Abstract. MicroRNA (miR)-497 has been reported as a tumor suppressor in various cancer types. Nonetheless, the regulation of triple-negative breast cancer (TNBC) by miR-497 remains poorly understood. The present study aimed to investigate the potential function and mechanism of miR-497 in TNBC. A total of 36 TNBC and matched non-cancerous tissue samples were collected for analysis. Reverse transcription-quantitative PCR was performed to detect the miR-497 levels in TNBC tissue. The association between miR-497 expression, clinical characteristics and survival was then analyzed. To investigate the role of miR-497 in TNBC, MTT, colony formation, Transwell invasion, cell cycle and cell apoptosis assays were conducted following transfection of miR-497 mimics into the MDA-MB-231 and MDA-MB-468 cell lines. Luciferase reporter assays and western blot analysis were used to confirm the regulation of a putative target of miR-497. The results indicated that the expression of miR-497 was downregulated in the TNBC specimens. Further analysis demonstrated that the expression of miR-497 was downregulated in patients with advanced TNBC stages and that low miR-497 was associated with poor prognosis in patients with TNBC. Transfection of miR-497 mimics inhibited TNBC cell proliferation and induced cell apoptosis. Moreover, cell migration was inhibited following overexpression of miR-497, which also led to the arrest of the breast cancer cells in the G₀/G₁ phase of the cell cycle. Yes-associated protein 1 (YAP1), a critical molecule in the Hippo pathway, was identified as a target of miR-497. Notably, the protein and mRNA expression levels of YAP1 in MDA-MB-231 and MDA-MB-468 cells were downregulated following overexpression of miR-497. Overall, the findings of the present study indicated that miR-497 inhibited TNBC cell proliferation and migration and induced cell apoptosis by negatively regulating YAP1 expression. Thus, targeting miR-497 may represent a potential strategy for the treatment of TNBC.

Introduction

Breast cancer is one of the most common malignant tumors in female patients (1). Based on molecular characterization of the estrogen receptor (ER), progesterone receptor (PR), Ki67 antigen and human epidermal growth factor receptor-2 (HER2), breast cancer is typically divided into different types, including luminal A, luminal B, HER-2-positive, basal-like and ‘normal-like’ breast tumors. Triple-negative breast cancer (TNBC) is defined as a subset of basal-like breast cancer, which is negative for ER, PR and HER2. Due to the lack of a specific hormonal biomarker, surgical resection and chemotherapy are currently the mainstays of systemic treatment for patients with TNBC (2,3). A previous study has demonstrated that TNBC exhibits higher rates of metastasis and recurrence compared with other breast cancer subtypes (4). Thus, the development of new therapeutic targets for the treatment of TNBC is essential.

MicroRNA (miRNA/miR) is a class of small non-coding RNA molecules of ~22 nucleotides typically acting as vital regulators of target mRNA transcripts by binding to 3'-untranslated regions (3'-UTRs) (5). MicroRNA molecules have been reported to be deregulated in various cancer types, including TNBC, suggesting that they may be involved in cancer development and progression (6). A number of studies have demonstrated that miR-497 is downregulated in various malignant tumors, such as thyroid cancer (7), lung cancer (8) and hepatocellular carcinoma (9). In addition, miR-497 levels have been shown to be significantly reduced in breast cancer tissue and cell lines compared with matched non-cancerous breast tissue samples and MCF-10A cells, respectively (10). Several downstream targets of miR-497 have only recently
been identified, such as Bcl2, SRY-box transcription factor 5, proline, glutamate and leucine rich protein 1, and insulin-like growth factor 1 receptor (IGF1R). Moreover, the function and mechanism of miR-497 in TNBC remain largely undetermined. Yes-associated protein 1 (YAP1) is a major downstream transducer of the Hippo pathway commonly identified as an oncogene (14). Previous studies have demonstrated that YAP1 is involved in various physiological process, including cell proliferation, cell apoptosis, stem cell differentiation and tumorigenesis (15,16). Specifically, when the Hippo pathway is inactive, YAP1 translocates to the nucleus, binds to other transcription factors, such as TEA domain transcription factor 4 (TEAD4), and drives the expression of target anti-apoptotic and proliferation genes (17). Furthermore, upon activation of the pathway, YAP1 is phosphorylated by the phosphorylated and activated form of large tumor suppressor (LATS) 1/2, leading to cytoplasmic retention of YAP1 by the 14-3-3 protein or degradation (17). Previous studies, including own research, have confirmed that dysregulation of YAP1 results in tumorigenesis, including in TNBC (18-21). Several miRNA molecules, such as miR-195-5p (22), miR-630 (23) and miR-1285-3p (24) were identified as YAP1 regulators. Nevertheless, further understanding of the post-transcriptional control of YAP1 in TNBC is necessary.

Therefore, the aim of the present study was to examine the function and mechanism of miR-497 in TNBC. The expression of miR-497 in was evaluated in tissue samples from patients with TNBC. The findings of the current study may provide a potential target for the treatment of TNBC.

Materials and methods

Clinical samples. In the present study, 36 pairs of TNBC and adjacent non-cancerous tissue samples were collected from patients in the Department of Breast and Thyroid Surgery of Shanghai No. 10 People's Hospital (Shanghai, China). All samples were snap-frozen in liquid nitrogen. None of the patients received any cancer treatment prior to surgery. TNBC diagnosis was based on a pathological report of ER, PR and cerbb-2 expression status, as well as a fluorescence in situ hybridization report of HER2 expression status. TNBC is defined as a tumor that is ER-negative, PR-negative and HER2-negative. When the cerbb-2 status is 2+ or 3+, the HER2 status is 3+.

Cell culture and transfection. The human TNBC cell lines MDA-MB-231, MDA-MB-468, MCF-7 and SKBR3, and 293T cells were purchased from The Cell Bank of Type Culture Collection of The Chinese Academy of Sciences. The cells were maintained in Dulbecco's Modified Eagle's Medium (Gibco; Thermo Fisher Scientific, Inc.) supplemented with 10% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific, Inc.), penicillin (100 units/ml) and streptomycin (100 μg/ml). The immortalized breast epithelial cell line, MCF-10A, was purchased from Shanghai Zhongqiao Xinzhou Biotechnology Co., Ltd. The MCF-10A cells were cultured in Mammary Epithelial Cell Medium (ScienCell Research Laboratories, Inc.). All cells were incubated at 37°C with 5% CO₂.

RNA extraction and reverse transcription-quantitative PCR (RT-qPCR). Total RNA was extracted from cells or tissues using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.). cDNA was synthesized using the PrimeScript RT kit for mRNA and Prime-Script miRNA cDNA Synthesis kit (both Takara Bio, Inc.) for miRNA, according to the manufacturer's instructions. qPCR was carried out using SYBR® FAST qRT-PCR Master Mix kit (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol on a 7900HT fast RT-PCR instrument (Applied Biosystems; Thermo Fisher Scientific, Inc.). The primer sequences were designed and synthesized by Guangzhou RiboBio Co., Ltd.
The primer sequences were as follows: miR-497 forward, 5'-GTGCAGGTCCAGGGT-3' and reverse, 5'-TAGCTTGCA
GCACACTGTGTAT-3'; U6 forward, 5'-GCTTCGGCACAGA CATATACAAAT-3' and reverse, 5'-CGTCTACAGAATT TGCCGTTCAT-3'; YAPI forward, 5'-AGAACTAGAAGC
ACAAATAGCCT-3' and reverse, 5'-GTCTAGTCAGTGCT TAGCATTGCT-3'; and GAPDH forward, 5'-GCTTGGGACA
GCATATACTAAAT-3' and reverse, 5'-TGCTAGCTG
GCATGGCGGATCGATC-3'. Relative mRNA and miRNA
levels were normalized to GAPDH and U6, respectively, and
were obtained from the threshold cycle (Cq) values using the
2-ΔΔCq method (25). qPCR parameters for mRNA and miRNA
quantification were as follows: 2 min at 95°C, followed by
40 cycles of 30 sec at 95°C and 45 sec at 60°C. Each sample
was tested in triplicate.

Cell proliferation assays. For the MTT assays, transfected
cells (2x10^4 cells/well) were first plated into 96-well plates.
Cell proliferation was detected at 24, 48, 72 and 96 h detected
using an MTT kit (Sigma-Aldrich; Merck KGaA) according to
the manufacturer's instructions. The 490-nm optical density
was measured using a microplate reader.

For the colony formation assays, transfected cells
(500 cells/well) were transferred to six-well plates. The
cell culture was terminated after 7-10 days or when the colonies
were visible. The plates were washed twice with PBS, and the
colonies were fixed in 95% ethanol for 10 min at room tempera
ture, dried and stained with 0.1% crystal violet solution for
10 min at room temperature, and each plate was washed three
times with water.

Transwell assays. After 48 h from transfection, cells of each
group were harvested and made into single cell suspension
at a density of 5x10^5/ml using serum-free medium. The Transwell
assays were carried out using a 24-well insert with
Matrigel-coated upper chambers (BD Biosciences). The trans
fected cells were plated into the upper chamber in serum-free
medium. Medium containing 10% FBS was added to the
lower chamber. The 24-well Matrigel-coated chambers were
incubated at 37°C for 24 h. Subsequently, cells were fixed with
4% paraformaldehyde for 10 min at room temperature and
stained with a 0.1% crystal violet solution for 10 min at room
temperature. Representative images were obtained using a
light microscope (magnification, x200) and stained cells were
counted in five randomly selected fields.

Cell cycle analysis. The transfected cells were harvested
and fixed in 70% ethanol overnight at 4°C. After washing
twice with cold PBS, 250 µl of a 0.05 g/l propidium iodide
(Pi; Beyotime Institute of Biotechnology) staining solution
was added into each sample, followed by incubation for
30 min at room temperature. The cell cycle distribution
data was acquired using a FACSCanto II flow cytometer
(BD Biosciences) and analyzed using the ModFit LT 3.2 (Verity
Software House, Inc.).

Apoptosis assay. Cells transfected with miR-497 mimics or
NC were incubated in six-well plates for 24 h. The cells were
subsequently stained with fluorescein (FITC)-conjugated
Annexin V and propidium iodide (BD Biosciences) for 30 min
at room temperature. The Annexin V incubation reagent
(100 µl) was prepared by combining 10 µl of the 10X binding
buffer (BD Biosciences), 10 µl of propidium iodide (Pi), 1 µl
of Annexin V-FITC and 79 µl of deionized, distilled H2O. The
cells were gently resuspended in the Annexin V incubation
reagent at a concentration of 10^4-10^5 cells/100 µl. The rate of
apoptosis was detected using a FACSCanto II flow cytometer
(BD Biosciences) and analyzed using the CellQuest Pro
software v1.0 (BD Biosciences).

Dual-luciferase reporter assay. 293T cells were seeded in
12-well plates (BD Biosciences) and cultured until the cells
reached 80-90% confluence. The 3'-UTR segments of the
YAPI mRNA sequence containing the predicted miR-497
binding sites were amplified by PCR using the PrimerStar kit
(Takara Bio, Inc.) according to the manufacturer's protocol. The
corresponding mutant constructs were created by mutating the
seed regions of the miR-497-binding sites (5'-UGCUUGCU-3'
to 5'-ACGAGCA-3'). Fragments were subcloned into the XhoI
site in the 3'-UTR of Renilla luciferase of the psiCHECK-2
reporter vector (Shanghai Aibo Si Biological Technology
Co., Ltd.). Cells were transiently co-transfected with 0.2 µg
psiCHECK-2/YAPI 3'-UTR or psiCHECK-2/YAPI 3'-UTR
mutant reporter plasmids together with 100 nmol/l miR-497
mimic or miR-NC using Lipofectamine 2000, according to the
manufacturer's instructions. After 48 h, firefly and Renilla
luciferase activities were measured using a Dual Luciferase
Assay (Promega Corporation). Firefly luciferase activity was
normalized to Renilla luciferase activity, and the ratio of
firefly/Renilla luciferase activity was presented.

Western blot analysis. Cells were washed in ice-cold PBS
and resuspended in RIPA lysis buffer (100 µl/well; Beyotime
Institute of Biotechnology). Subsequently, the cells were
collected and centrifuged at 12,000 x g for 30 min at 4°C
(Eppendorf 5804R; Eppendorf). Supernatants were collected and
the protein concentrations were quantified using a BCA
protein assay kit (Beyotime Institute of Biotechnology).
Protein samples were denatured with 5X SDS loading buffer
(Beyotime Institute of Biotechnology) at 100°C for 10 min.
Total protein (20 µg/lane) was separated by 0.45-µm nitrocellulose membrane (Beyotime
Institute of Biotechnology). Following 60 min of blocking at room
temperature with 5% skimmed milk, the membrane was
incubated overnight at 4°C with primary antibodies against
YAPI (1:1,000; cat. no. BS1701; BioWorld Technology, Inc.)
and β-actin (1:1,000; cat. no. AP0060; BioWorld Technology, Inc.). After washing with PBS-Tween (0.2%),
blots were washed and incubated for 1 h at room temperature with the anti-mouse
secondary fluorescence antibody (1:2,000; cat. no. 00002-1;
BioWorld Technology, Inc.). Finally, immunoreactive protein
bands were detected with an Odyssey Scanning system
(LI-COR Biosciences).

Database analysis. Online databases were used to elucidate
the target genes of miR-497 in breast cancer. Database analysis
was performed using starBase3.0 (http://starbase.sysu.edu.cn)
and TargetScan 7.2 (http://www.targetscan.org) according to
the guidelines of the websites.
Let al: miR-497 INHIBITS TNBC

Results

miR-497 expression is reduced in TNBC tissue samples, which is associated with poor prognosis in patients with TNBC. The expression of miR-497 in the TNBC and matched non-cancerous breast tissue samples was determined by RT-qPCR. The results showed that miR-497 was significantly downregulated in TNBC tissue compared with normal tissue samples (P<0.001; Fig. 1A). Furthermore, the expression of miR-497 was significantly decreased in the MDA-MB-231 and MDA-MB-468 cell lines compared with MCF-10A (P<0.01; Fig. 1B). The experiments carried out in the MCF-7 (Luminal A type) and SKBR3 (HER-2-overexpressing type) cells also exhibited a similar trend (P<0.001; Fig. 1B). To further investigate the clinicopathological and prognostic significance of miR-497, the clinical data of the 36 patients with TNBC was collected and
analyzed together with the miR-497 levels. As demonstrated in Fig. 1C and D, the expression of miR-497 was significantly lower in the TNBC patients with an advanced TNM stage of the disease (P<0.05; Fig. 1C) and in those with lymph node metastasis compared with those without (P<0.05; Fig. 1D). The Kaplan-Meier method was used to evaluate the association between the expression of miR-497 and the survival rate of patients with TNBC. Patients with low expression of miR-497 had a shorter survival compared to those with high expression (P<0.05; Fig. 1E). The MDA-MB-231 and MDA-MB-468 cells were transfected with miR-497 mimics for subsequent experiments. RT-qPCR analysis confirmed that miR-497 expression was upregulated in miR-497 mimics-transfected MDA-MB-231 and MDA-MB-468 cells compared with in cells transfected with miR-NC (P<0.001; Fig. 1F).

miR-497 inhibits proliferation of TNBC cells. Decreased expression of miR-497 in TNBC tissues may reflect tumor-suppressing role in TNBC. To further explore the function of miR-497, its effect on the proliferation of TNBC cells was evaluated. MDA-MB-231 and MDA-MB-468 cells were transfected with miR-497 mimics or NC. Notably, the representative results obtained from the colony formation assay showed fewer colonies in the miR-497 mimics group compared with the NC group (P<0.01; Fig. 2A and B). Moreover, the MTT assay also demonstrated that overexpression of miR-497 significantly inhibited the viability of the MDA-MB-231 and MDA-MB-468 cell lines compared with NC at the 96-h time point (P<0.05; Fig. 2C and D). These findings confirmed that miR-497 inhibited the proliferation and viability of the TNBC cells in vitro.

miR-497 inhibits the invasion of TNBC cells. To investigate whether miR-497 overexpression affected the TNBC cell invasion, a Transwell assay was conducted. As shown in Fig. 3, the MDA-MB-231 and MDA-MB-468 cell lines exhibited similar trends in terms of invasion (Fig. 3A). The number of cells penetrating the membrane significantly decreased 24 h following transfection with miR-497 mimics compared with the NC (P<0.001; Fig. 3B). This observation indicated that overexpression of miR-497 suppressed TNBC cell invasion in vitro.
miR-497 inhibits TNBC by disrupting the cell cycle and inducing apoptosis. Flow cytometry suggested that overexpression of miR-497 significantly increased the apoptosis rate in MDA-MB-231 and MDA-MB-468 cells compared with NC. The cell cycle evaluation demonstrated that the percentage of cells in the G₀/G₁ phase increased in the miR-497 mimics group compared with the NC group in both MDA-MB-231 and MDA-MB-468 cell lines (Fig. 4). Thus, the upregulation of miR-497 could impact the cell cycle distribution and induce apoptosis in TNBC cells.

YAP1 is upregulated in TNBC and is a direct target for miR-497 in TNBC cells. Online databases were used to...
elucidate the mechanism of miR-497 in breast cancer. Based on the analysis carried out in databases, miR-497 exhibited a high prediction score for interaction with YAP1. The expression levels of YAP1 in 36 paired samples from patients with TNBC and cell lines were measured using RT-qPCR and western blotting. YAP1 mRNA and protein levels were increased in the TNBC tissues in comparison with normal tissues (Fig. 6A and B). YAP1 mRNA and protein levels were higher in the TNBC cells (MDA-MB-231 and MDA-MB-468) compared with MCF-10A cells (Fig. 6C and D). To determine whether miR-497 regulates endogenous YAP1 at the mRNA or protein levels, miR-497 mimics or NC were
transfected into the MDA-MB-231 and MDA-MB-468 cells, and the levels of YAP1 mRNA and protein were detected 48 h following transfection. YAP1 mRNA and protein levels in the MDA-MB-231 and MDA-MB-468 cells were markedly downregulated after transfection with miR-497 mimics (Fig. 7A and B). To establish whether miR-497 directly targeted YAP1, a luciferase reporter assay was carried out in 293T cells (Fig. 7C). In the wt YAP1 group, luciferase activity decreased following transfection with the miR-497 mimics compared with NC, while no evident differences were found in the mut YAP1 groups (Fig. 7D). Thus, miR-497 binds to the 3'-UTR of YAP1 mRNA, suggesting that YAP1 is a direct target of miR-497 in TNBC cells.

Discussion

Breast cancer is the most common malignant tumor in female patients. The incidence and mortality of breast cancer in China has markedly increased in recent years (26). It is noteworthy that the five-year disease-free survival rate of TNBC is the lowest among all molecular types of breast cancer (26). The health and quality of life of patients with TNBC is significantly challenged upon the occurrence of recurrence or metastasis. Thus, the determination of new targets to classify TNBC as well as the development of appropriate treatment are important. Recently, various miRNA molecules have been reported to be aberrantly expressed during the occurrence and development of TNBC. Some of these miRNA molecules are upregulated in TNBC tissue, such as miR-155, miR-21, whereas others are downregulated, including miR-10b, miR-125b and miR-145 (27). Sánchez-González et al (28) found that low miR-149 expression was associated with reduced macrophage infiltration and patient survival in lymph node-positive TNBC. Moreover, Lee et al (29) reported that miR-137 was markedly downregulated in TNBC tissue, and proposed this miRNA as a target for the treatment of TNBC.

The purpose of the present study was to explore the potential function and mechanism of miR-497 in TNBC. The results indicated that expression of miR-497 was downregulated in TNBC specimens and in the MDA-MB-231 and MDA-MB-468 cell lines. The clinical outcome analysis demonstrated that low expression of miR-497 was associated with advanced TNM stage, lymph node metastasis and reduced patient survival. Therefore, it was hypothesized that miR-497 may function as a tumor suppressor in TNBC. To confirm this, miR-497 mimics were transfected into the MDA-MB-231 and MDA-MB-468 cells to overexpress miR-497. miR-497 markedly suppressed the growth and invasion of the transfected TNBC cells in vitro. Furthermore, overexpression of miR-497 also induced apoptosis and arrested the cell cycle in the G<sub>0</sub>/G<sub>1</sub> phase. Overall, the results of the current study demonstrated that miR-497 exhibited anti-cancer properties, which might attenuate the progression of TNBC. These results were partly analogous to those of previous studies concerning other types of cancer and molecular types of breast cancer (30-33).

Online databases were used to establish the molecular mechanisms of miR-497 in the progression of TNBC. YAPI was identified as the potential targets of miR-497. A luciferase reporter assay to validate the regulation of the putative target YAPI by miR-497. The results suggested that miR-497 specifically bound to the 3'-UTR of the YAPI mRNA. Several targets of miR-497 have been previously identified in various cancer types. For instance, Shen et al (30) found that
miR-497 significantly inhibited Bcl-w levels in breast cancer. Subsequently, Bcl-2 (10), cyclin E1 (31), VEGFR2 (32) and IGF-1R (33) were identified as targets of miR-497. Moreover, YAP1 was identified as a target of miR-497 in thyroid papillary carcinoma (7). It has also been reported that some long non-coding RNA molecules could bind to miR-497. For example, Li et al (34) suggested that DLX6-AS1 regulated the progression of neuroblastoma by targeting YAP1 via miR-497. Moreover, Duan et al (35) reported that LINC02476 promoted the malignant phenotype of hepatocellular carcinoma by sponging miR-497. However, our study is the first to show the relevance of miR-497 modulation in TNBC.

YAP1 is a major downstream transducer of the Hippo signaling pathway, which is known as a critical player in multiple human cancer types, including TNBC (36). The Hippo signaling pathway comprises numerous components and its upstream genes include mammalian Ste20-like kinases 1/2 (MST1/2) and LATS1/2. Moreover, the downstream genes include YAP1 and transcriptional coactivator with the PDZ-binding motif (37). Guo et al (38) determined that the overexpression of YAP1 was associated with poor prognosis of breast cancer patients and induces breast cancer cell growth by inhibiting PTEN. A recent study also reported that YAP-independent mechanotransduction drives breast cancer progression, suggesting a new mechanism underlying the role of YAP1 in breast cancer (39). In the present study, YAP1 mRNA and protein levels were upregulated in TNBC tissue and cell lines. Several miRNA molecules have been previously found to be critical upstream regulators of YAP1. For instance, Li et al (40) established that miR-141-3p regulated the proliferation and senescence of stem cells from apical papilla by targeting YAP1. Furthermore, Chen et al (41) demonstrated that miR-590-5p suppressed chemoresistance of hepatocellular carcinoma by targeting the expression of YAP1. Our previous study also suggested that miR-506 inhibited cell growth and disrupted the cell cycle by targeting YAP in breast cancer cells (19). In the current study, YAP1 mRNA and protein levels in the MDA-MB-231 and MDA-MB-468 cells were downregulated following overexpression of miR-497, indicating that miR-497 was an upstream regulator of YAP1.

This study had certain limitations. Firstly, only 36 cases of TNBC tissues could be obtained due to the limited number of TNBC patients in our hospital. The reliability based on these samples is relatively low and the results require validation in a larger number of samples. Secondly, in vivo experiments were not conducted due to the limitations of the laboratory conditions. Lastly, the downstream proteins of YAP1 should be explored to gain more comprehensive understanding of the role of miR-497 in TNBC.

In conclusion, the present study demonstrated that miR-497 was downregulated in TNBC tissue samples and cells. It was also confirmed that miR-497 inhibited cell proliferation and migration via direct regulation of YAP1 expression. This suggests that miR-497 may represent a potential therapeutic target for TNBC.

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