culture solution (90% DMEM medium + 10% FBS). Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) was applied to transfer miR-431 mimics, miR-431 inhibitors, FGF9 siRNA or FGF9 plasmid (GenePharma Co., Ltd.) into MDA-MB-231 cells.

RNA isolation and RT-qPCR. Total RNA isolation was performed using TRIZOL reagent (Invitrogen; Thermo Fisher Scientific, Inc.). In addition, cDNA solution was obtained using PrimeScript reverse transcription kit (Qiagen, Inc.). RT-qPCR assay was performing using miScript SYBR Green PCR kit (Qiagen, Inc.) based on the manufacturer's instruction. U6 or GAPDH was used as the control of miR-431 or FGF9, which were quantified with the $2^{-\Delta\Delta cq}$ method. The primers used in our work were as follows: miR-431, forward primer: 5'-CAG GCC GTC ATG CAA A-3', reverse primer: 5'-CGC TTC AGA ATT TGC GTG TCA T-3'; U6, forward primer: 5'-CTC GCT TCG GCA GCA CA-3', reverse primer: 5'-AAC GCT TCA CGA ATT TGC GT-3'; FGF9 forward primer: 5'-GGA CTA AAC GGC ACC AGA AA-3', reverse primer: 5'-CCA TCC AAG CCT CCA TCA TA-3'; GAPDH forward, 5'-ACA TCG CTC AGA CAC CAT G-3', reverse, 5'-TGT AGT TGA GGT CAA TGA AGG G-3'.

MTT assay. Transfected MDA-MB-231 cells ($2x10^3$ cells/well) were prepared in a 96-well plate. MDA-MB-231 cells were incubated for 24, 48, 72 or 96 h in DMEM medium. Next, 10 μl of MTT solution was added to incubate the cells for 4 h. MTT solution was aspirated and Formazan solution was added to fully dissolve the crystals. The absorbance at 490 nm was examined by a microscope (Olympus Corp., Tokyo, Japan).

Transwell assay. The upper chamber was added with 60 μl of diluted Matrigel to observe cell invasion. After 30 min, MDA-MB-231 cell suspension ($2x10^3$ cells/well) was added to the Transwell upper chamber. Next, 500 μl of DMEM medium (10% FBS) was added to 24-well plates in the lower chamber. After 24 h, 0.1% crystal violet was applied to stain the invaded cells. Cell migration experiment is the same as the cell invasion experimental step except that Matrigel is not used. Observation and photographing were performed by light microscopy.

Table I. Relationship between miR-431 expression and the clinicopathological characteristics of breast cancer patients.

		miR-431		
Characteristics	Cases	High	Low	P-value
Age (years)				0.07
≥50	40	16	24	
<50	58	18	40	
Tumor size				0.01[a]
<2 cm	27	10	17	
≥2 cm	71	24	47	
Lymph node metastasis				0.005[a]
No	28	9	19	
Yes	70	25	45	
Her-2 status				0.25
Positive	52	18	34	
Negative	46	16	30	
ER status				0.31
Positive	45	15	30	
Negative	53	19	34	
PR status				0.06
Positive	36	16	20	
Negative	62	18	44	

Statistical analyses were performed by the χ^2 test. [a]P<0.05 was considered as statistically significant.

Western blot analysis. Protein samples were acquired by using RIPA lysis buffer (Beyotime). Protein was separated by 10% SDS-PAGE. Protein samples were transferred to PVDF membranes. Blocked with 5% non-fat milk, protein samples were incubated overnight at 4˚C with E-cadherin, N-cadherin, vimentin, Bcl-2, Bax and GAPDH primary antibodies (Abcam). After washing, protein samples were incubated with secondary antibodies (Abcam) for 1 h. ECL kit (Beyotime) was used to assess protein bands. In addition, protein was quantified with Image Lab Software (Bio-Rad).

Dual luciferase reporter assay. The pmirGLO luciferase reporter vector (Promega Corporation) was inserted with 3'-UTR of wt-FGF9 or Mut-FGF9. Then, MDA-MB-231 cells with the luciferase vector and miR-431 mimics were incubated for 48 h. Finally, luciferase activities were assessed by dual-luciferase reporter assay system (Promega Corporation).

Statistical analysis. Data were analyzed and illustrated using SPSS 17.0 and Graphpad Prism 6, respectively, and shown as mean ± SD. Differences were analyzed using Student's t-test or one-way ANOVA. Univariate Kaplan-Meier method with

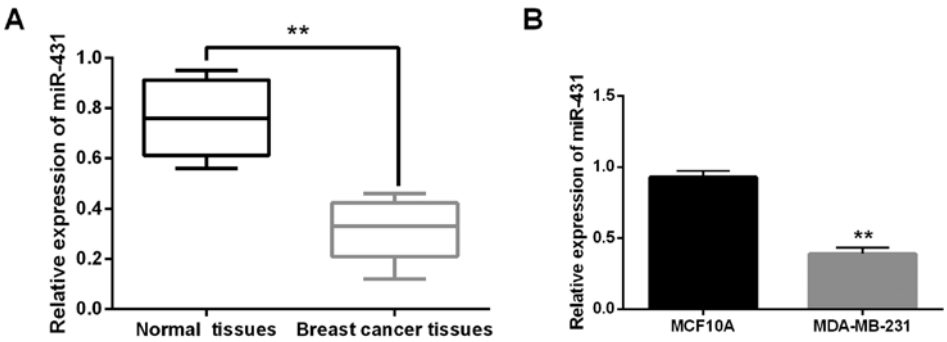

Figure 1. Dysregulation of miR-431 in breast cancer. (A) mRNA miR-431 expression in breast cancer tissues. (B) miR-431 expression in MDA-MB-231 and MCF10A cells. **P<0.01.

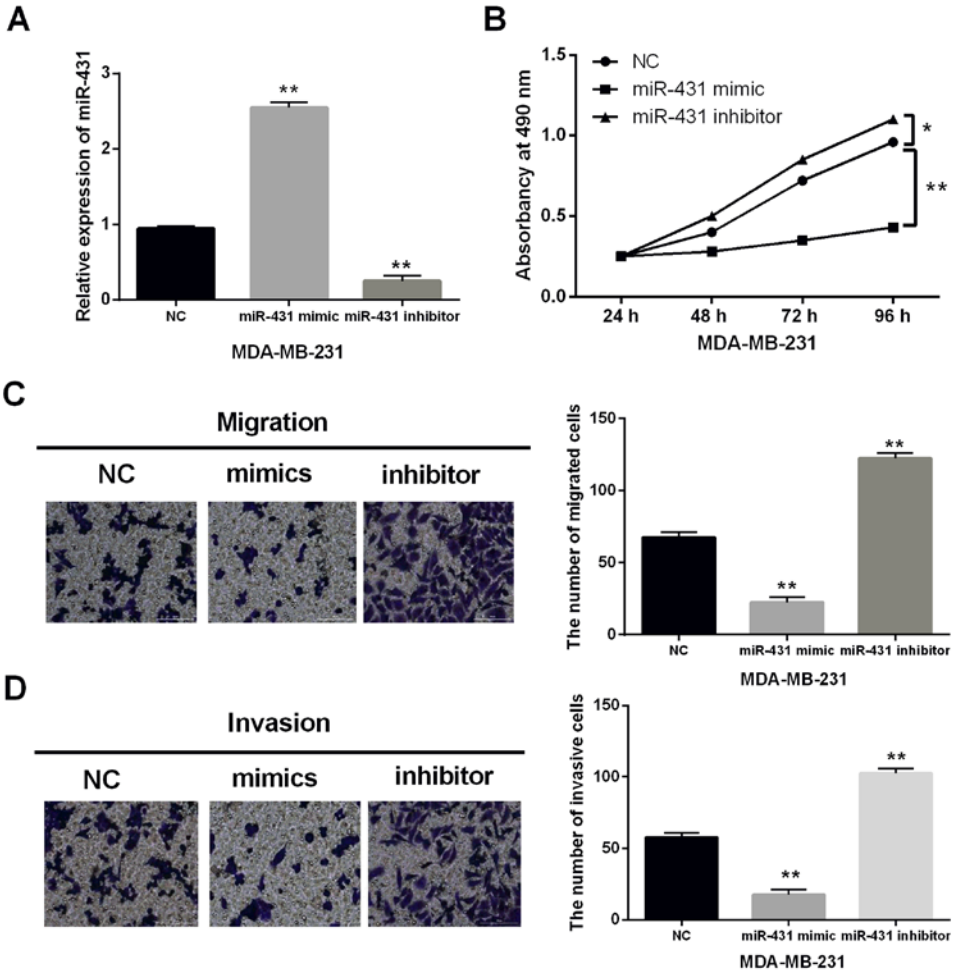

Figure 2. miR-431 restrains cell proliferation and metastasis in breast cancer. (A) miR-431 expression in MDA-MB-231 cells with its mimics or inhibitor. (B-D) Cell proliferation, migration and invasion in MDA-MB-231 cells with miR-431 mimics or inhibitor. *P<0.05, **P<0.01.

log-rank test and χ^2 test was used to analyze the association between miR-431 and patient survival rate or clinical features. Differences were considered significant at P<0.05.

Results

Dysregulation of miR-431 was identified in breast cancer. miR-431 expression was detected in breast cancer tissues to explore dysregulation. It was found that miR-431 was down-regulated in breast cancer tissues compared to normal tissues (P<0.01, Fig. 1A). Similarly, miR-431 expression was lower in MDA-MB-231 cells than that in MCF10A cells (P<0.01, Fig. 1B). Correlation was identified between miR-431 expression and clinical features in breast cancer patients. miR-431 expression was found to be correlated with tumor size and lymph node metastasis (P<0.05, Table I). The results indicated that miR-431 may be dysregulated in breast cancer.

miR-431 restraines cell proliferation and metastasis in breast cancer. To further illuminate the role of miR-431 in breast

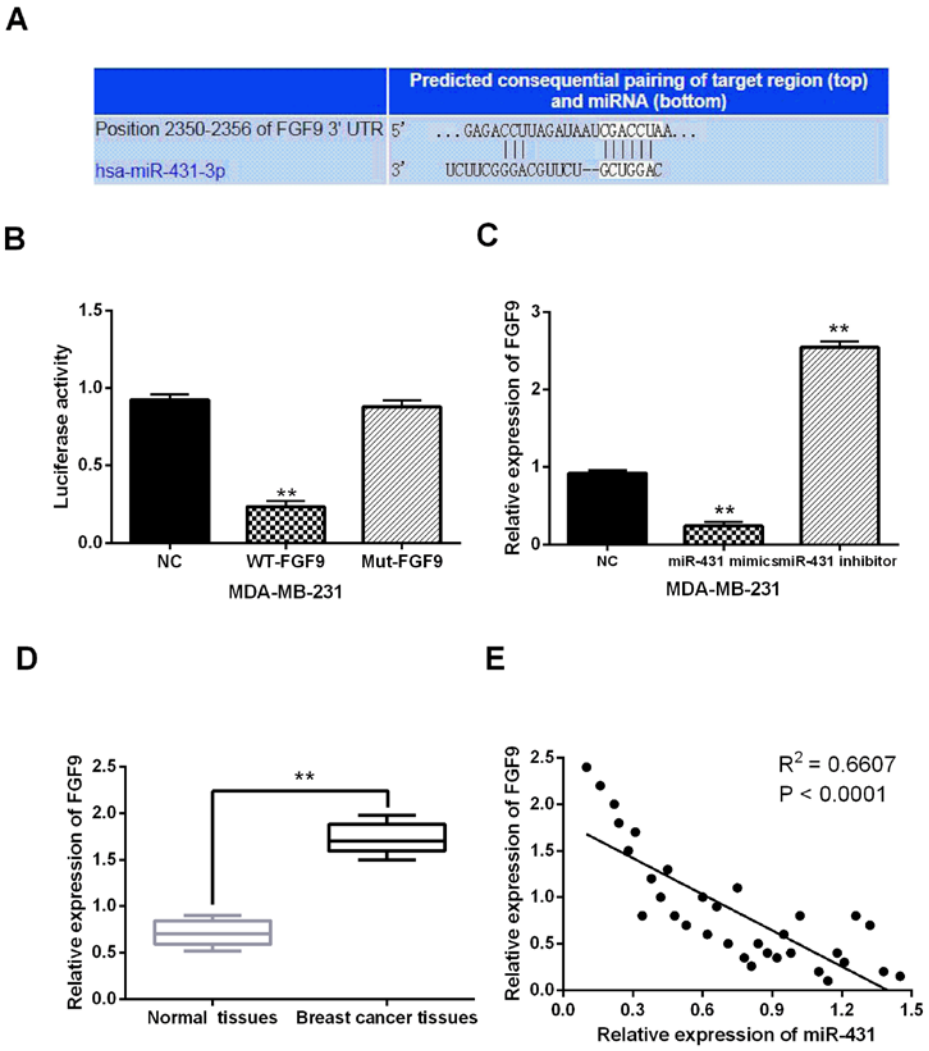

Figure 3. miR-431 directly targets FGF9. (A) The binding sites between FGF9 and miR-431. (B) Luciferase reporter assay (C) FGF9 expression regulated by miR-431 mimics or inhibitor in MDA-MB-231 cells. (D) FGF9 expression in breast cancer tissues. (E) miR-431 was negatively correlated with FGF9 in breast cancer tissues. **P<0.01.

cancer, gain and loss functional experiment was performed in MDA-MB-231 cells with miR-431 mimics or inhibitor. It was found that miR-431 mimics enhanced the expression level in MDA-MB-231 cells, when miR-431 inhibitor decreased its expression (P<0.01, Fig. 2A). MTT assay indicated that MDA-MB-231 cell proliferation was repressed by miR-431 mimics and accelerated by miR-431 inhibitor (P<0.01, Fig. 2B). Moreover, cell metastasis was assessed by cell migration and invasion. We found that miR-431 mimics restrained cell migration and invasion, whereas miR-431 inhibitor facilitated cell metastasis in MDA-MB-231 cells (P<0.01, Fig. 2C and D). Hence, upregulation of miR-431 restrained cell proliferation and metastasis in breast cancer.

miR-431 directly targets FGF9. Targets of miR-431 were searched in TargetScan database (http://www.targetscan.org/) to explain its regulatory mechanism in breast cancer. It predicted that miR-431 has a site binding to the 3'-UTR of FGF9 (Fig. 3A). Then, luciferase reporter assay was conducted in MDA-MB-231 cells for verification. It showed that miR-431 mimics reduced Wt-FGF9 luciferase activity, but did not affect Mut-FGF9 luciferase activity (P<0.01, Fig. 3B). Moreover, we found that FGF9 was downregulated by miR-431 mimics, and upregulated by miR-431 inhibitor in MDA-MB-231 cells (P<0.01, Fig. 3C). In addition, upregulation of FGF9 was identified in breast cancer tissues in contrast to normal tissues (P<0.01, Fig. 3D). Furthermore, a negative correlation between miR-431 and FGF9 expression was detected in breast cancer tissues (P<0.0001, R2=0.6607; Fig. 3E). Collectively, miR-431 directly targets FGF9 and the expression is inversely regulated in breast cancer.

Upregulation of FGF9 impairs the anti-tumor effect of miR-431 in breast cancer. FGF9 vector was transfected into MDA-MB-231 cells to further explore their interaction in breast cancer. RT-qPCR indicated that downregulation of FGF9 induced by miR-431 mimic was recovered by FGF9 vector (Fig. 4A). Similarly, the reverse effect of FGF9 on cell proliferation was observed in MDA-MB-231 cells with miR-431 mimics (Fig. 4B). Moreover, the inhibitory effect of miR-431 on MDA-MB-231 cell migration and invasion was impaired by upregulation of FGF9 (Fig. 4C and D). Based on these results, upregulation of FGF9 impaired the anti-tumor effect of miR-431 in breast cancer.

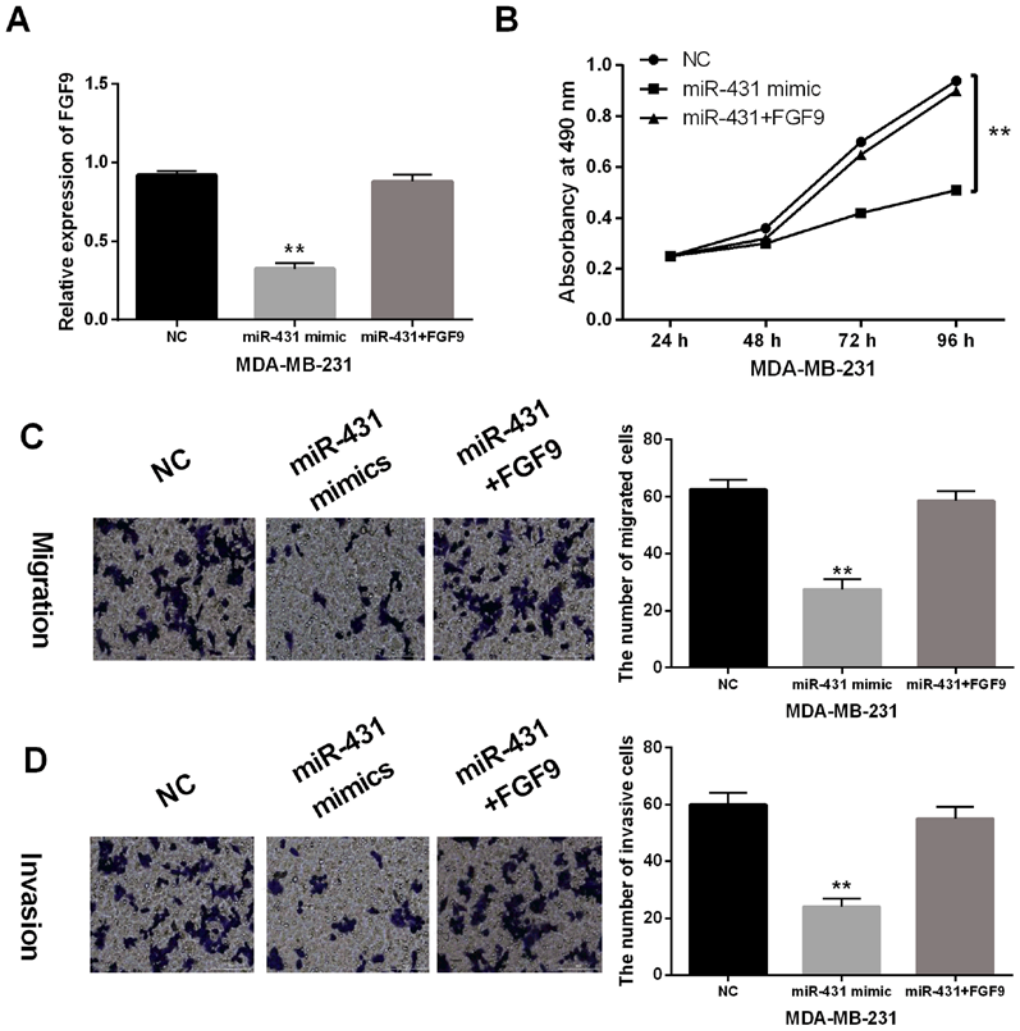

Figure 4. Upregulation of FGF9 impaired the anti-tumor effect of miR-431 in breast cancer. (A) FGF9 expression in MDA-MB-231 cells with miR-431 mimics and FGF9 vector. (B-D) Cell proliferation, migration and invasion in MDA-MB-231 cells containing miR-431 mimics and FGF9 vector. **P<0.01.

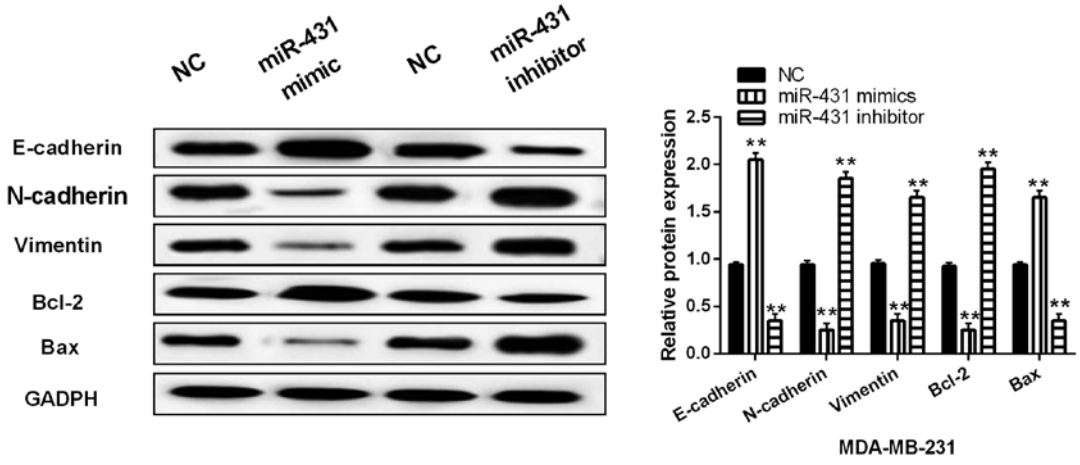

Figure 5. miR-431 hindered EMT and induced apoptosis in breast cancers cells. The expression of E-cadherin, N-cadherin, vimentin, Bax and Bcl-2 was regulated by miR-431 mimics or inhibitor in MDA-MB-231 cells. **P<0.01.

miR-431 hindered EMT and induced apoptosis in breast cancers cells. Finally, expression of genes related to EMT and apoptosis were assessed in MDA-MB-231 cells with miR-431 mimics or inhibitor. miR-431 was found to regulate the expression of E-cadherin, N-cadherin and vimentin. Upregulation of miR-431 promoted E-cadherin expression and suppressed expression of N-cadherin and vimentin (P<0.01, Fig. 5). Downregulation of miR-431 showed

the opposite effect on expression of vimentin, N-cadherin and E-cadherin (P<0.01, Fig. 5). Next, the expression of apoptosis-associated proteins (Bcl-2/Bax) regulated by miR-431 was detected in MDA-MB-231 cells. Bcl-2 expression was inhibited by miR-431 overexpression and enhanced by knockdown of miR-431 (P<0.01, Fig. 5). Inversely, miR-431 mimics promoted Bax expression. In addition, miR-431 inhibitor reduced Bax expression (P<0.01, Fig. 5). Thus, miR-431 hindered EMT and induced apoptosis in breast cancers cells.

Discussion

Many miRNAs have been found to serve as tumor promoter or suppressor in breast cancer, such as miR-29c and miR-374a (17,18). In this study, miR-431 was found to serve as a tumor inhibitor in breast cancer. In particular, downregulation of miR-431 was identified in breast cancer, which was associated with aggressive behavior. In addition, miR-431 restrained cell proliferation and induced apoptosis in breast cancer. Furthermore, miR-431 blocked breast cancer metastasis and EMT, and miR-431 directly targets FGF9. Moreover, upregulation of FGF9 impaired the anti-tumor effect of miR-431 in breast cancer. These results demonstrated that miR-431 was an important regulator in breast cancer progression.

Consistent with our results, downregulation of miR-431 was also found in lung cancer and hepatocellular carcinoma (19,20). Furthermore, Pan *et al* (21) showed that low miR-431 expression was related to lymph node metastasis and clinical TNM stage in hepatocellular carcinoma. Similar results were also identified in breast cancer. Functionally, it was reported that miR-431 inhibited migration, invasion and EMT in hepatocellular carcinoma cells by targeting ZEB1 (22). Moreover, miR-431 suppressed proliferation and metastasis of lung cancer via down-regulating DDX5 (23). The role of miR-431 in breast cancer was the same as the above findings. In addition, we also found that miR-431 induced breast cancer apoptosis through enhancing Bax and repressing Bcl-2 expression. Similar results have not been reported in previous studies. Moreover, previous studies implied that miR-431 exerted effect in human diseases by mediating certain target genes, including FOXA1 and UROC28 (24,25). Here, FGF9 was confirmed to be a target of miR-431.

In the present study, FGF9 was upregulated in breast cancer tissues. Furthermore, FGF9 had negative correlation with miR-431 expression. Some other miRNAs were demonstrated to negatively regulate FGF9 expression, such as miR-182 and miR-219a (26,27). Moreover, it was reported that miR-26a suppressed tumor growth and metastasis via targeting FGF9 in gastric cancer (28). Liang *et al* (29) reported that miR-187 repressed the proliferation of cervical cancer cells through downregulation of FGF9. In addition, downregulation of miRNA-214 contributed to migration and invasion of gastric cancer cells through targeting FGF9 and inducing EMT (30). Consistent with the above results, miR-431 restrained cell viability and metastasis in breast cancer through targeting FGF9. Furthermore, miR-431 blocked EMT and induced apoptosis to play an inhibitory role in breast cancer.

In conclusion, downregulation of miR-431 was related to aggressive behavior in breast cancer. Functionally, miR-431 restrained cell proliferation and metastasis in breast cancer. Moreover, miR-431 hindered EMT and induced apoptosis in breast cancer cells. In addition, miR-431 served as an inhibitor in breast cancer through binding to FGF9. Although the role of miR-431 has been illuminated in this study, the complex regulatory mechanisms of miR-431 still need to be explored.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

WW wrote the manuscript, analyzed and interpreted the patients' data. YD performed PCR and MTT assay. XL and YP were responsible for Transwell assay, Western blot and Dual luciferase reporter assay. JD and DL helped with statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Jining No. 1 People's Hospital (Jining, China). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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