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ORIGINAL ARTICLE

miR-365 inhibits cell invasion and migration of triple negative breast cancer through ADAM10

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Summary

Purpose: *Triple negative breast cancer (TNBC) refers to breast cancer that lacks progesterone receptor (PR), estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2). MicroRNA-365 (miR-365), a new-found microRNA, has been reported to possess significant functions in a multitude of human cancers. The purpose of this study was to detect thoroughly the molecular mechanisms of miR-365 that underlie the progress of TNBC.*

Methods: *The mRNA levels of miR-365 and A Disintegrin and Metalloprotease 10 (ADAM10) were measured by real-time polymerase chain reaction (RT-PCR). Luciferase activity report was applied to verify that ADAM10 was a direct target gene of miR-365. Cell proliferation ability was measured by MTT assay. Transwell assay was utilized to test cell migratory and invasive abilities.*

Results: *We found that miR-365 was low-expressed in breast cancer tissues and 5 TNBC cell lines compared with the paracancerous samples and a normal cell line MCF10A. Meanwhile, we discovered that the expression of ADAM10 was higher in the 5 TNBC cell lines than in the normal cell line MCF10A. The proliferation, migration and invasion abilities were suppressed by overexpression of miR-365, whereas they were enhanced by interfering miR-365 in breast cancer. The luciferase reporter assay demonstrated that miR-365 directly targeted ADAM10 through directly binding to the 3'-untranslated region (3'-UTR). And the expression of ADAM10 was reduced by exogenous overexpression of miR-365, while it was increased by transfecting of miR-365 inhibitor in MDA-MB-231 and BT483 cells. Furthermore, re-expression of ADAM10 reversed partial functions of the suppressive roles on cell proliferation, migration and invasion by miR-365 TNBC.*

Conclusions: *MiR-365 inhibited the proliferation, migration and invasion through directly binding to the 3'-UTR of ADAM10 mRNA in TNBC. It is suggested that miR-365/ADAM10 axis may present a new target for the treatment of breast cancer.*

Key words: *miR-365, proliferation, migration, invasion, ADAM10*

Introduction

Breast cancer, the most widespread threat for women's health, is one of the most common malignant tumor worldwide [1]. An estimated 1.3 million women suffer from breast cancer, and 450 thousand patients died each year of this disease [2]. Previous studies have suggested to divide breast cancer into 5 subtypes that included Luminal A subtype, Luminal B subtype, HER2-overexpressing subtype, basal-like subtype and unclassified subtype [3,4]. The majority of TNBC belongs to the basal-like subtype, which doesn't resemble the biological behavior and clinical pathologic features of the other breast cancer subtypes [5,6]. In recent years, TNBC has become a new hotspot of research, and has the characteristics of early recurrence, rapid progress and poor prognosis compared with other subtypes [7,8].

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miRNAs, which are small, non-coding single-stranded RNAs, with approximately 22-28 nucleotides in length, are crucial molecules that act as tumor suppressors or oncogenes in human cancer [9]. miRNAs play an important role in gene silencing by directly binding to the 3'-UTR of the target mRNAs and regulating the expression of the target genes at post-transcriptional level [10-12]. MiR-365, a new-found microRNA, has been reported to play important roles in several human cancers including malignant melanoma, lung cancer, osteosarcoma, colon cancer, gastric cancer, hepatocellular carcinoma and ovarian cancer [13-18]. Han et al demonstrated that the mRNA levels of miR-365 was obviously lower in breast cancer than in healthy controls, and overexpression of miR-365 inhibited cell growth and chemoresistance of breast cancer [19]. Previous studies have reported that miR-365 inhibited cell growth and metastasis by directly binding to the 3'-UTR of ADAM10 mRNA in hepatocellular carcinoma [20].

More than 30 members of the A Disintegrin and Metalloprotease (ADAMs) family have been authenticated as multifunctional, membrane-bound cell surface glycoproteins [21]. ADAM10 is a member of ADAMs family, which has been reported to be overexpressed and played important roles in a variety of malignant tumors, such as prostate cancer, liver cancer and gastric cancer [22-24]. ADAM10 has been reported to mediate drug resistance and it was associated with prognosis of HER2-positive breast cancer patients [25].

In our study, we aimed to search the relationship between the expression of miR-365 and ADAM10 in TNBC. mRNA level of miR-365 was tested in tissues and cell lines, and the biological functions of miR-365 were examined in TNBC. Furthermore, we also carried out rescue test to investigate whether miR-365 affect cell proliferation, migration and invasion through ADAM10 in TNBC.

Methods

Tissues and cell lines

Fifty-eight human TNBC tissue samples and the matched paracancer tissue samples were obtained from Tongji Hospital during 2012 to 2016. Signed informed consents were obtained from all participants before study entry. This study was approved by the Ethical Committee of Tongji Hospital.

Five human TNBC breast cancer cell lines (MCF-7, BT549, BT483, BT474, MDA-MB-231) and a normal human breast tissue cell line (MCF10A) were purchased from American Type Culture Collection (ATCC, Rockville, MD, USA). All cell lines were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco, Gaithersburg, MD, USA) supplemented with 10% fetal bovine serum (FBS) (HyClone, Logan, USA) and 1% penicillin/streptomycin (Gibco, Waltham, MA). All the cells were cultured at 37°C in an atmosphere with 95% oxygen and 5% CO_2.

Quantitative real-time-polymerase chain reaction (qRT-PCR)

Total RNAs were extracted by using the TRIzol Reagent (Invitrogen, Carlsbad, CA, USA) from tissues and cell lines. miRNAs were extracted using the MiRcute Extraction and Separation of miRNAs Kit (Tiangen, Beijing, China). The reverse transcription was performed to synthesize the complementary deoxyribose nucleic acids (cDNAs) using the PrimeScript II 1st Strand cDNA Synthesis Kit (TaKaRa, Dalian, China) according to the manufacturer's protocol. RT-PCR was conducted using SYBR Green PCR Master Mix (Applied TaKaRa, Otsu, Shiga, Japan). Glyceraldheyde 3-phosphate dehydrogenase (GAPDH) and snRNA U6 (U6) were used as normalizers for ADAM10 and miRNA-365, respectively. The RT-PCR experiments were carried out on Roche Light Cycler 480 instrument (Roche, Basel, Switzerland). The relative expression was calculated with $2^{-\Delta\Delta CT}$.

Western blotting

Tissues and cell lines were prepared to extract total proteins using Radioimmunoprecipitation Assay Lysis Buffer (RIPA; Beyotime, Shanghai, China) containing phenylmethylsulfonyl fluoride (PMSF) (Beyotime). The protein was quantified by bicinchoninic acid (BCA) reagent Kit (Solarbio, Beijing, China). After separation by running sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), the protein samples were transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After blocked in 5% skim milk for 30 min, the membranes were probed with anti-ADAM10 monoclonal primary antibody (1:1,000; Sigma-Aldrich, St. Louis, Missouri, USA) at 4°C overnight. The membranes were washed with tris buffered saline-tween (TBST), followed by incubation with horseradish peroxidase-linked secondary antibody (1:5000, Novus Biologicals, Littleton, CO, USA) for 2 h at room temperature and the protein was visualized with electrochemiluminescence using the Bio-Rad Gel Doc XR instrument (Bio-Rad, Hercules, CA, USA). Each experiment was performed in triplicate.

Transfection

To test the effect of miR-365 on cell migration and invasion, the miR-365 mimic or inhibitor were transfected into the breast cancer cell line MDA-MB-231, which was used to overexpress or knockdown of miR-365. To detect the influence of ADAM10 on the suppressive roles of miR-365, pcDNA3.1-ADAM10 was used to overexpress the expression of ADAM10 in miR-365 mimic-tranfected MDA-MB-231 cells.

The MDA-MB-231 cells were seeded into 6-well plates before transfection. According to the manufacturer's recommendations, the tranfection was performed using lipofectamine 3000 reagent (Invitrogen, Carlsbad, CA, USA).

MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)

The cells containing 5 mg/mL of the sterile filtered MTT solution (Santa Cruz Biotechnology, CA, USA) were incubated for 4 h in a moist chamber at 37°C in 96-well plates. Subsequently, 150μL of dimethyl sulfoxide (DMSO) was added to the cells, followed by shaking and incubation for 10 min, and the solubilized formazan product was determined at an optical density (OD) of 490nm using a microplate reader.

Transwell assay

The ability of cell migration and invasion were measured using transwell chambers with or without Matrigel (Clontech, Mountain View, CA, USA). The transwell chambers were put into a 24-well plate, with 500μL medium containing 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA). Cell suspension 200μL with 1×10^5/mL concentration was inoculated into transwell chambers. The cells were cultured at 37°C in a humidified atmosphere the f 5% CO_2 for 48h. After 24 h of incubation at 37°C with 95% oxygen and 5% CO_2, cells on the upper surface of the membrane were removed by cotton swabs, whereas the cells that moved to the lower surface were fixed with methanol and then stained with 0.1% crystal violet. The number of cells was counted at five randomly selected fields under a light microscope (Olympus).

Plasmid construction and Luciferase reporter assay

The target genes of miR-365 was predicted by the TargetScan website (www. targetscan.org). The binding site sequences of miR-365 are 5'-GCAGGAAAUAGAAGGGGCAUUA-3', and the 3'UTR sequence of ADAM10 was inserted into pcDNA3.1 vector (pcDNA3.1-ADAM10-WT). The binding site was mutated (the mutated sequences are 5'-GCAGGAAAUAGAAGCCCGACUA-3') using the QuikChange Multi Site-Directed Mutagenesis Kit (Santa Clara, CA, USA) and then cloned into the pcDNA3.1 vector (pcDNA3.1-ADAM10-MUT). The effectiveness of cloning was detected by sequencing.

MDA-MB-231 cells were co-transfected with miR-365 or negative control (NC) and pcDNA3.1-ADAM10-WT (WT) or pcDNA3.1-ADAM10-MUT (MUT). Luciferase activity was measured using a Dual-Luciferase Reporter Assay System (Promega, Madison, WI, USA), and Renilla luciferase was used as normalizer.

Statistics

All data were presented as mean ± SD (standard deviation) from at least 3 independent experiments. Statistical analyses were performed using SPSS 17.0 (SPSS

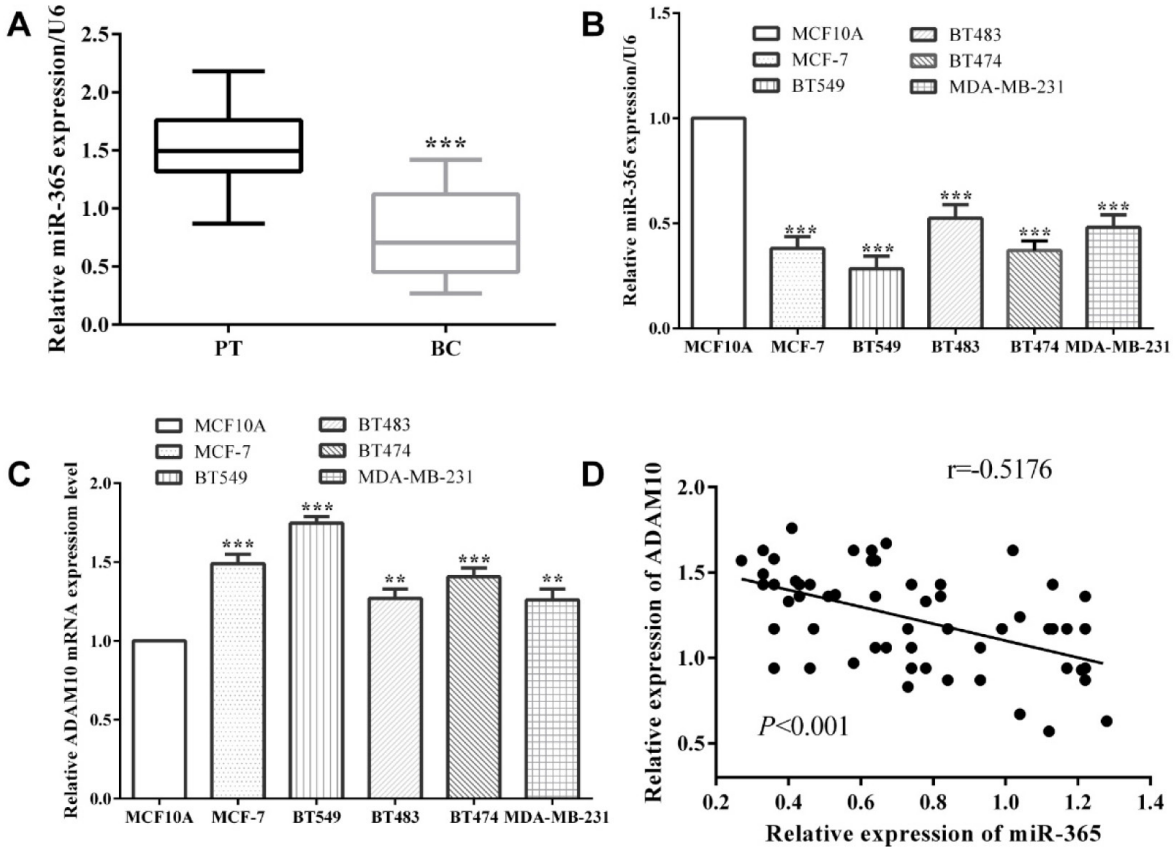

Figure 1. MiR-365 is low-expressed in breast cancer tissues and cell lines. **A:** The relative expression level of miR-365 in breast cancer (BC) tissues and the matched paracancer tissues (PT). **B:** The mRNA level of miR-365 in five TNBC cell lines and a normal breast cancer cell line by qRT-PCR. **C:** The mRNA level of ADAM10 in TNBC cell lines was up-regulated compared with the normal breast cancer cell line. **D:** The expression of miR-365 had a negative correlation between ADAM10 (** p<0.01; *** p<0.001).

Inc., Chicago, IL, USA). Association of miR-365 expression and Wnt5a expression was estimated using Pearson's correlation analysis. The differences between the groups were analyzed using Student's t-test or one-way analysis of variance (ANOVA). Statistically significance was set at $p<0.05$.

Results

MiR-365 was significantly down-regulated in breast cancer tissues and cell lines

The mRNA level of miR-365 in 58 pairs of breast cancer and the matched paracancer tissues was measured by qRT-PCR. The results showed that the expression of miR-365 was obviously increased in breast cancer tissues compared with the noncancer tissues ($p<0.0001$) (Figure 1A). We also calculated the expression of miR-365 in 5 breast cancer cell lines and a normal breast cell line Hs861.1, and found that miR-365 was abundant in TNBC cell lines BT549, MCF-7, BT483, MDA-MB-231 and BT474 compared with the normal breast cell line MCF10A ($p<0.0001$) (Figure 1B). On the other hand, the expression of ADAM10 was tested in TNBC cell lines and showed that it was overexpressed in the breast cancer cell lines MCF-7 ($p=0.0001$), BT549 ($p<0.0001$), BT483 ($p=0.0015$), BT474 ($p=0.0002$) and MDA-MB-231 ($p=0.0030$) versus normal breast cell MCF10A (Figure 1C). What's more, the mRNA level of miR-365 had a negative correlation with the expression of ADAM10 ($p<0.0001$, $r=-0.5176$) (Figure 1D). Due to the relative expression of miR-365, TNBC cell lines BT483 and MDA-MB-231 were selected to perform the following experiment.

MiR-365 inhibited the proliferation, migration and invasion of TNBC cell lines

To overexpress or knockdown of miR-365, the miR-365 mimic or the miR-365 inhibitor

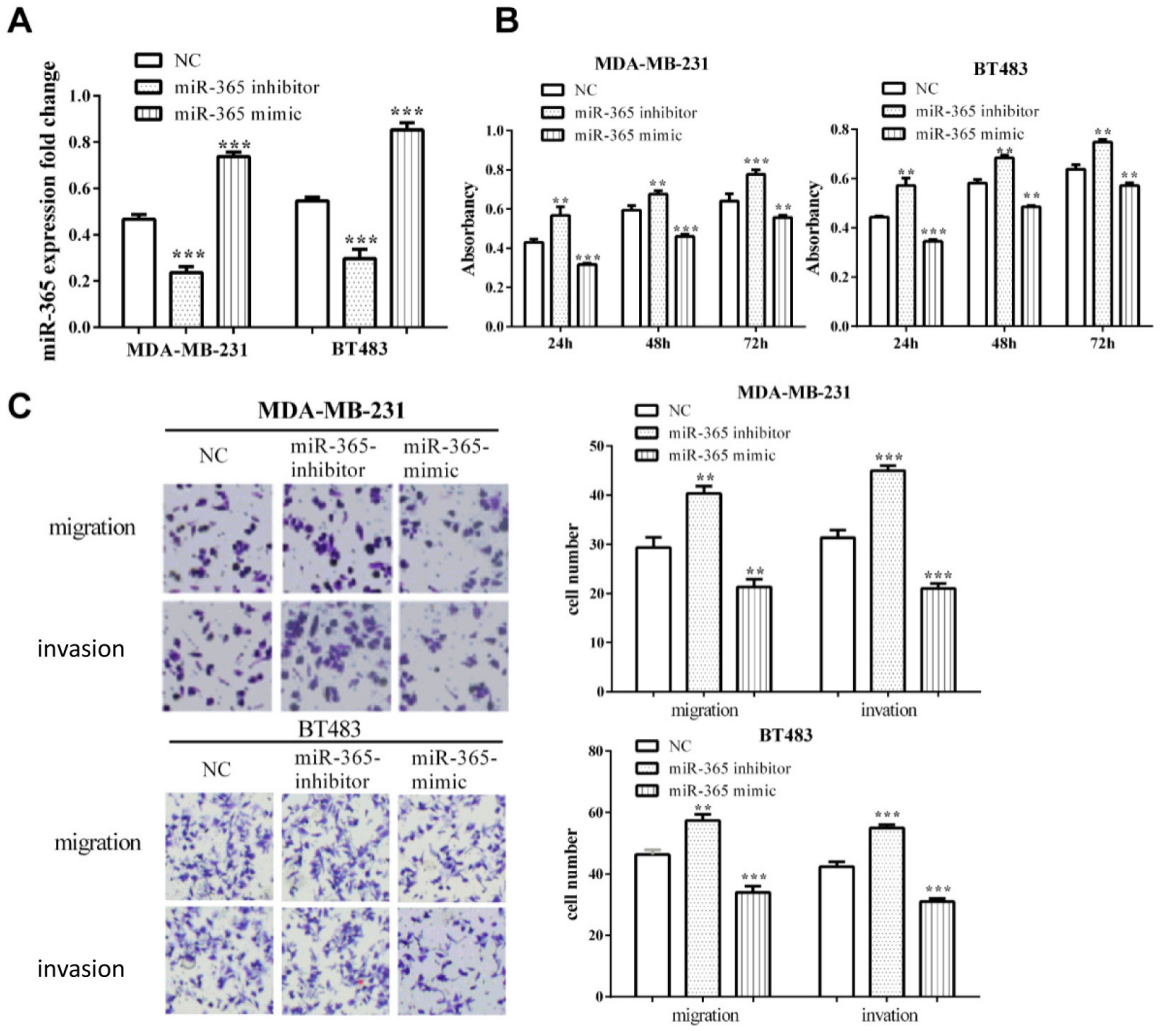

Figure 2. MiR-365 inhibits the proliferation, migration and invasion of TNBC cells. **A:** The effectiveness of overexpressed and knockdown of miR-365 in TNBC cell lines MDA-MB-231 and BT483. **B:** Cell proliferation ability of TNBC cells was measured by MTT assay when overexpressed and knocked down by miR-365. **C:** Transwell assay was used to analyze the migration and invasion in MDA-MB-231 and BT483 cells (** $p<0.01$; *** $p<0.001$).

were transfected into the TNBC cell lines MDA-MB-231 and BT483, respectively. The effectiveness of up- (p=0.0009 and <0.0001) or down-regulating (p=0.0003 and 0.0006) the expression of miR-365 is shown in Figure 2A.

MTT assay was used to test the influence of miR-365 on cell proliferation. As shown in Figure 2B, overexpression of miR-365 significantly reduced the absorbance compared with the control and it was time-dependent (p values at 24h, 48h and 72h were <0.0001, <0.0001, 0.0060 in MDA-MB-231 cells and<0.0001, <0.0001, <0.0001 in BT483 cells). On the other hand, the absorbance was increased with knockdown of miR-365, indicating that miR-365 inhibits the proliferation of TNBC cells (p value in MDA-MB-231 and BT483 cells at 24h, 48h and 72h were 0.0010, 0.0015, 0.0009 and 0.0002, <0.0001, 0.0007).

Transwell assay was used to measure cell migration and invasion in MDA-MB-231 and BT483 cells. As with the results of cell proliferation, when miR-365 was overexpressed, the number of cells removed under the transwell chamber was significantly reduced (p values of migration were 0.0011, 0.0018 and of invasion 0.0004, 0.0003) compared with the control, and vice versa. On the contrary, inhibition of miR-365 expression increased the moved cells number (p values of migration and invasion in MDA-MB-231 and BT483 cells were 0.0011, 0.0004 and 0.0011, 0.0004, respectively).

ADAM10 was a direct target of miR-365 and the expression of ADAM10 was mediated by miR-365

A publicly available online algorithm, TargetScan, is used to predict the potential targets for miR-365. One of the target genes of miR-365 is ADAM10, which has been reported to be involved in tumor progression in various cancers. The potential binding sites of ADAM10 to miR-365

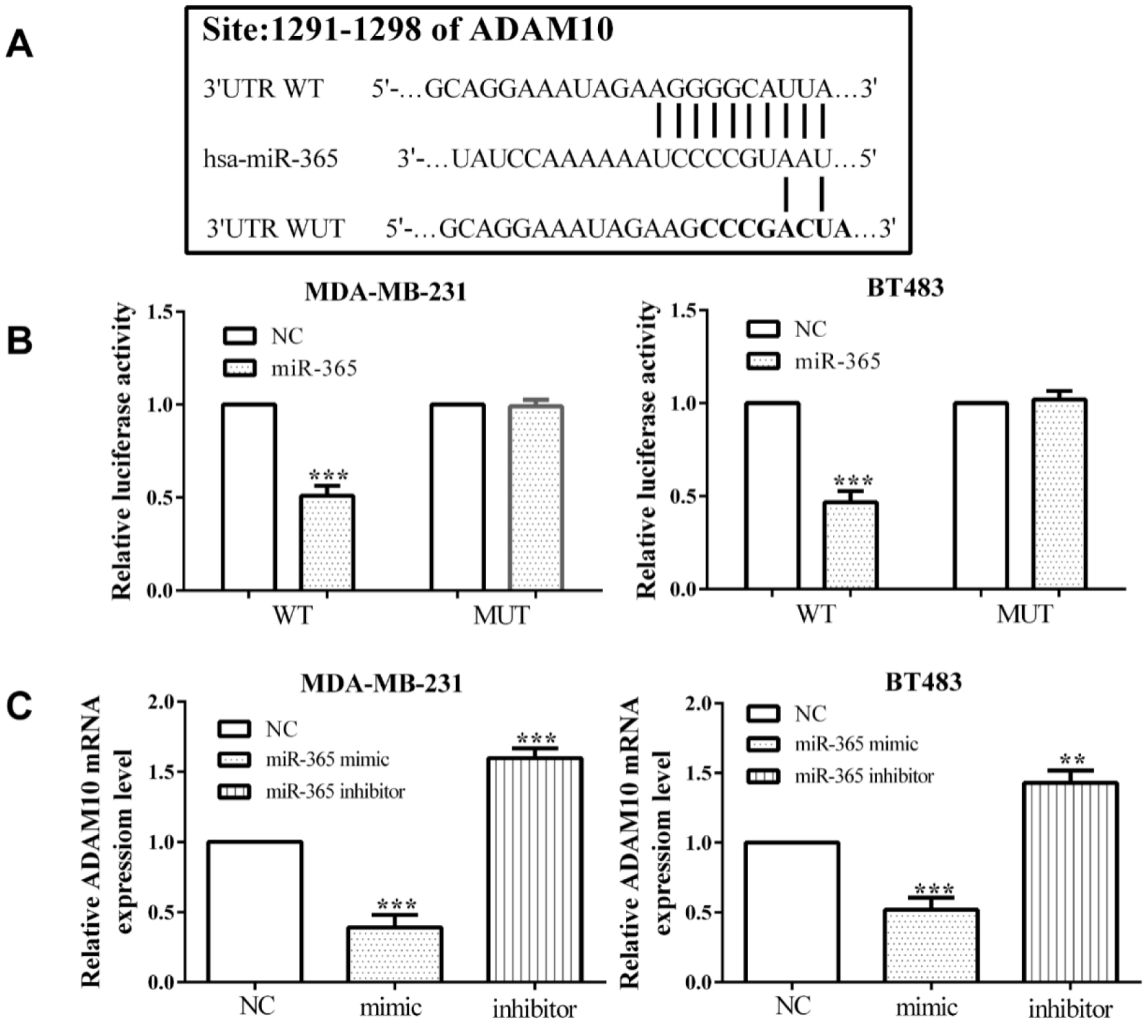

Figure 3. ADAM10 was the target of miR-365 and its expression was mediated by miR-365. **A:** The binding site of ADAM10 for miR-365 is located at 3'-UTR of mRNA. **B:** The luciferase activity was calculated when cells were co-transfected with miR-365, and the wild type or the mutant 3'UTR of ADAM10 mRNA. **C:** The expression level of ADAM10 after transfection with miR-365 mimic or miR-365 inhibitor in MDA-MB-231 and BT483 cells (** p<0.01; *** p<0.001).

are located at 1291-1298 at the 3'UTR of its mRNA. The sequences and mutation sequences were 5'-GCAGGAAAUAGAAGGGGCAUUA-3' and 5'-GCAGGAAAUAGAAGCCCGACUA-3', as shown in Figure 3A. To validate the interaction between the expression of ADAM10 and miR-365, the miR-365 mimic or control and vectors containing the wild type or mutated ADAM10 were co-transfected into the TNBC cell lines MDA-MB-231 and BT483. The luciferase activity was remarkably decreased when co-transfected with the miR-365 mimic and the wild type ADAM10 ($p<0.0001$ and <0.0001) in MDA-MB-231 and BT483 cells, with little change when co-transfected with the mutated ADAM10 and the miR-365 mimic ($p=0.6560$ and 0.4918) (Figure 3B), suggesting that ADAM10 was a direct target of miR-365. Now that miR-365 could directly target the 3'UTR of ADAM10 mRNA, we next examined whether miR-365 mediates the expression of ADAM10 in NTBC cells MDA-MB-231 and BT483 by varying the expression of miR-365. As expected, overexpression or knockdown of miR-365 significantly reduced ($p=0.0003$, 0.0006, respectively) or increased ($p=0.0001$, 0.0010, respectively) the mRNA level of ADAM10 in the MDA-MB-231 and BT483 cells (Figure 3C).

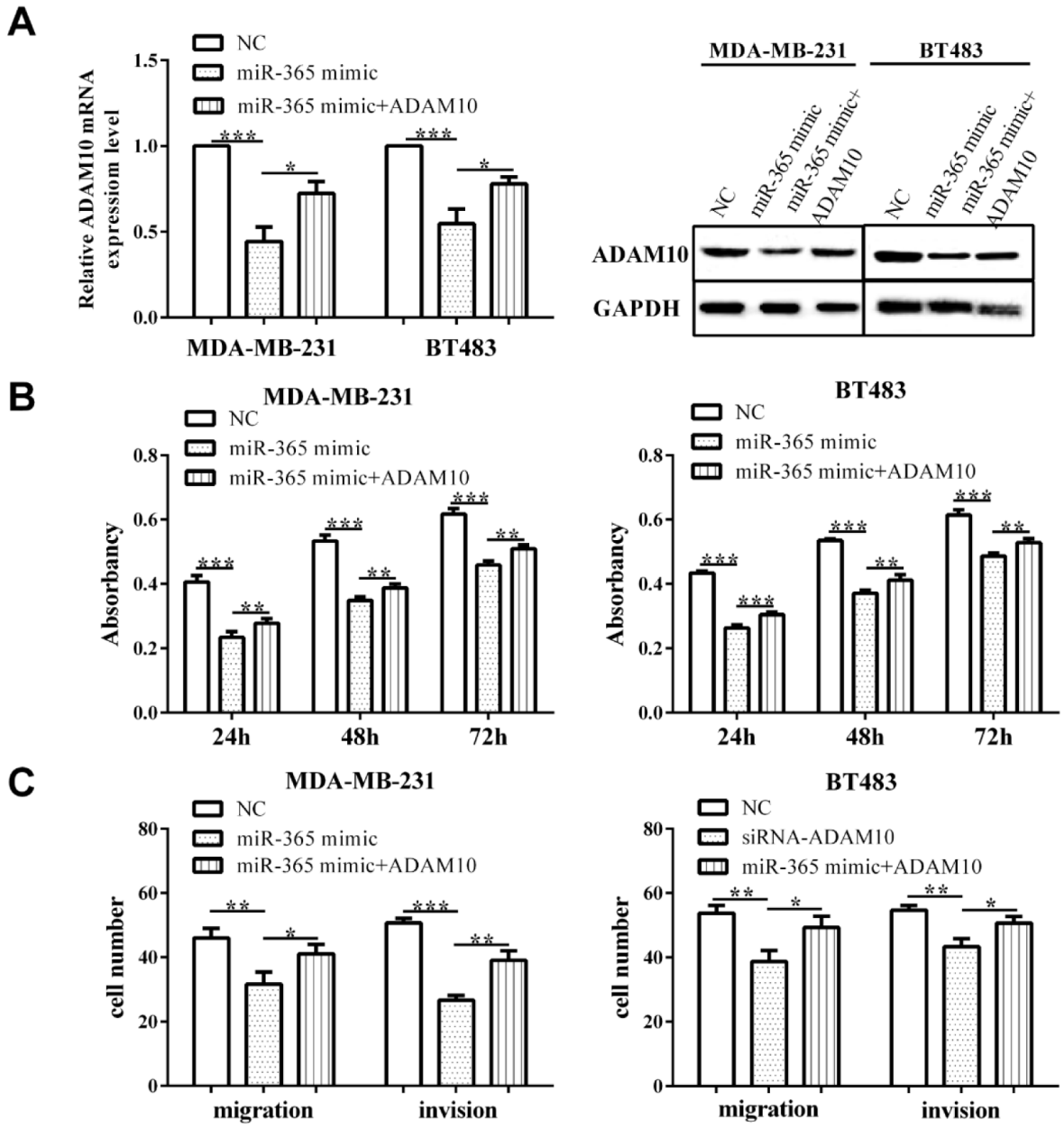

Figure 4. ADAM10 could reverse partial functions of miR-365. **A:** qRT-PCR and Western blotting display the mRNA level of ADAM10. **B:** The ability of proliferation was detected after co-transfection with miR-365 mimic and ADAM10. **C:** The ability of the migration and invasion were measured in MDA-MB-231 and BT483 cells (* $p<0.05$; ** $p<0.01$; *** $p<0.001$).

ADAM10 could reverse partial functions of miR-365

To investigate whether miR-365 inhibited the proliferation, migration and invasion through ADAM10, we co-transfected with miR-365 mimic and ADAM10 the MDA-MB-231 and BT483 cells, and the transfected efficiency was tested by qRT-PCR (p=0.0117 and 0.0131 compared with transfected miR-365 mimic) and Western blotting (Figure 4A). The ability of cell proliferation (p<0.0001, p<0.0001), migration (p=0.0001, p=0.0002) and invasion (p=0.0021, p<0.0001) were significantly inhibited by transfecting with the miR-365 mimic. Meanwhile, the ability of cell proliferation (p=0.0011, p=0.0014), migration (p=0.0287, p=0.0205) and invasion (p=0.0032, p=0.0177) were increased after co-transfection with miR-365 mimic and ADAM10, compared with transfection with only miR-365, as presented in Figure 4B and 4C. The results suggested that ADAM10 could reverse partial functions of miR-365 on cell proliferation, migration and invasion.

Discussion

Breast cancer remains one of the most common ma¬lignancies worldwide, and its incidence is increasing year by year. Therefore, it is necessary to further explore the molecular mechanisms of breast cancer genesis, metastasis and recurrence, and to find relative molecular markers. MiRs typically act as oncogenes or tumor suppressor genes in malignant tumors [26-30]. For example, miR-365 promoted cell apoptosis in colon cancer and also inhibited breast cancer cell cycle progress [13]. Also, miR-365 suppressed cancer cell progression in ovarian carcinoma [15], and inhibited cell growth, invasion and metastasis in malignant melanoma [16]. Consistent with the previous studies, we found that miR-365 was frequently downregulated in TNBC and its expression was obviously lower in tumor tissues than in non-cancer tissues. Similar with previous research, this study confirmed that miR-365 could inhibit the proliferation, migration and invasion in TNBC cells.

Several targets of miR-365 have been reported, such as Wnt5a, Cyclin D1, NRP1 respectively in ovarian cancer, colon cancer and malignant melanoma [13,15,16]. Also, ADAM10 has been reported to be a target gene of miR-365, which was overexpressed and played significant roles in breast cancer [25,31]. ADAM10 was reported to be a member of the ADAM family which is known as multifunctional, membrane-bound cell surface glycoproteins [21]. Several miRs are involved in the regulation of ADAM10, for example, Jing et al found that downregulation of miR-140 could decrease the proliferation and invasion via directly targeting ADAM10 in hepatocellular carcinoma [32]. Several miRs, including miR-494, miR-122, miR-144 and miR-448, could downregulate the protein expression of ADAM10 and inhibit the migration and invasion in a variety of cancers [31,33-35]. Initially, we confirmed that ADAM10 was a novel target of miR-365 by directly binding to the 3'-UTR of mRNA in breast cancer cells. Furthermore, to explore the function of ADAM10 in miR-365-induced proliferation, migration and invasion of breast cancer cells, the miR-365 mimic and ADAM10 overexpression plasmid were co-transfected in TNBC cells. What was proved was that overexpression of ADAM10 could inhibit the ability of the proliferation, migration and invasion in TNBC cells, suggesting that ADAM10 could reverse partial functions of miR-365.

In conclusion, our results revealed that miR-365 was frequently low-expressed and ADAM10 was overexpressed in TNBC. Moreover, the abilities of the proliferation, migration and invasion were enhanced by interfering miR-365, which were reduced by overexpression of miR-365 in TNBC cells through directly targeting to the 3'-UTR of ADAM10 mRNA. ADAM10 could reverse partial suppressive functions of miR-365 on cell proliferation, migration and invasion. Thus, these findings indicated that miR-365 may be a potential diagnostic marker of TNBC.

Conclusions

Taken together, miR-365 was low-expressed in breast cancer tissues and cell lines. Overexpression of miR-365 inhibited the cell proliferation, migration and invasion by directly mediating the 3'UTR of ADAM10 mRNA. ADAM10 could reverse partial suppressive functions of miR-365 on cell proliferation, migration and invasion.

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Conflict of interests

The authors declare no conflict of interests.

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