Abstract. A total of 60 breast cancer (BC) tissues and adjacent healthy tissues from patients who underwent surgery in Renmin Hospital of Wuhan University were collected for analysis in the present study. Results from reverse transcription-quantitative polymerase chain reaction (RT-qPCR) demonstrated that, compared with the adjacent healthy tissues, the expression levels of microRNA (miR)-142-5p were significantly elevated in BC tissues. Bioinformatics analysis was performed using TargetScan for the prediction of potential target sites that matched the seed region of miR-142-5p; phosphatase and tensin homolog (PTEN) exhibited the highest score and was selected for further analysis. Results of RT-qPCR analysis demonstrated that, compared with the adjacent healthy tissues, the mRNA expression levels of PTEN were significantly decreased in breast cancer tissues. miR-142-5p and PTEN expression levels were positively and negatively associated, respectively, with patient tumor size and metastasis. MDA-MB-231 cells were divided into three groups including the Control group, the miR-NC inhibitor group and the miR-142-5p inhibitor group. As for alterations in cell behavior, including cell viability and cell apoptosis, and protein expression levels, there were no significant differences between Control and miR-NC inhibitor groups. MTT assay results revealed that, compared with Control and miR-NC inhibitor groups, miR-142-5p inhibitor reduced MDA-MB-231 cell proliferation. Flow cytometric analysis demonstrated that, compared with Control and miR-NC inhibitor groups, miR-142-5p inhibitor treatment induced MDA-MB-231 cell apoptosis. Western blotting results demonstrated that, compared with Control and miR-NC inhibitor groups, miR-142-5p inhibitor treatment significantly increased the expression of PTEN, reduced the activation of phosphatidylinositol-4,5-bisphosphate 3-kinase/RACα serine/threonine-protein kinase signaling. Finally, PTEN was demonstrated to interact with miR-142-5p from the results of dual-luciferase reporter assay in the present study. The findings of the present study suggested that miR-142-5p may be a potential therapeutic target for the future investigations and insights for breast cancer.

Introduction

Breast cancer (BC) is the leading cause of cancer-related mortality in women between the ages of 20 and 59 years (1,2), and affects 12% of women worldwide (3). A number of risk factors have been associated with the occurrence of BC in women, including obesity, early menarche, late menopause, hormone replacement therapy, late first-full pregnancy and diets rich in high-fat foods or red meats (4). Therefore, it is necessary to investigate effective diagnostic methods for BC (5).

MicroRNAs (miRNAs) are a class of small non-coding RNAs that provide a novel perspective to predict and screen for cancer, and previous studies have reported that miRNA expression levels may be aberrant in tumors (6-8). Associations between the clinicopathological features of BC and miRNA expression levels have been reported previously (9,10). miR-142-3p was demonstrated to directly regulate its target genes in a several types of cancer, including non-small cell lung cancer, colon cancer and hepatic cancer (11-13). miR-142 expression levels were elevated in human BC stem cells (BCSCs) compared with non-tumorigenic BC cells (14). In addition, miR-142-5p expression levels were reported to be markedly higher in the lymph node-cancer group compared with expression in the non-lymph node-cancer group, which were detected by miRNA microarray analysis (15). Upregulation of miR-142-5p was identified in atherosclerotic plaques, and regulated oxidized low-density lipoprotein-induced apoptosis in macrophages (16). miR-142-5p was involved in squamous lung cancer via regulation of cell cycle related genes (17). miR-142-5p contributes to Hashimoto's thyroiditis by targeting CLDN1 (18) and promotes the development of colorectal cancer by targeting SDHB (19). However, the function of miR-142-5p in BC has not yet been reported. Consequently, the present study aimed to investigate a target gene of miR-142-5p in BC cells and to provide a novel potential target for the treatment of BC.

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Key words: microRNA-142-5p, breast cancer, phosphatase and tensin homolog
Materials and methods

Study population. BC tissues and the adjacent healthy tissues were obtained from 60 female patients who underwent surgery in Renmin Hospital of Wuhan University (Wuhan, China) between March, 2013 and July, 2016. Clinicopathological characteristics of patients' age, tumor size and metastasis were collected and are presented in Table I. There were 40 patients aged <50 years and 20 patients aged ≥50 years. Written informed consent was obtained from all the patients prior to the start of the study; the present study was approved by the ethics committee of Renmin Hospital of Wuhan University.

Cell culture. Normal breast epithelial cell line MCF-10A and BC cell lines SK-BR-3 and MDA-MB-231 were purchased from the American Type Culture Collection (Manassas, VA, USA) and cultured in Dulbecco's modified Eagle's medium (DMEM)/Ham's F12 medium supplemented with 10% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA), penicillin (100 U/ml) and streptomycin (100 µg/ml) in an incubator at 37°C with humidified atmosphere of 5% CO₂. MDA-MB-231 cells with the highest miR-142-5p expression levels were selected for the remaining in vitro experiments as these cells exhibited the highest expression levels of miR-142-5p compared with other cell lines.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted from BC tissues (1 cm³) and cell cultures (1x10⁶ cells/well) using a miRNeasy kit (Qiagen Inc., Valencia, CA, USA) according to the manufacturer's protocol. Reverse transcription of miR142-5p (Qiagen Inc., Valencia, CA, USA) and cell cultures (1x10⁶ cells/well) using a miRNeasy kit (Qiagen Inc., Valencia, CA, USA) according to the manufacturer's protocol. Reverse transcription of miR142-5p (Qiagen Inc., Valencia, CA, USA) and cell cultures (1x10⁶ cells/well) using a miRNeasy kit (Qiagen Inc., Valencia, CA, USA) according to the manufacturer's protocol. Reverse transcription of miR142-5p and phosphatase and tensin homolog (PTEN) to cDNA was performed using miRNA cDNA Synthesis Kit (Takara bio, Inc., Otsu, Japan) and First Strand cDNA Synthesis kit (Takara Inc., Miami, FL, USA) and analyzed by Cell Quest software version FCS2.0 (BD Biosciences, Franklin Lakes, NJ, USA).

Western blotting. Total protein was extracted from MDA-MB-231 cell (1x10⁶ cells/plate of 6-well plates) using radioimmunoprecipitation assay buffer (Beyotime Institute of Biotechnology, Shanghai, China). Protein concentration was determined by a bicinchoninic acid kit (Beyotime Institute of Biotechnology). Proteins (15 µg/lane) were separated and transferred onto polyvinylidene difluoride membranes. The membranes were blocked with 5% non-fat milk at room temperature for 2 h and incubated with the following primary antibodies overnight at 4°C: PTEN (1:1,000; cat. no. 9552; Cell Signaling Technology, Inc., Danvers, MA, USA); phosphorylated (p) - phosphoinositide 3-kinase (PI3K; 1:1,000; cat. no. 4228; Cell Signaling Technology, Inc.); p-RAα serine/threonine-protein kinase (AKT; 1:1,000; cat. no. D9E; Cell Signaling Technology, Inc.); and GAPDH (1:1,000; cat. no. FL-355; Santa Cruz Biotechnology, Inc., Dallas, TX USA). Subsequently, membranes were incubated with anti-rabbit horseradish peroxidase-conjugated secondary antibody (1:1,000; cat. no. 7074; Cell Signaling Technology, Inc.) for 2 h at room temperature. Following washing with TBS + 0.1% Tween-20, blots were visualized with an Enhanced Chemiluminescence kit (Beyotime Institute of Biotechnology). Experiments were repeated in triplicate. Protein expression levels were normalised to GAPDH, and Quantity One version 4.6.2 (Bio-Rad Laboratories, Inc., Hercules, CA, USA) was used for densitometric analysis.

Luciferase activity assay. To verify whether PTEN was a direct target of miR-142-5p, a position of the PTEN 3'UTR containing a putative miR-142-5p target site was cloned into the luciferase
open reading frame. The plasmids of PTEN were cloned into reporter pLuc control vector (Promega Corporation, Madison, WI, USA). MDA-MB-231 cells (1x10^4 cells/plate) were seeded in 48-well plates and incubated for 24 h in an incubator at 37˚C in a humidified atmosphere of 5% CO₂, followed by co-transfection with miR-142-5p inhibitor (20 nM) or miR-NC inhibitor (20 nM) and either PTEN wild-type (WT)-3’ untranslated region (UTR; 1 mg, pLuc-PTEN-WT 3’UTR) or PTEN mutant (Mut) -3’UTR (1 mg, pLuc-PTEN-Mut 3’UTR) by Lipofectamine® 2000 (Thermo Fisher Scientific, Inc.). After 48 h transfection, the luciferase activity was examined by Dual Luciferase Reporter Assay system (Promega Corporation, Madison, WI, USA), and the results were normalized to the Renilla luciferase activity.

**Statistical analysis.** Data were analyzed by software of SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and expressed as the mean ± standard error of mean. Data between two groups were analyzed by t-test and data among three groups were analyzed by one-way analysis of variance followed with Student-Newman-Keuls test. P<0.05 was considered to indicate a statistically significance difference.

**Results**

**Differing miR-142-5p expression levels between tumoral tissues and adjacent healthy tissues.** RT-qPCR was used to analyze the relative expression levels of miR-142-5p in tumoral tissues and adjacent healthy tissues. The results demonstrated that miR-142-5p expression levels were significantly higher in the BC tissues compared with the adjacent healthy tissues (Fig. 1). This result suggested that miR-142-5p may be an oncogene during the development of BC.

**PTEN may be a target of miR-142.** Potential targets of miR-142-5p were predicted by TargetScan (http://www.targetscan.org/vert_71), and the analysis revealed three target sequences of miR-142-5p in positions 2,189-2,195, 2,427-2,433 and 2,503-2,509 within the 3’UTR of PTEN (not shown). The target site at position 2,189-2,195 scored 59 (the lowest), the target sequence at position 2,427-2,433 scored 88 and at position 2,503-2,509 of 3’UTR of PTEN was used for further analysis. RT-qPCR was used to examine the relative expression levels of PTEN in BC tissues and the adjacent healthy tissues. The results demonstrated that PTEN mRNA expression levels were lower in BC tissues compared with adjacent healthy tissues (Fig. 2B). This result suggested that PTEN may be a tumor suppressor gene during the development of BC.

**Association between miR-142-5p or PTEN expression and patient clinicopathological characteristics.** The characteristics of 60 patients with BC including age, tumor size and metastasis were presented in Table I. Gene expression levels of miR-142-5p and PTEN in BC tissues were investigated using RT-qPCR; results were presented as fold change compared with the adjacent healthy tissues. No significant associations were identified between miR-142-5p or PTEN expression level in BC tissues compared with adjacent healthy tissues.
and patient age. Conversely, compared with tumor size <5 cm and patients with no metastasis, miR-142-5p expression levels were significantly higher (P=0.04), whereas PTEN expression levels were significantly lower (P=0.01) in patients with tumors ≥5 cm and who exhibited metastasis.

Relative expression levels of miR-142-5p in MCF-10A, SK-BR-3 and MDA-MB-231 cell lines. RT-qPCR analysis was performed to investigate the variations in miR-142-5p expression levels among three different cell lines. The results indicated that miR-142-5p expression levels were the lowest in MCF-10A normal breast epithelial cells, no significant difference was observed between MCF-10A and SK-BR-3, whereas the highest expression level was detected in MDA-MB-231 BC cells (Fig. 3A). Therefore, MDA-MB-231 cells were selected for further analysis in the present study. The MDA-MB-231 cells were divided into three groups, including the Control group, the miR-NC inhibitor group and the miR-142-5p inhibitor group. The successful transfection of miR-142-5p inhibitor into MDA-MB-231 cells was identified by the reduced miR-142-5p expression level in the miR-142-5p inhibitor-treated group compared with the other two groups (Fig. 3B).

In addition, the effects of miR-142-5p inhibition on PTEN expression were investigated by RT-qPCR. In MDA-MB-231 cells transfected with miR-142-5p inhibitor, the mRNA expression levels of PTEN were significantly increased compared with Control group and miR-NC group (Fig. 3C). These results
suggested a potential the interaction between miR-142-5p and PTEN.

Effects of miR-142-5p inhibition on MDA-MB-231 cell viability. MTT assays were conducted to examine the effects of miR-142-5p inhibition on cell viability. No significant differences in viability were identified between Control and miR-NC inhibitor-treated groups; whereas the inhibition of miR-142-5p significantly reduced MDA-MB-231 cell viability at 24 and 48 h following transfection compared with Control and miR-NC inhibitor groups (Fig. 4).

Effects of miR-142-5p inhibition on MDA-MB-231 cell apoptosis. Flow cytometry results revealed no significant differences between Control and miR-NC inhibitor groups, and that the inhibition of miR-142-5p significantly increased MDA-MB-231 cell apoptosis (Fig. 5).

Effects of miR-142-5p inhibition on PTEN, p-PI3K and p-AKT protein expression levels. The protein expression levels of PTEN, p-PI3K and p-AKT were examined by western blot analysis, which revealed no significant difference between the Control and miR-NC inhibitor groups; the...
inhibition of miR-142-5p significantly increased the expression of PTEN and reduced the expression of p-Pi3K and p-AKT in MDA-MB-231 cells compared with the Control and miR-NC inhibitor-treated groups (Fig. 6).

Interaction between miR-142-5p and PTEN. To verify whether PTEN was a direct target of miR-142-5p, a portion of the PTEN 3'UTR containing a putative miR-142-5p target site was cloned into the luciferase open reading frame. Co-transfection of the miR-142-5p inhibitor and the PTEN-3'UTR-WT vector into MDA-MB-231 cells (pLuc-PTEN-WT 3'UTR) exhibited a significant increase in the luciferase activity compared with miR-NC inhibitor. However, no significant difference was identified in luciferase activity in cells co-transfected with the miR-142-5p inhibitor and the mutant PTEN 3'UTR vector (pLuc-PTEN-Mut 3'UTR); similar levels of luciferase activity were observed in the cells harboring the mutant 3'UTR and WT-NC control cells (Fig. 7).

Discussion

BC affects 12% women worldwide (3), thus it is urgent to investigate current diagnostic methods (5). miR-142 was upregulated in BCSCs compared with in non-tumorigenic BC cells (14). Additionally, miR-142-5p expression levels were reported to be higher in patients with BC with lymph node metastasis compared with patients without lymph node metastasis (15). The present study aimed to investigate a target of miR-142-5p in BC cells and provide a novel target for the treatment of BC.

RT-qPCR revealed that miR-142-5p expression levels were significantly higher in BC tissues compared with adjacent healthy tissues. These data suggested a potential oncogenic role of miR-142-5p in BC, which was consistent with previous studies of BC (14,15). Subsequently, TargetScan was employed to predict the mRNA targets of miR-142-5p, which revealed that the target sequence of miR-142-5p was present in the 3'UTR of PTEN. In addition, RT-qPCR demonstrated that the expression levels of PTEN were lower in BC tissues compared with adjacent healthy tissues, which was in accordance with a previous report that PTEN gene expression levels were lower in 93 human BC tissues compared with in healthy breast tissues (21). These results suggested that the overexpression of miR-142-5p may inhibit PTEN mRNA expression in BC tissues.

The PTEN protein is a protein tyrosine phosphatase that is encoded by the PTEN gene (22) and may be mutated in human brain, breast and prostate cancers (23). Subsequently, the association of miR-142-5p and PTEN expression with clinicopathological characteristics in patient with BC were investigated. No significant association between miR-142-5p or PTEN expression levels and patient age was observed in present study; however, miR-142-5p and PTEN expression levels were positively and negatively associated, respectively, with patient tumor size and metastasis. The results of the present study suggested that miR-142-5p may have negatively affected the expression levels of PTEN in BC tissues. Additionally, in vitro experiments were conducted to investigate the effect of miR-142-5p expression in human BC cell lines. The MDA-MB-231 BC cell line exhibited a high expression level of miR-142-5p, which was reduced upon transfection with the miR-142-5p inhibitor, whereas mRNA expression levels of PTEN increased. These data further suggested an interaction and a negative association between miR-142-5p and PTEN expression.

Results from the present study demonstrated that inhibition of miR-142-5p significantly reduced MDA-MB-231 cell viability and increased apoptosis. These data were in line with previous studies that have reported an upregulation
of miR-142-5p expression levels in breast cancer patients with lymph node metastasis compared with those without lymph node metastasis (15), atherosclerotic plaques (16), Hashimoto's thyroiditis (18) and in the serum of patients with colorectal cancer (19), which was associated with the promotion of cell proliferation and colony formation, and with the inhibition of apoptosis in colorectal cancer cell lines by targeting succinate dehydrogenase (ubiquinone) iron-sulfur subunit B (19). miR-142-5p was also reported to be elevated in human renal cell carcinoma tissues, and was demonstrated to induce growth and migration of renal cell carcinoma cells by targeting TGFB anti-proliferation factor 3 (24); however, the mechanisms responsible for the alterations in BC required further investigation. Therefore, western blotting was performed in the present study to analyze protein expression levels of PTEN; in cells transfected with the miR-142-5p inhibitor, a significant increase in the expression of PTEN was observed. These results suggested that the expression of PTEN may be affected by miR-142-5p. The present study also aimed to determine the molecules that may be regulated and influenced by PTEN by using western blot analysis.

The PI3K signaling pathway is an important kinase cascade that regulates cell proliferation, migration, apoptosis and angiogenesis through its downstream effector AKT; dysregulation of this pathway may be caused by mutations or altered expression levels of an upstream regulator of AKT activity such as PTEN (25,26). Previous studies have also reported that mutations in PI3Kα were common in BC and the mutation frequency ranged between 27 and 36% (27). Additionally, PTEN was reported to be a regulator of PI3K cytoplasmic signaling (28) and an inhibitor of the growth-promoting PI3K/AKT/mechanistic target of rapamycin (mTOR) signaling pathway (29). Furthermore, a lack of PTEN protein expression was reported to be associated with overactivation of the PI3K/AKT/mTOR signaling pathway (30). In the present study, western blotting revealed that the inhibition of miR-142-5p significantly reduced the expression of p-PI3K and p-AKT in MDA-MB-231 cells, which agreed with the above studies that further inferred that PI3K or AKT expression was attributed to PTEN.

Results from the luciferase activity assay demonstrated that PTEN was a direct target of miR-142-5p, confirmed by higher luciferase activity after miR-142-5p inhibitor administration in WT group than in the mutant group. Additionally, similar levels of luciferase activity were observed in the cells harboring the WT 3'UTR between the miR-142-5p inhibitor group and miR-NC group in the present study. In a recent study, miR-142-5p was found to target 3'UTR of PTEN in cutaneous squamous cell carcinoma by Bai et al (31), which was in line with the findings of the present study.

In conclusion, miR-142-5p may be a possible target for treating BC in the future; the PTEN/p-PI3K/p-AKT signaling pathway was associated with the effects of miR-142-5p in MDA-MB-231 cells. However, the effects of miR-142-5p mimics on BC were not analyzed in the present study and should be investigated in the future; the effects on PI3K or AKT expression attributed to PTEN, can only be inferred, as no direct evidence has been provided. It is necessary for this to be explored in future studies.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
WX designed and carried out the experiments and analyzed the data. WW designed the experiments, analyzed the data and prepared the manuscript. Both authors have seen and approved the manuscript.

Ethics approval and consent to participate
The present study was approved by the ethics committee of Renmin Hospital of Wuhan University (Wuhan, China).

Consent for publication
Written informed consent was obtained from all patients prior to the start of the study.

Competing interests
The authors declare that they have no competing interests.

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