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ORIGINAL RESEARCH

ITGA7 functions as a tumor suppressor and regulates migration and invasion in breast cancer

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Background: Breast cancer is the most common malignancy in women and the underlying mechanism of breast cancer cell metastasis is still far from uncover. *Integrin subunit alpha 7* (*ITGA7*) is a functioning protein. It has been detected in many malignancies. But the function of *ITGA7* in breast cancer is not clear. Our aim is to explore *ITGA7* expression and its role in breast cancer.
Methods: Real-time PCR was performed to determine *ITGA7* expression in BC tissues and normal adjacent tissues. The specific functions of *ITGA7* in breast cancer cell lines (MDA-MB-231 and BT-549) transfected with small interfering RNA were determined through migration, invasion assays. Western blot assays were performed to determine the expression of c-met and vimentin.
Results: *ITGA7* was down-regulated in breast cancer tissues compared to the adjacent normal tissues (T:N =7.68±27.38: 41.01± 31.47, $P<0.001$) and this observation was consistent with the TCGA cohort (T:N =4.51±0.45:5.40±0.61, $P<0.0001$). In vitro experiments showed that knocking down *ITGA7* significantly inhibited the migration and invasion of the breast cancer cell lines (MDA-MB-231 and BT-549). Meanwhile, knockdown of *ITGA7* promoted c-met and vimentin expression, which may induce invasion and migration.
Conclusion: *ITGA7* plays an important tumorigenic function and acts as a suppress gene in breast cancer. Our findings indicate that *ITGA7* was the gene associated with breast cancer.
Keywords: breast cancer, *ITGA7*, migration, invasion

Introduction

Breast cancer is the most common malignancy in women. As the reason for cancer-related death, breast cancer ranks second after lung cancer.[1,2] Many studies have proven that invasion of cancer cells was the major reason for cancer-related death.[3,4] With acknowledging development of medical technology, doctors can treat breast cancer patients by surgery, chemotherapy, endocrine therapy, or targeted therapies.[5] But the treatment is not always satisfactory. So, it is still important to explore the mechanism of breast cancer and find new biomarkers at an early stage.

C-met is a key regulator of cancer progression, and it has been reported that upregulated c-met is related with poor survival rates and malignant activities of breast cancer.[6,7] During cancer progression, cancer cells can experience a feature change from an epithelial to a mesenchymal phenotype, which is called epithelial–mesenchymal transition (EMT).[8,9] Hung et al[10] found that osthole suppresses HGF-induced EMT via repression of the c-Met/Akt/mTOR pathway in human breast cancer cells.

Integrin subunit alpha 7 (*ITGA7*) belongs to the integrin alpha chain family, and the coding gene is located on chromosome 12q13.2.[11] It has been found that *ITGA7* is expressed in many cancers including malignant melanoma, prostate and liver

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carcinomas, and glioblastoma.[12,13] Low levels of *ITGA7* mediate cell adhesion migration on specific laminin isoforms and influence tumors growth and motility.[14] Ziober et al[12] found that upregulation of *ITGA7* could reduce melanoma cell tumor growth, motility, and metastasis.[12] Ren et al[13] found that downregulation of *ITGA7* expression increased the rate of migration in lung cancer cells. However, the relationship between *ITGA7* and breast cancer is not exactly clear.

In order to clarify the expression and effect of *ITGA7* in breast cancer, our study examined *ITGA7* expression in breast cancer tissues and paired adjacent nontumor tissues by using real-time quantitative PCR (RT-qPCR), and we verified our clinical specimen data by using The Cancer Genome Atlas (TCGA) database. Besides, we characterized the function of *ITGA7* in breast cancer cell lines. We found that downregulated *ITGA7* could promote breast cancer cell migration and invasion.

Materials and methods

Patients and breast tissue samples

In this present study, we obtained 36 breast cancer tissues and paired adjacent nontumor tissues from the Department of Thyroid and Breast Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China. All patient-derived specimens and information were collected and recorded based on the protocols provided by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University. These 36 fresh tissues were snap-frozen in liquid nitrogen immediately and stored at –80°C. Breast cancer mRNA expression data were downloaded from the TCGA data portal (https://tcga-data.nci.nih.gov/tcga/). Gene expression data were available for 1,100 breast cancer samples compared to 113 normal samples.

Ethical approval

Ethical approval for this study was obtained from the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Cell cultures and growth conditions

MDA-MB-231, BT-549, SK-BR-3, MDA-MB-468, MCF-7, and MCF-10A cells were used in this study. These cells were obtained from Shanghai Cell Biology, Institute of the Chinese Academy of Sciences (Shanghai, People's Republic of China). MDA-MB-231, MCF-7, and SK-BR-3 were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS) (Gibco). BT-549 were cultured in Roswell Park Memorial Institute-1640 medium (Gibco) supplemented with 10% FBS (Gibco). MDA-MB-468 cells were cultured in L-15 medium (Gibco) supplemented with 10% FBS (Gibco). MCF-10A cells were cultured in DMEM-F12 (Gibco) supplemented with 100 U/mL of penicillin, 100 µg/mL of streptomycin, 2 mM of L-glutamine, 20 ng/mL of epidermal growth factor, and 10% FBS (Gibco) MDA-MB-468 cells were incubated in a standard cell culture incubator (Thermo, Waltham, MA, USA) at 37°C without CO_2.The others were incubated in a standard cell culture incubator (Thermo) at 37°C with 5% CO_2.

Cell transfection

MDA-MB-231 and BT-549 were transfected using Lipofectamine RNAiMAX transfection reagent (Invitrogen, Carlsbad, CA, USA) by following the manufacturer's protocol. About 100,000 cells were plated 1 day before transfection. *ITGA7* was silenced by transfecting 10 nM siRNA for 48 h. The siRNA sequences used in the study were the *ITGA7* siRNAs that targeted the following sequences: *ITGA7* siRNA-1, forward 5′-GCAUCAAGAGCUUCGGCUATT-3′and reverse 5′-UAGCCGAAGCUCUUGAUGCTT-3′; *ITGA7* siRNA-2, forward 5′-GCUGCCCACUCUACAGCUUTT-3′ and reverse 5′-AAGCUGUAGAGUGGGCAGCTT-3′; *ITGA7* siRNA-3, forward 5′-GGUCAUCCUCCUGGCUGUATT-3′and reverse 5′-UACAGCCAGGAGGAUGACCTT-3′. Both siRNAs were provided by Genepharma (Shanghai, People's Republic of China) company.

RNA extraction and RT-qPCR

Total RNA was lysed using TRIzol reagent according to the manufacturer's instructions (Invitrogen). The purity of the isolated RNA was measured at 260/280 nm by spectrophotometry (Thermo). After measurement, RNA samples were stored at –80°C. Real-time reactions were run and analyzed by using a real-time PCR system (Applied Biosystems 7500, ThermoFisher Scientific). The relative expression of mRNA was calculated using the comparative cycle threshold (CT) ($2^{-\Delta\Delta CT}$) method with GAPDH as the endogenous control to normalize the data. The sequences of the primers used were as follows:

ITGA7 forward: 5′-GCTGTGAAGTCCCTGGAAGT GATT-3′ and reverse: 5′-GCATCTCGGAGCATCAAGTTC TT-3′; GADPH forward: 5′-GTCTCCTCTGACTTCA ACAGCG-3′ and reverse: 5′-ACCACCCTGTTGCTGTA GCCAA-3′.

Invasion and migration assay

For cell Transwell assays, cells were trypsinized with trypsin and collected in the medium containing 10% FBS. Invasion of cells was measured in Matrigel (BD, Franklin Lakes, NJ,

USA)-coated Transwell inserts (6.5 mm, Costar, Manassas, VA, USA) containing polycarbonate filters with 8 μm pores. The inserts were coated with 50 μL of 1 mg/mL Matrigel matrix according to the manufacturer's recommendations. A total of 40,000 cells (~250 μL) were transferred into the upper chamber. About 700 μL medium containing 20% FBS was filled in the lower chamber. Then the plate was placed into the incubator. After 24 h, the membrane was fixed with 4% paraformaldehyde and stained with 0.4% crystal violet solution for 15 min. Motility assays were similar to invasion assay except that the Transwell insert was not coated with Matrigel. Cell migration and invasion ability were assessed by counting the cells that had migrated and invaded through the membrane. Five random fields of view were selected and images captured under a microscope at a magnification of 20×.

Western blot analysis

Whole cell lysates were separated by 10% sodium dodecyl sulfate–polyacrylamide gels electrophoresis (BioRad, Berkeley, CA, USA) and transferred to a PVDF membrane (Millipore, Billerica, MA, USA). The membranes were blocked with 5% nonfat milk for 2 h at room temperature. According to the manufacturer's protocol, the membranes were probed with polyclonal antibody overnight at 4°C. The membranes were then incubated with the anti-mouse IgG or anti-rabbit IgG as secondary antibody (Abcam, Cambridge, MA, USA) for 1 h at room temperature. The primary antibodies used were as follows: Vimentin (Abcam, ab92547), *ITGA7* (Abcam, ab203254), and human GAPDH (Sigma, St. Louis, MO, USA).

Statistical analysis

All statistical analyses were performed using SPSS 23.0 software (IBM Corporation, Armonk, NY, USA). Data are presented as mean ± standard error. The differences were considered to be statistically significant at $P<0.05$. Student's *t*-test (2-tailed) was performed to analyze differences between groups.

Result

ITGA7 was downregulated in breast cancer tissues

In order to investigate the function of *ITGA7* in breast cancer tumorigenesis, the expression levels of *ITGA7* were investigated in 36 breast cancer tissues and paired adjacent nontumor tissues by using RT-qPCR. We found that *ITGA7* expression was significantly lower in breast cancer tissues, compared to the adjacent normal tissues (T:N =7.68±27.38:41.01±31.47, $P<0.001$) (Figure 1A). TCGA also showed that *ITGA7* was downregulated in breast cancer compared to the adjacent normal tissues (T:N =4.51±0.45:5.40±0.61, $P<0.001$) (Figure 1B). In a word, these results implied that *ITGA7* might function as a tumor suppressor in breast cancer.

The relationship between *ITGA7* expression and clinical features

To understand the relation between *ITGA7* and breast cancer, we investigated the relationship of *ITGA7* with clinicopathological features. In the TCGA cohort, we divided the patients into low-expression group and high-expression

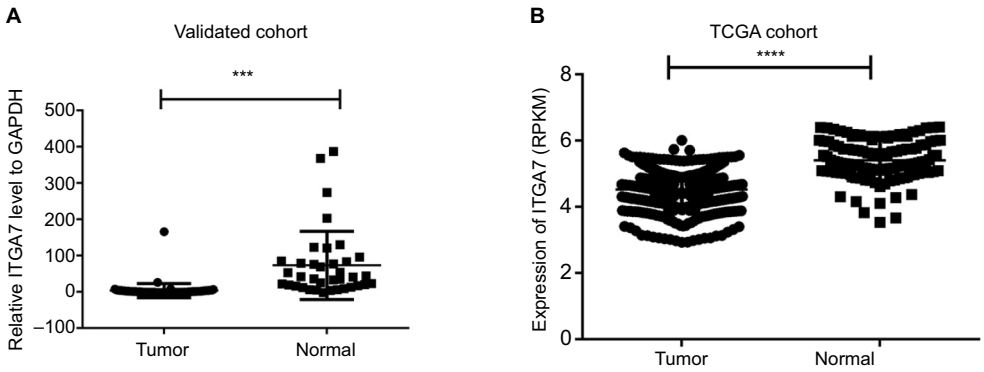


Figure 1 *ITGA7* expression in breast cancer in validated cohort and TCGA cohort.
Notes: (A) *ITGA7* expression was examined by RT-qPCR in 36 paired human breast cancer tissues and adjacent noncancerous tissues (paired *t*-test, $P<0.001$). A logarithmic scale of $2^{-\Delta\Delta Ct}$ is used to represent the fold change in quantitative real-time PCR detection. **(B)** The TCGA cohort contained 1,100 breast tumor tissues and 113 normal tissues. RPKM is used to represent expression of *ITGA7*. The analysis was done using the Mann–Whitney *U*-test. ***$P<0.001$: ****$P<0.0001$.
Abbreviations: *ITGA7*, integrin subunit alpha 7; RPKM, reads per kilobases per million reads; RT-qPCR, real-time quantitative PCR; TCGA, The Cancer Genome Atlas.

group according to the median value. The results revealed that lymph node metastasis (P=0.030) and tumor size (P=0.024) were significantly related to the *ITGA7* expression (Table 1). In the validated cohort, we divided all patients into the low-expression group (n=18) and high-expression group (n=18) according to the median value as same. The results showed that age (P=0.169) and lymph node metastasis (P=0.075) were not related to the expression of *ITGA7* negatively (Table 2). These results indicated that low *ITGA7* expression may influence the ability of migration of breast cancer cells and was associated with unfavorable prognosis in breast cancer.

ITGA7 regulates migration and invasion of breast cancer lines

To confirm the role of *ITGA7* in breast cancer, we assessed *ITGA7* expression level in several breast cancer cell lines and normal breast cell lines by using RT-qPCR. We found that expression level of *ITGA7* was higher in MDA-MB-231 and BT-549 than in other breast cell lines (Figure 2A). So, we selected MDA-MB-231 and BT-549 for further experiments. To further examine whether *ITGA7* functions in breast cancer progression, we knocked down *ITGA7* expression in MDA-MB-231 and BT-549 using siRNA. As can be seen in Figure 2B–D, both mRNA and protein levels of *ITGA7* were significantly reduced.

Table 1 The relationship between *ITGA7* and clinicopathologic characteristics in TCGA cohort

Clinicopathologic characteristics	Low expression (%)	High expression (%)	χ^2	*P*-value
Age (years)			0.001	0.973
≤60	296	296		
>60	243	242		
Tumor size			7.475	0.024*
<2 cm	123	155		
2–5 cm	335	291		
>5 cm	81	92		
Lymph node metastasis			8.951	0.030*
N0	256	274		
N1	195	160		
N2	60	57		
N3	28	47		
Distant metastasis			0.854	0.356
No	530	427		
Yes	9	11		
Clinical stage			1.662	0.197
I–II	415	396		
III–IV	124	142		

Note: *P-value <0.05.
Abbreviations: *ITGA7*, integrin subunit alpha 7; TCGA, The Cancer Genome Atlas.

Table 2 The relationship between *ITGA7* and clinicopathologic characteristics in the validated cohort

Clinicopathologic characteristics	Low expression (%)	High expression (%)	χ^2	*P*-value
Age			1.893	0.169
≤60	17	14		
>60	1	4		
Tumor size			20.029	0.598
<2 cm	10	9		
2–5 cm	8	8		
>5 cm	0	1		
Lymph node metastasis			3.167	0.075*
No	6	10		
Yes	12	8		
Distant metastasis			0.001	0.97
No	17	16		
Yes	1	2		
Estrogen receptor			0.106	0.744
Negative	8	10		
Positive	10	8		
Progesterone receptor			0.106	0.744
Negative	8	10		
Positive	10	8		
Her-2 receptor			0.432	0.511
Negative	7	8		
Positive	11	10		
Clinical stage			4.886	0.067
I–II	10	13		
III–IV	8	5		

Note: *P-value <0.05.
Abbreviation: *ITGA7*, integrin subunit alpha 7.

Previous studies have proven that a cancer cell's abilities of migration and invasion were correlated with tumor progression.[15,16] We next examined whether knocking down *ITGA7* affected the functions of breast cancer cell lines. Our results showed that downregulated *ITGA7* significantly enhanced migration capacity of MDA-MB-231 and BT-549 compared with the control groups (Figure 3A and B). The invasion assays also showed that downregulated *ITGA7* effectively enhanced invasion capacity of MDA-MB-231 and BT-549 (Figure 4A and B).

ITGA7 regulates migration and invasion via addition to c-met-regulated vimentin

We found that knockdown of *ITGA7* led to significantly increased c-met in MDA-MB-231 and BT-549 (Figure 5A). In a previous study,[10,28] repression of the c-Met/Akt/mTOR pathway was found to suppress EMT. Vimentin is important in EMT and tumor progression.[17,18] In order to explore the

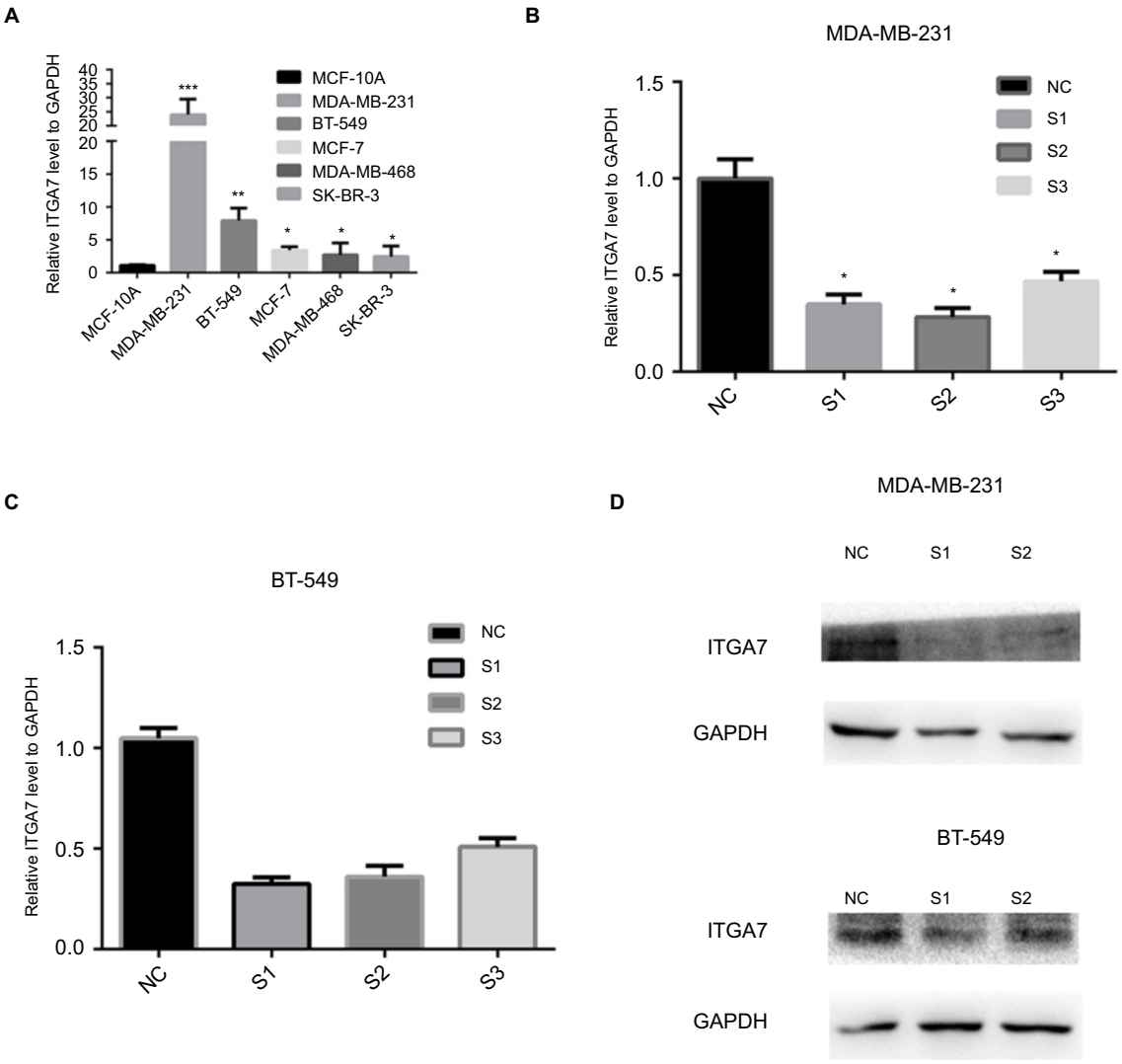


Figure 2 The expression level of *ITGA7* in breast cancer cell lines.
Notes: (A) The relative expression of *ITGA7* gene (compared with the *GAPDH* gene) using RT-qPCR. Compared to the other cell lines, *ITGA7* was expressed at a higher level in MDA-MB-231 and BT-549. **(B–D)** MDA-MB-231 and BT-549 cells were transfected with siRNA-1, siRNA-2, or si-NC for 48 h, and both mRNA and protein levels of *ITGA7* were significantly reduced. Compared with corresponding control group, the expression of *ITGA7* gene in S1 and S2 group was lower. We defined *ITGA7* siRNA-1 as S1, *ITGA7* siRNA-2 as S2, and *ITGA7* siRNA-3 as S3. **P*<0.05; ***P*<0.01; ****P*<0.001.
Abbreviations: *ITGA7*, integrin subunit alpha 7; NC, negative control; RT-qPCR, real-time quantitative PCR.

potential mechanism of *ITGA7* in breast cancer, we measured the expression level of epithelial markers and mesenchymal markers in MDA-MB-231 and BT-549 using Western blotting. The result showed that cells with knocked down *ITGA7* had significantly higher vimentin expression level (Figure 5B). Our result showed that knockdown of *ITGA7* may regulate vimentin via enhancing c-met.

Discussion

Breast cancer represents the highest health burden in the world, which is consistent with recently published data which reports that breast cancer is a significant part of the cause of cancer-related death in women worldwide.[2] Although much progress in medical research had been made in breast cancer,[19–21] there is still much left unknown about the molecular mechanisms of breast cancer. Some studies have demonstrated that *ITGA7* gene was associated with malignant melanoma, prostate and liver carcinomas, and glioblastoma.[12] However, there is still known little about its function in breast cancer.

In our study, the main aim was to prove the potential role of *ITGA7* in breast cancer. We found that *ITGA7* in breast cancer tissues was downregulated compared to paired adjacent nontumor tissues by RT-qPCR. This result was further identified in TCGA cohort. We analyzed the clinical features of breast cancer patients from TCGA and found that lymph

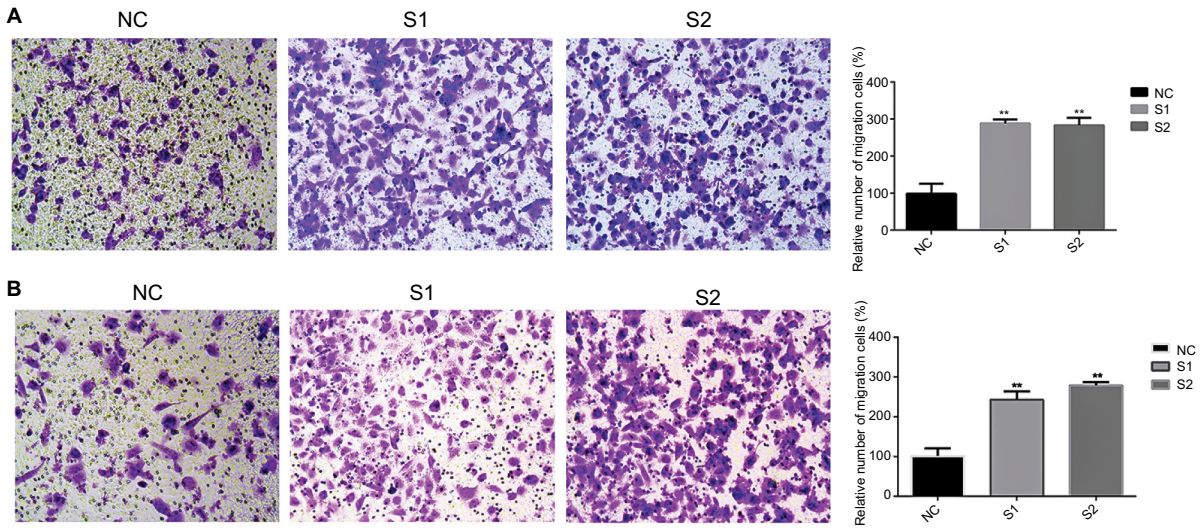


Figure 3 Downregulation of *ITGA7* gene expression in MDA-MB-231 and BT-549 cells inhibits migration.
Notes: These experiments were done at least 3 independent times. **(A)** In MDA-MB-231, Transwell migration assays in downregulation *ITGA7* cells and their corresponding control cells. **(B)** In BT-549, Transwell migration assays in downregulation of *ITGA7* cells and their corresponding control cells. Quantitative results of migration assays. The stained cells were then counted manually from 5 randomly selected fields and normalized with cell proliferation. $^{**}P<0.01$ in comparison with the NC group using Student's t-test. We defined *ITGA7* siRNA-1 as S1 and *ITGA7* siRNA-2 as S2.
Abbreviations: *ITGA7*, integrin subunit alpha 7; NC, negative control.

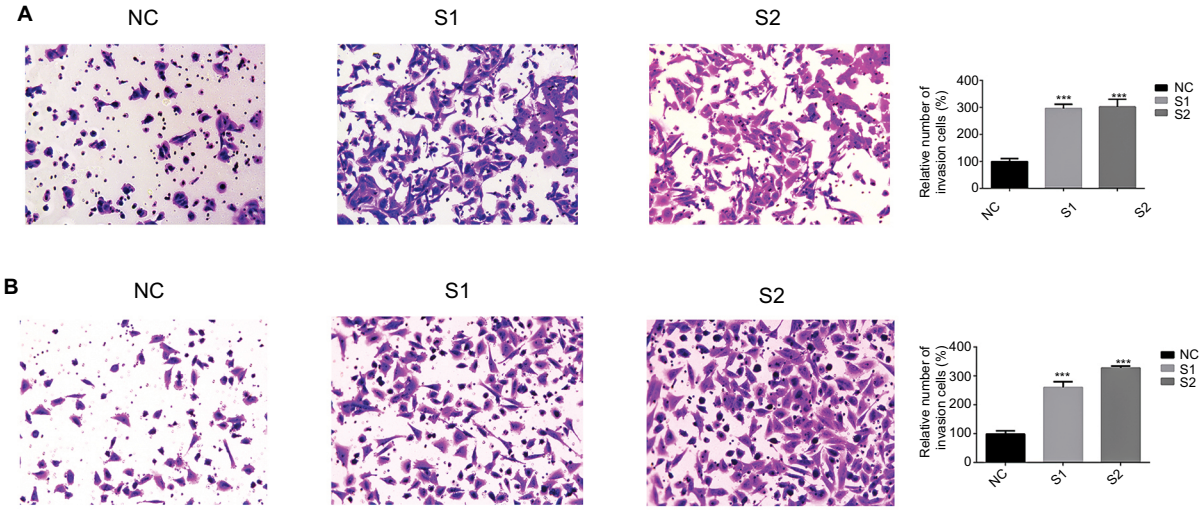


Figure 4 Downregulation of *ITGA7* gene expression in MDA-MB-231 and BT-549 cells inhibits invasion.
Notes: These experiments were done at least 3 independent times. **(A)** Transwell invasion assays in downregulation *ITGA7* cells and their corresponding NC cells in MDA-MB-231. **(B)** Transwell invasion assays in downregulation *ITGA7* cells and their corresponding negative control cells in BT-549. Quantitative results of invasion assays. The stained cells were manually counted from 5 randomly selected fields and normalized with cell proliferation. $^{***}P<0.001$ in comparison with the NC group using Student's t-test. We defined *ITGA7* siRNA-1 as S1 and *ITGA7* siRNA-2 as S2.
Abbreviations: *ITGA7*, integrin subunit alpha 7; NC, negative control.

node metastasis (P=0.030) and tumor size (P=0.024) were significantly related with the *ITGA7* expression. These findings suggest that *ITGA7* may play an important role in breast cancer and encouraged us to proceed with the next step to study the *ITGA7* gene in cell lines. We found that *ITGA7* was expressed at a higher level in MDA-MB-231 and BT-549 than in other breast cell lines. Then, using cellular and molecular technology, we found that knockdown of *ITGA7* led to an increase in migration and invasion abilities, which is consistent with *ITGA7* being associated with breast cancer.

In recent decades, the development of c-met has been increasingly recognized to play pivotal roles in promoting tumor process.[22–24] Jia et al[25] found that inhibiting c-MET could enhance the response of the colorectal cancer cells

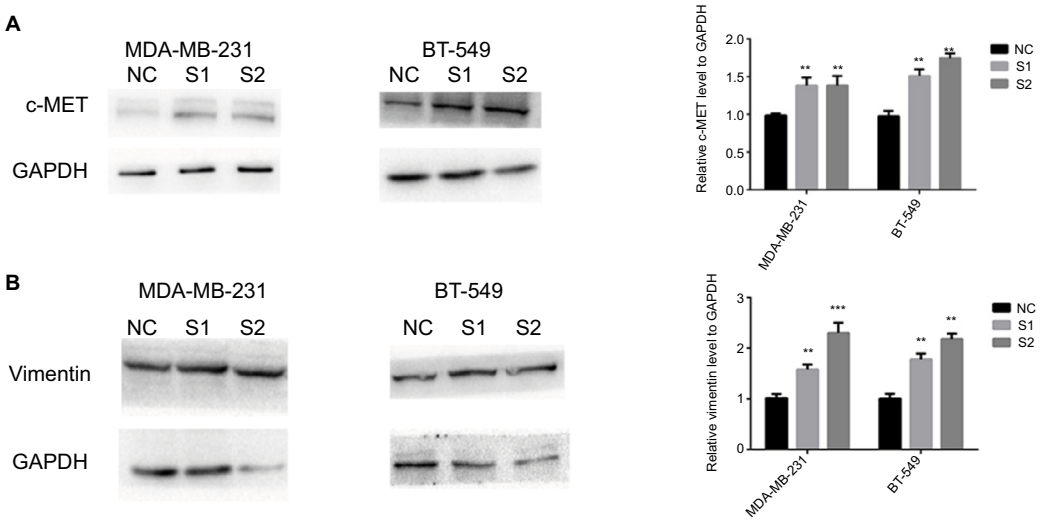


Figure 5 Downregulation of *ITGA7* regulates migration and invasion via addition to c-met-regulated vimentin.
Notes: These experiments were done at least 3 independent times. We defined *ITGA7* siRNA-1 as S1 and *ITGA7* siRNA-2 as S2. **(A)** The influence of *ITGA7* expression on c-MET in MDA-MB-231 and BT-549 cells by Western blot. **(B)** The influence of *ITGA7* expression on vimentin in MDA-MB-231 and BT-549 cells by Western blot. $^{**}P<0.01$ and $^{***}P<0.001$ in comparison with the NC group using Student's t-test. We defined *ITGA7* siRNA-1 as S1 and *ITGA7* siRNA-2 as S2.
Abbreviations: *ITGA7*, integrin subunit alpha 7; NC, negative control.

to irradiation in vitro and in vivo. Our study proved that knocking down *ITGA7* could enhance c-met. EMT is a developmental multistep molecular process which may induce tumor process.[26,27] Recently, EMT was found that facilitate the progression of breast cancer. It has been reported that repression of the c-Met/Akt/mTOR pathway could suppress EMT in breast cancer.[10] So, we tested the EMT-related epithelial marker and the mesenchymal markers after *ITGA7* knockdown. We found that the mesenchymal marker vimentin was induced after *ITGA7* knockdown. Together, these results mean that knockdown of *ITGA7* enhances breast cancer cell migration and invasion via c-met regulated vimentin.

However, our study still has several limitations. For one thing, gain-of-function experiments need to be conducted to further validate the results. For another, we need to expand the validation group to provide reliable clinicopathological features and findings.

Conclusion

By using bioinformatics analysis and cellular and molecular approaches, the role of *ITGA7* gene as a suppressor gene in breast cancer was demonstrated. We found that knockdown of *ITGA7* could enhance breast cancer cell migration and invasion. This study indicated that *ITGA7* may act as a potential drug target in breast cancer.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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