Am J Transl Res 2017;9(12):5594-5602
www.ajtr.org /ISSN:1943-8141/AJTR0064006

Original Article

The long non-coding RNA SUMO1P3 facilitates breast cancer progression by negatively regulating miR-320a

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Received May 4, 2017; Accepted October 21, 2017; Epub December 15, 2017; Published December 30, 2017

Abstract: Although the long non-coding RNA (lncRNA) SUMO1P3, small ubiquitin-like modifier 1 pseudogene 3, has been shown to play a role in human cancer, the biological function and mechanism of SUMO1P3 in breast cancer remained unclear. In this study, we showed that SUMO1P3 expression was higher in breast cancer tissues when compared to adjacent normal tissues and we found that high levels of SUMO1P3 expression associated significantly with tumor progression and poor survival of breast cancer patients. Moreover, we found that knockdown of SUMO1P3 suppressed proliferation, migration, and invasion of breast cancer cells. Bioinformatics analysis and luciferase reporter assays confirmed that SUMO1P3 binds to miR-320a, which has been identified as a tumor suppressor in various cancers, including breast cancer. We also confirmed that the tumor-promoting effects of SUMO1P3 in breast cancer are partly mediated by negative regulation of miR-320a. Our data indicates that SUMO1P3 functions as an oncogenic lncRNA in breast cancer and may serve as a novel diagnostic and biological target for breast cancer diagnosis and treatment.

Keywords: SUMO1P3, breast cancer, prognosis, miR-320a

Introduction

Breast cancer is the most commonly diagnosed malignancy among women worldwide and its incidence in China has increased approximately 3% annually [1, 2]. Although significant developments have been made in the diagnosis and treatment of breast cancer, it still causes substantial female mortality [3]. Thus, identification of the mechanism of carcinogenesis and identification of effective diagnostic and therapeutic targets for breast cancer are still urgently needed.

Long non-coding RNAs (lncRNAs) are non-coding RNA transcripts that are longer than 200 nucleotides [4]. LncRNAs were once considered transcriptional "noise" without biological function because they do not code for proteins [5]. Evidence has accumulated showing that lncRNAs play crucial roles in numerous physiological and pathological processes, including the initiation and progression of cancers, cell proliferation, differentiation, and apoptosis [6]. Pseudogenes, such as small ubiquitin-like modifier 1 pseudogene 3 (SUMO1P3), constitute a separate class of lncRNAs.

SUMO1P3 was originally identified as a potential biomarker for the diagnosis of gastric cancer [7]. Zhan et al. showed that SUMO1P3 expression increased significantly in bladder cancer tissues and that this increased SUMO1P3 expression correlated with higher histological grades and advanced TNM stages of cancer. In addition, knockdown of SUMO1P3 inhibited cell proliferation and induced apoptosis of bladder cancer cells [8]. However, the biological function and mechanism of SUMO1P3 in breast cancer remains unclear.

In this study, we examined the expression of SUMO1P3 in breast cancer tissues and in matched adjacent normal breast tissues, and we investigated the function of SUMO1P3 in breast cancer cell lines. We also examined the interaction between SUMO1P3 and miR-320a to reveal the underlying mechanism of SUMO1P3 in breast cancer. To the best of our knowledge, our study is the first to show that

Table 1. Primer list

Gene	Forward primer	Reverse primer
SUMO1P3	ACTGGGAATGGAGGAAGA	TGAGAAAGGATTGAGGGAAAAG
GAPDH	CGCTCTCTGCTCCTCCTGTTC	ATCCGTTGACTCCGACCTTCAC

Table 2. Associations between SUMO1P3 expression and pathological and clinical variables

Clinicopathological parameters	N^2	SUMO1P3 expression		χ^2	*P* value
		H	L		
All	74	52	22		
Age (years)				0.105	0.746
< 60	45	31	14		
≥ 60	29	21	8		
Tumor size				6.081	0.014
< 2 cm	31	17	14		
≥ 2 cm	43	35	8		
ER status				2.663	0.103
Negative	33	20	13		
Positive	41	32	9		
PR status				1.367	0.242
Negative	36	23	13		
Positive	38	29	9		
Her-2 status				0.950	0.330
Negative	59	43	16		
Positive	15	9	6		
Lymph node metastasis				4.594	0.032
Negative	33	19	14		
Positive	41	33	8		
Ki-67				3.353	0.067
Negative	35	21	18		
Positive	39	31	8		
TNM stage				4.335	0.037
I-II	65	43	22		
III	9	9	0		

SUMO1P3 functions as an oncogene in the development of breast cancer.

Materials and methods

Human tissue samples

Seventy-four pairs of breast cancer tissue and adjacent normal tissue were collected from patients undergoing resection surgery at the Breast Cancer Center, Shanghai East Hospital from 2005-2010. All of the tissue specimens were frozen and stored in liquid nitrogen until further use. None of the patients received preoperative chemotherapy or radiation. This study was conducted with approval from the Ethics and Research Committees of Shanghai East Hospital and was performed in accordance with the Declaration of Helsinki Principles. All of the subjects provided written informed consent. The clinical characteristics of the patients are summarized in **Table 2**.

Cell culture

The breast epithelial cell line MCF-10A and human breast cancer cell lines MCF7, MDA-MB-231, MDA-MB-468, and SKBR-3 were purchased from American Type Culture Collection (ATCC, USA) and were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 50 U/ml penicillin, and 0.1 mg/ml streptomycin. All of the cells were maintained at 37°C in a 5% CO_2 humidified atmosphere.

SUMO1P3 short hairpin RNA and small interfering RNA

Lentivirus-encoding short hairpin RNA (shRNA) targeting SUMO1-P3, sh-SUMO1P3, was purchased from Shanghai GenePharma Co. Ltd (Shanghai, China). Anti-miR-320a, miR-320a mimic, and scrambled siRNA (si-NC) were purchased from Shanghai GenePharma Co. Ltd (Shanghai, China). Transfections were performed using the Lipofectamine 3000 kit (Invitrogen) according to the manufacturer's instructions. Knockdown efficiency was assessed by qRT-PCR.

RNA extraction and real-time PCR

Total RNA from tissues and cells was isolated using Trizol reagent (Invitrogen, Carlsbad, USA) according to the manufacturer's instructions. RNA was reverse transcribed with the PrimeScript RT Reagent Kit (Invitrogen, USA) and qRT-PCR was performed using SYBR

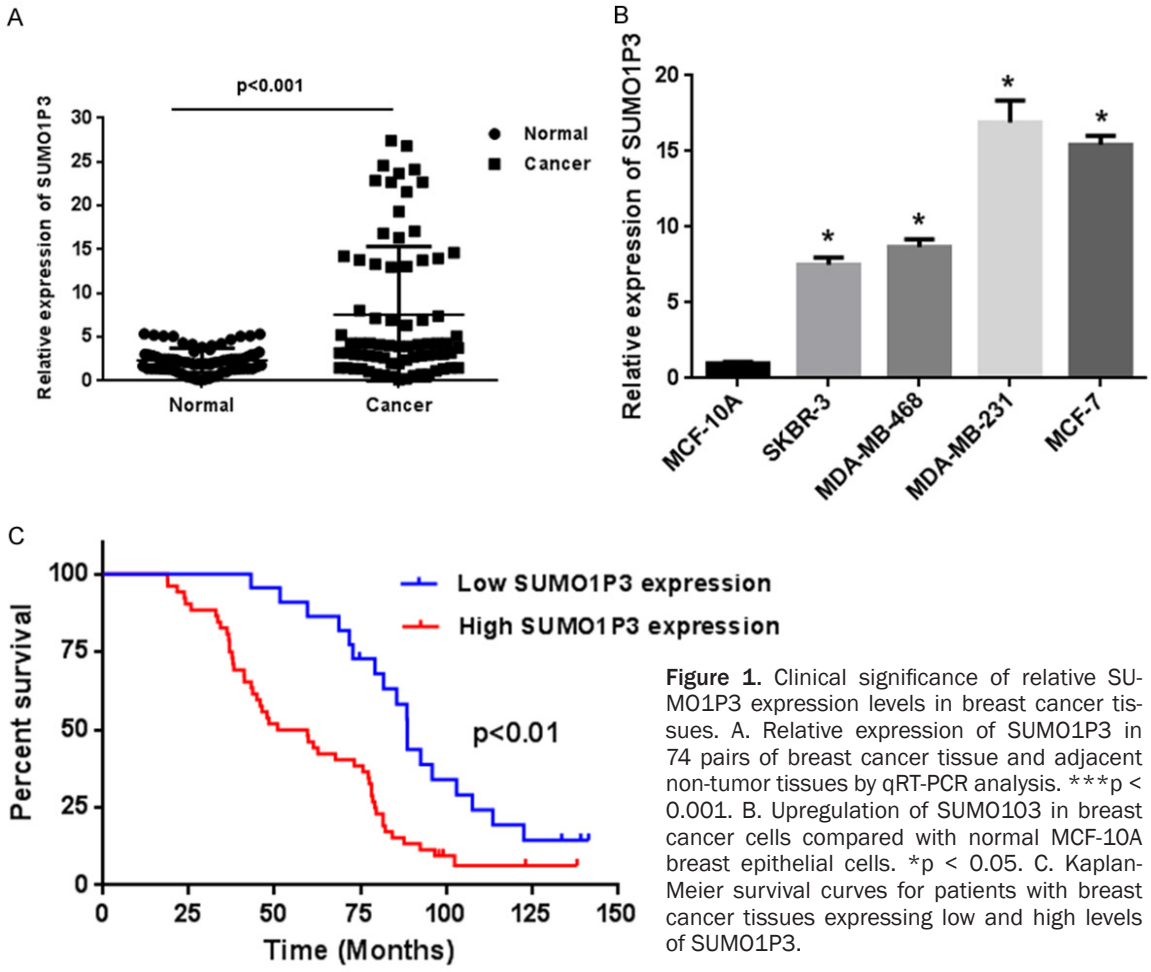

Figure 1. Clinical significance of relative SUMO1P3 expression levels in breast cancer tissues. A. Relative expression of SUMO1P3 in 74 pairs of breast cancer tissue and adjacent non-tumor tissues by qRT-PCR analysis. ***p < 0.001. B. Upregulation of SUMO103 in breast cancer cells compared with normal MCF-10A breast epithelial cells. *p < 0.05. C. Kaplan-Meier survival curves for patients with breast cancer tissues expressing low and high levels of SUMO1P3.

Premix Ex Taq (TaKaRa, China) according to the manufacturer's instructions. GAPDH was used as an internal control. The primer sequences for SUMO1P3 and GAPDH are listed in **Table 1**. qRT-PCR was performed using the ABI PRISM 7500 PCR System (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions.

Cell proliferation assay

Following transfection with sh-SUMO1P3 alone or with sh-SUMO1P3 and miR-320a or with sh-SUMO1P3 and si-NC, cell proliferation was assessed using the Cell Counting Kit-8 (CCK-8; Dojindo Molecular technologies, Inc., Kyushu, Japan) according to the manufacturer's instructions. Two thousand cells were placed into the wells of 96-well plates and 100 μl of CCK-8 was added to the wells. The concentration of formazan present was measured by determining the absorbance at 450 nm according to the manufacturer's instructions.

Cell migration and invasion assays

BD 24-well transwell chambers (Costar, Massachusetts, USA) with or without a matrigel coating were used to evaluate cell migration or invasion according to the manufacturer's instructions. 1×10^5 cells suspended in 0.3 ml of serum-free medium were added to the upper compartments of 24-well plates and 0.8 ml of DMEM supplemented with 10% FBS were added to the lower compartments. After 24 h, the membranes in the lower chambers were fixed with 4% formaldehyde and stained with 1% crystal violet. The number of cells that migrated or invaded through the membrane was determined by microscopy using at least five fields. These experiments were performed in triplicate.

Dual-luciferase reporter assay

A reporter plasmid containing SUMO1P3 wild type (wt) or SUMO1P3 mutant type (mut) was

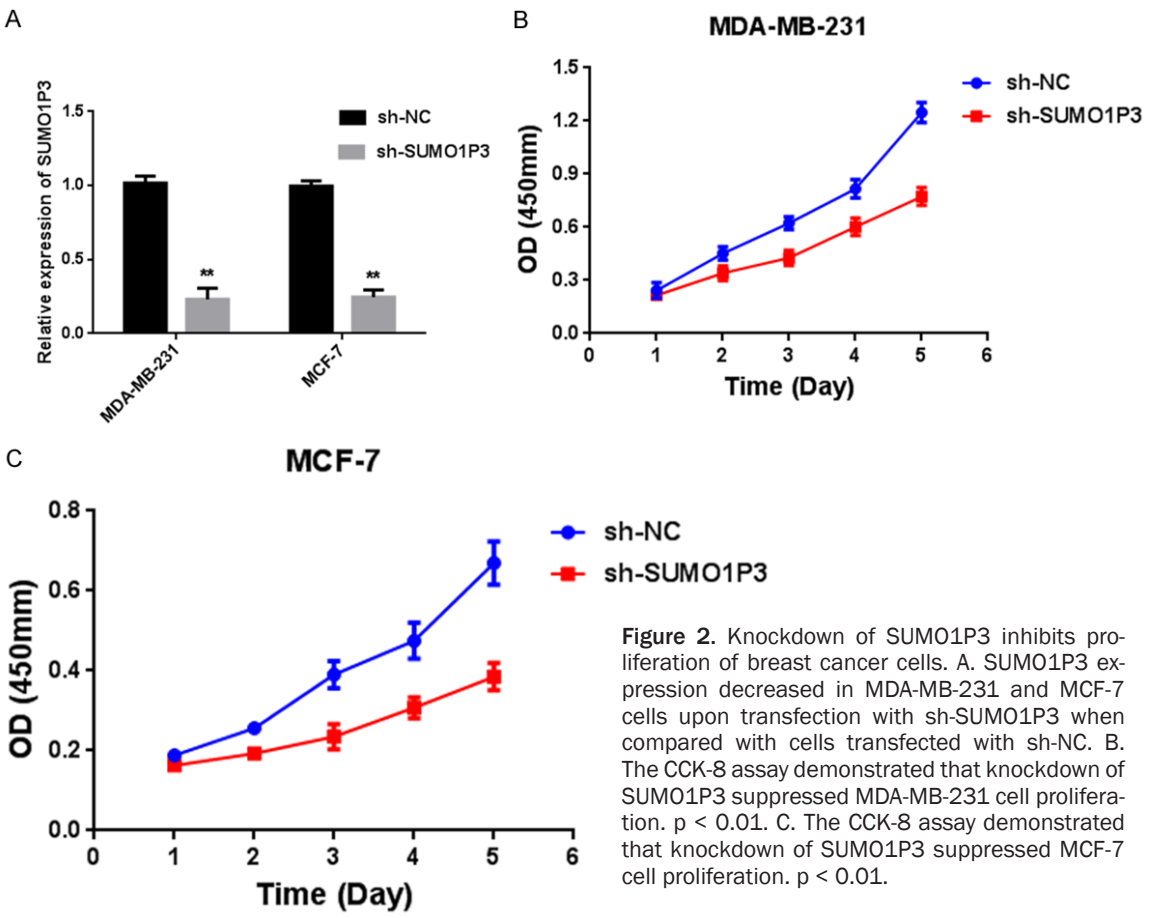

Figure 2. Knockdown of SUMO1P3 inhibits proliferation of breast cancer cells. A. SUMO1P3 expression decreased in MDA-MB-231 and MCF-7 cells upon transfection with sh-SUMO1P3 when compared with cells transfected with sh-NC. B. The CCK-8 assay demonstrated that knockdown of SUMO1P3 suppressed MDA-MB-231 cell proliferation. $p < 0.01$. C. The CCK-8 assay demonstrated that knockdown of SUMO1P3 suppressed MCF-7 cell proliferation. $p < 0.01$.

co-transfected with the miR-320a mimic or the si-NC RNA into MCF-7 cells. The reporter plasmid and the internal control plasmid containing renilla luciferase were transfected using Lipofectamine 3000 (Invitrogen) and 48 h after transfection, luciferase activity was measured using the dual-luciferase reporter gene assay system (Promega, Madison, USA). Renilla luciferase activity was normalized to firefly luciferase activity.

Statistical analysis

All of the data were presented as mean ± SD, were analyzed using GraphPad Prism 5 (GraphPad Software, USA), and were from at least three independent experiments. Chi-square tests were performed to analyze associations between SUMO1P3 levels and clinicopathological factors. The Kaplan-Meier method was used to create survival curves and the log-rank test was used to determine statistical significance. Differences between groups were analyzed using the Student's t-test. Pearson correlation analysis was performed to assess the relationship between SUMO1P3 expression and miR-320a expression. Data were considered statistically significant when $p < 0.05$.

Results

Expression of SUMO1P3 was upregulated in breast cancer tissues

To investigate the role of SUMO1P3 in breast cancer, we measured relative expression of SUMO1P3 in 74 pairs of breast cancer tissue and adjacent non-tumor tissue by qRT-PCR analysis. As shown in **Figure 1A**, SUMO1P3 expression was higher in breast cancer tissues than in the corresponding adjacent non-tumor tissues. We then examined SUMO1P3 expression in four human breast cancer cell lines and in the normal breast epithelial cell line MCF-10A. We found higher SUMO1P3 expression levels in the breast cancer cell lines than in the normal breast epithelial cell line (**Figure 1B**). These results indicate that there is an increase

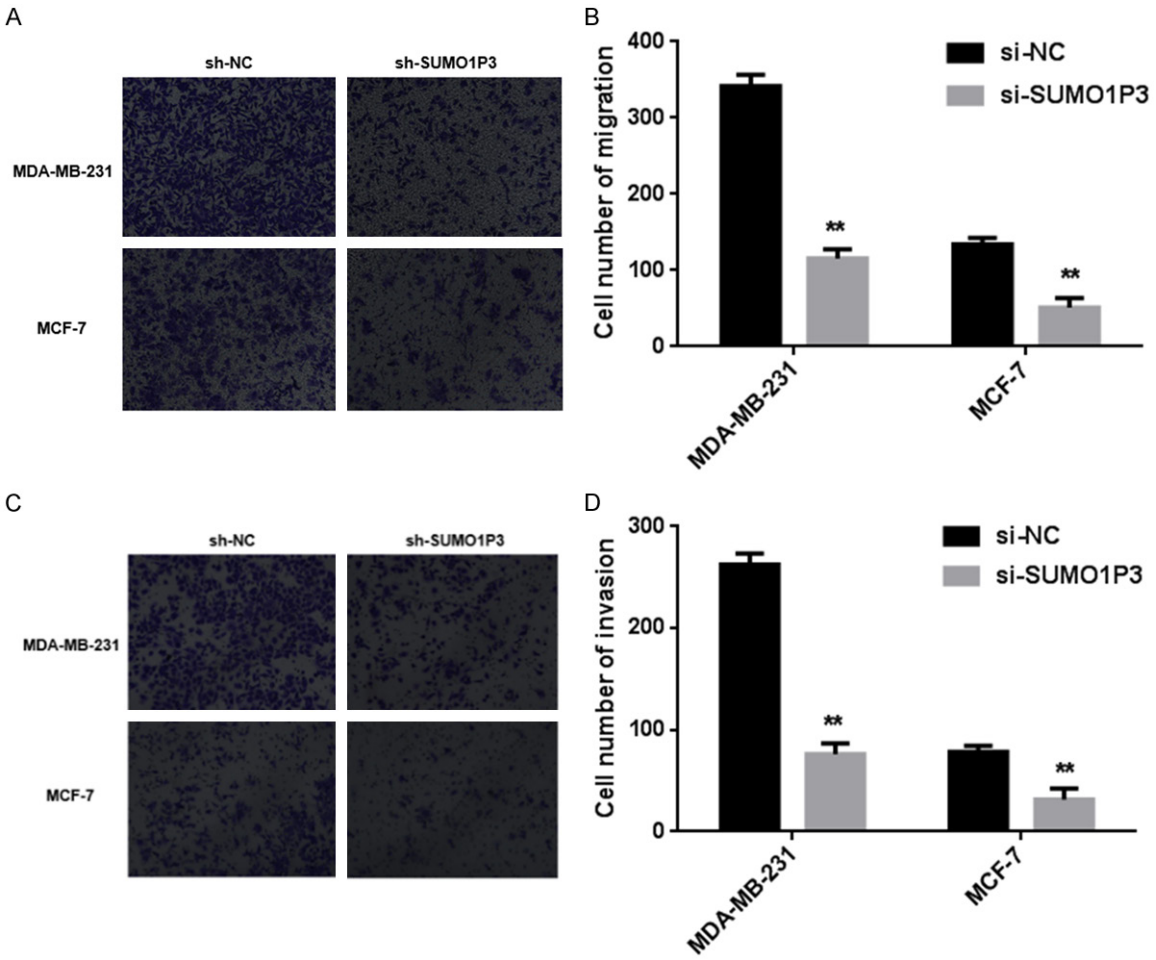

Figure 3. Knockdown of SUMO1P3 suppresses breast cancer cell migration and invasion. A. Images showing that knockdown of SUMO1P3 inhibited migration of MDA-MB-231 and MCF-7 cells. B. Quantification of MDA-MB-231 and MCF-7 cell migration in SUMO1P3-knockdown and control cells. **p < 0.01. C. Images showing that knockdown of SUMO1P3 inhibited invasion of MDA-MB-231 and MCF-7 cells. D. Quantification of MDA-MB-231 and MCF-7 cell invasion in SUMO1P3-knockdown and control cells. **p < 0.01.

in SUMO1P3 expression in human breast cancer tissues and in breast cancer cell lines.

Next, we explored associations between SUMO1P3 expression levels and clinicopathological factors in 74 breast cancer patients (**Table 2**). The data indicated that increased SUMO1P3 expression associates with tumor size (p = 0.014), lymph node metastasis (p = 0.032), and TNM stage (p = 0.037), but there were no significant correlations between SUMO1P3 expression and age, estrogen receptor (ER) status, progesterone receptor (PR) status, Her-2 status, or Ki-67 status. Kaplan-Meier survival curves demonstrated that breast cancer patients who had lower levels of SUMO1P3 in their cancerous breast tissues had significantly better survival rates than breast cancer patients who had higher levels of SUMO1P3 in their cancerous breast tissues (**Figure 1C**).

Knockdown of SUMO1P3 suppresses proliferation of MDA-MB-231 and MCF-7 cells in vitro

To explore the biological function of SUMO1P3 in the development of breast cancer, we silenced SUMO1P3 expression in MDA-MB-231 and MCF-7 cells by transfection with SUMO1P3 shRNA. As shown in **Figure 2A**, MDA-MB-231 and MCF-7 cells transfected with SUMO1P3 shRNA expressed lower levels of SUMO1P3 than control untransfected MDA-MB-231 and MCF-7 cells. In addition, CCK-8 assays showed that knockdown of SUMO1P3 significantly suppressed proliferation of MDA-MB-231 and MCF-7 cells (**Figure 2B** and **2C**).

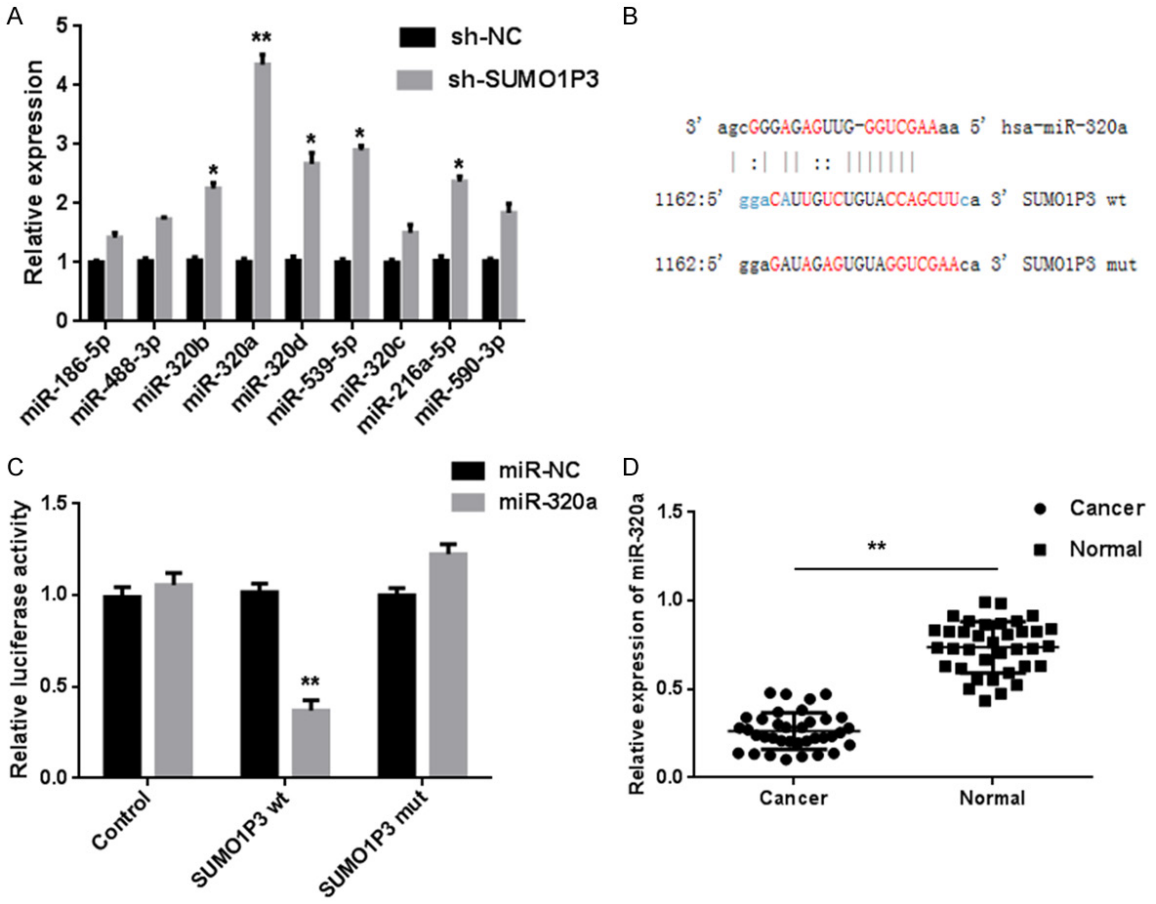

Figure 4. MiR-320a is a target of SUMO1P3. A. qRT-PCR was used to measure the expression of nine miRNAs in SUMO1P3-knockdown and in control cells. *p < 0.05, **p < 0.01. B. Putative complementary sites between SUMO1P3 and miR-320a. Mutations were generated in the SUMO1P3 nucleotides complementary to miR-320a. C. Luciferase activity in MDA-MB-231 cells co-transfected with the miR-320a mimic or sh-NC and in control luciferase reporters without the SUMO1P3 wt or SUMO1P3 mut insert. **p < 0.01. D. qRT-PCR was used to measure miR-320a expression in 36 pairs of breast cancer tissue and adjacent normal tissue. **p < 0.01.

Knockdown of SUMO1P3 inhibits cell migration and invasion

To determine whether SUMO1P3 plays a role in breast cancer cell migration and invasion, transwell assays were performed with MDA-MB-231 and MCF-7 cells. Transwell migration assays showed that knockdown of SUMO1P3 suppressed migration of MDA-MB-231 and MCF-7 cells when compared to the si-NC groups ($p < 0.05$, **Figure 3A** and **3B**). Transwell invasion assays demonstrated that knockdown of SUMO1P3 suppressed invasion of MDA-MB-231 and MCF-7 cells when compared to the si-NC groups ($p < 0.05$, **Figure 3C** and **3D**).

Identification of miR-320a as a target of SUMO1P3

Because it has been shown that numerous lncRNAs function as competing endogenous RNAs (ceRNAs) for specific miRNAs, we used miRanda to search for miRNAs that complementary base pair with SUMO1P3. We found nine miRNAs that SUMO1P3 could target, and we compared expression levels of these nine miRNAs in SUMO1P3-knockdown cells and in control cells. We found that expression of miR-320a was most affected by SUMO1P3 expression (**Figure 4A**).

A dual-luciferase reporter assay was performed to confirm the relationship between SUMO1P3 and miR-320a. We found that cells co-transfected with pLUC-SUMO1P3-wild type and the miR-320a mimic (the SUMO1P3-wt + miR-320a group) displayed significantly lower luciferase activity than cells co-transfected with pLUC-SUMO1P3-wild type and the si-NC RNA (the SUMO1P3-wt + NC group). In contrast, no significant difference was found in the relative

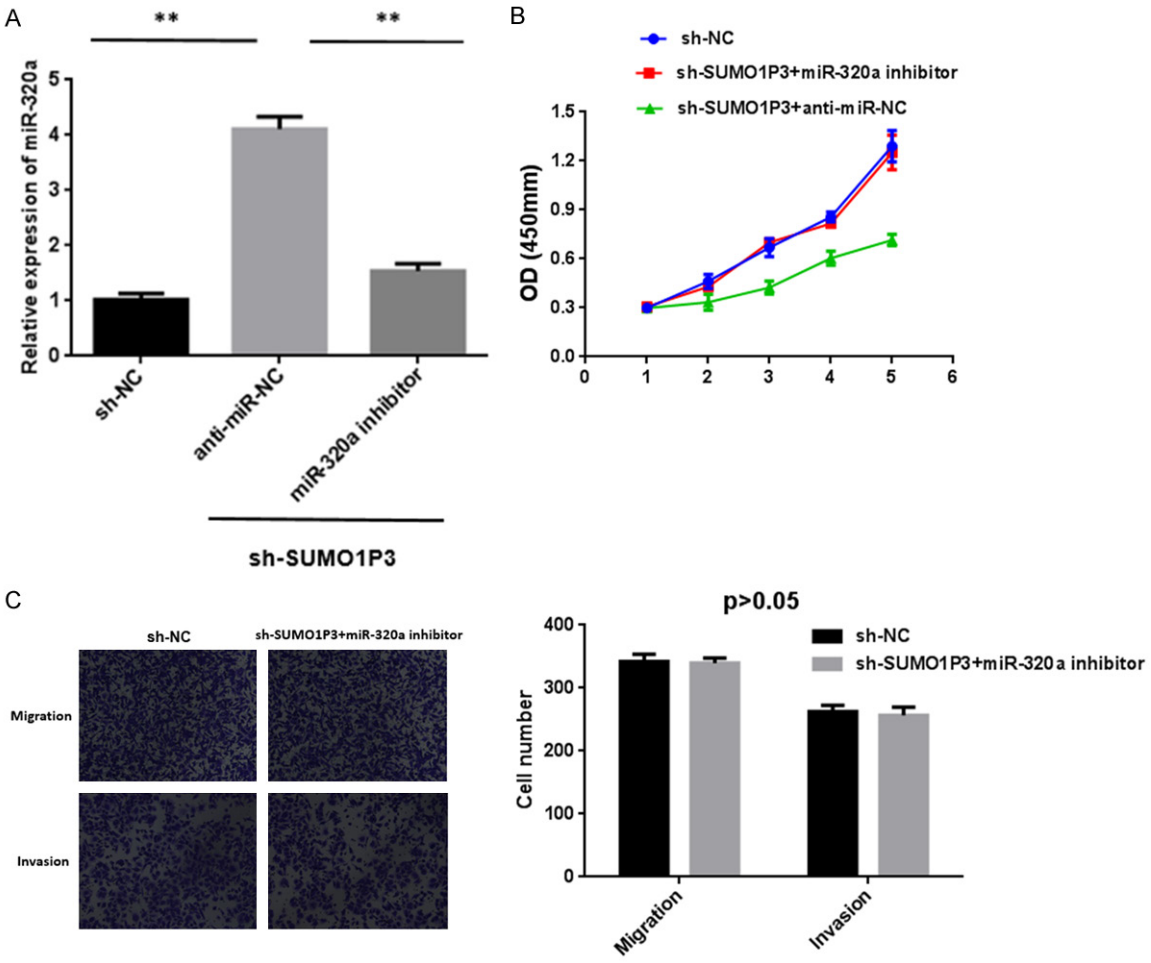

Figure 5. Tumor suppression in breast cancer cells induced by knockdown of SUMO1P3 was partially reversed by co-transfection with an miR-320a inhibitor. A. qRT-PCR was used to measure miR-320a expression in MDA-MB-231 cells that were stably co-transfected with sh-SUMO1P3 and miR-320a inhibitor or sh-NC. **p < 0.01. B. CCK-8 assays were performed to measure proliferation of MDA-MB-231 cells that were stably transfected with sh-SUMO1P3 and miR-320a inhibitor or sh-NC. C. Transwell assays were performed to measure migration and invasion of MDA-MB-231 cells that were stably transfected with sh-SUMO1P3 and miR-320a inhibitor or sh-NC.

luciferase activity between the SUMO1P3-mut + miR-320a and the SUMO1P3-mut + NC groups (**Figure 3C**).

Moreover, we examined miR-320a expression in 36 pairs of breast cancer tissue and adjacent normal tissue by qRT-PCR and found that miR-320a expression was significantly lower in breast cancer tissues than in adjacent normal tissues (**Figure 3D**). Furthermore, miR-320a expression associated negatively with SUMO1P3 expression in breast cancer tissues ($p < 0.05$). These data strongly suggested that SUMO1P3 targets and negatively regulates miR-320a expression in breast cancer tissues.

The oncogenic function of SUMO1P3 in breast cancer cells is dependent on miR-320a

We performed rescue experiments to determine whether knockdown of SUMO1P3 influenced breast cancer cell proliferation, migration, and invasion in a miR-320a-dependent manner. The data shown in **Figure 5A** confirms that anti-miRNA-NC or miR-320a inhibitor was transfected stably into MDA-MB-231 cells already transfected with sh-SUMO1P3. CCK-8 assays revealed that the suppression of proliferation of MDA-MB-231 cells that was induced by knockdown of SUMO1P3 was partially abolished in the presence of the miR-320a inhibitor (**Figure 5B**). In addition, the presence of the

miR-320a inhibitor rescued the inhibition of migration and invasion of MDA-MB-231 cells that was induced by knockdown of SUMO1P3 (**Figure 5C**). These data suggested that the oncogenic function of SUMO1P3 in breast cancer cells involves regulation of miR-320a.

Discussion

It has been shown that SUMO1P3 is upregulated in certain cancers and, thus, could be targeted to treat several types of cancers. In this study, we found that SUMO1P3 expression was significantly higher in breast cancer tissues when compared to adjacent normal tissues. Furthermore, we found that high SUMO1P3 expression associated significantly with cancer phenotypes, such as tumor size, lymph node metastasis, and TNM stage. Breast cancer patients with lower SUMO1P3 expression in their breast cancer tissues survived significantly better than patients with higher SUMO1P3 expression in their breast cancer tissues. These results demonstrated that a high level of SUMO1P3 expression may be a novel biological indicator of poor prognosis in breast cancer patients.

It has been shown that lncRNAs play critical roles in the development of various cancers. Lei.et al. showed that knockdown of MALAT1 suppressed proliferation of ovarian cancer cells [9]. Cai et al. found that overexpression of CCAT2 decreased cell proliferation via a Wnt signaling pathway [10]. In this study, we showed that knockdown of SUMO1P3 significantly inhibited the proliferation, migration, and invasion of breast cancer cells.

Recently, studies have supported novel regulatory mechanisms in the development of cancers that involve interactions between lncRNAs and miRNAs [11, 12]. LncRNAs can regulate miRNAs by acting as ceRNAs or as molecular sponges [13], for example, it has been suggested that lncRNA HOTAIR acts as a ceRNA for miR-331-3p in the development of gastric cancer [14]. The lncRNA Unigene56159 has been shown to promote the epithelial mesenchymal transition in hepatocellular carcinoma by acting as a ceRNA of miR-140-5p [15]. Xiao. et al. demonstrated that lncRNA UCA1 contributes to imatinib resistance in chronic myeloid leukemia cells by acting as a ceRNA of miR-16 [16]. Our data demonstrated that SUMO1P3 binds miR-320a, which has been shown to be a tumor suppressor in many cancers, including hepatocellular carcinoma [17], lung cancer [18], glioma [19], breast cancer [20-22], and adenoid cystic carcinoma [23]. We also explored whether miR-320a reversed the suppression of breast cancer cell proliferation, migration, and invasion induced by knockdown of SUMO1P3. We found that knockdown of SUMO1P3 impaired breast cancer cell proliferation, migration, and invasion, but co-transfection with miR-320a reversed these suppressive effects indicating that SUMO1P3 promotes the development of breast cancer by inhibiting miR-320a.

In conclusion, this is the first study that has demonstrated an increase in SUMO1P3 expression in breast cancer tissues and cell lines. We also showed that SUMO1P3 induces proliferation, migration, and invasion of breast cancer cells by binding to and inhibiting miR-320a. Our data suggest that SUMO1P3 may serve as a prognostic indicator for breast cancer patients and may be a potential biological target for future breast cancer therapeutics.

Acknowledgements

This research was supported in part by the National Nature Science Foundation of China (81573008), and the Fund of Pudong Health Bureau of Shanghai (PWRd2014-01).

Disclosure of conflict of interest

None.

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