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Downregulating integrin subunit alpha 7 (ITGA7) promotes proliferation, invasion, and migration of papillary thyroid carcinoma cells through regulating epithelial-to-mesenchymal transition

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Abstract

Thyroid cancer is one of the common malignancies of the endocrine system and the number of thyroid cancer cases is increasing constantly. Significant work has focused on the molecular mechanisms of thyroid cancer, but many mechanisms remain undiscovered. In this study, we employed a comprehensive analysis of whole-transcriptome resequencing derived from paired papillary thyroid cancer (PTC) and normal thyroid tissues. We performed a massive parallel whole-transcriptome resequencing of matched PTC and normal thyroid tissues in 19 patients and found that integrin subunit alpha 7 (ITGA7) was downregulated in thyroid tumor tissues, but the function of ITGA7 in this cancer is still unclear. We also discovered that ITGA7 gene in thyroid cancer tissues was downregulated compared to paired adjacent non-tumor tissues by real-time quantitative polymerase chain reaction. After transfection with small interfering RNA to knock down ITGA7, the abilities of colony formation, proliferation, migration, and invasion were enhanced in PTC cell lines (TPC1 and KTC-1). Meanwhile, ITGA7 knockdown decreased apoptotic cell death in thyroid cells but promoted the expressions of N-cadherin and vimentin and decreased E-cadherin expression by epithelial-to-mesenchymal transition, which may induce invasion and migration. In conclusion, these results indicated that ITGA7 is involved in the progress of PTC and might act as a tumor suppressor gene.

Key words: thyroid cancer, ITGA7, proliferation, papillary thyroid cancer (PTC), epithelial-to-mesenchymal transition (EMT)

Introduction

Thyroid cancer is one of the most widespread endocrine malignancies with an increasing prevalence of morbidity. It was reported that the number of global thyroid cancer cases is increasing by ~4% each year and will surpass the number of colorectal cancer cases in 2030 and become the fourth most prevalent cancer [1]. According to the U.S. National Cancer Institute, the estimated number of new thyroid cancers was 56,870 with an estimated 2010 deaths in the year of 2017 in the USA [2]. In China, the estimated number of cases was 90,000, and the estimated number of deaths was 6800 in 2015 [3]. Thyroid cancer is usually classified into four different

histological types, i.e. papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid carcinoma and medullary thyroid carcinoma [4]. Among those subtypes, PTC, the most common histologic type, is the main type of thyroid cancer [5], which almost accounts for 80%–85% of all thyroid cancer cases [6]. Although PTC has an excellent prognosis and the 5-year survival rate of PTC patients exceeds 90% [7], there are still some PTC patients who recur after conventional treatments. It is necessary to understand its tumorigenesis and to develop precise treatment approaches. At present, the potential molecular mechanisms of PTC are still unclear.

With the development of medical technologies, many studies have been carried out on PTC [8]. For example, Wang *et al.* [9] discovered that high expression of ARAP3 could enhance the proliferation and metastasis of PTC cells. Xia *et al.* [10] found that upregulated lncCCND2-AS1 could increase the proliferation and metastasis of PTC cells via influencing N-cadherin and vimentin. Jin *et al.* [11] found that GABRB2 positively affects the oncogenesis of PTC and upregulated GABRB2 expression is associated with its aggressive clinicopathological features.

By using the sequencing technology, we did whole-transcriptome resequencing of 19 paired PTC tissue samples in our unpublished work and found that integrin subunit alpha 7 (ITGA7) was downregulated in tumor tissues. ITGA7, with its coding gene located on chromosome 12q13.2 [12], belongs to the integrin alpha chain family, which mediates a wide spectrum of cell–cell and cell–matrix interactions, and thus plays a role in cell migration, morphologic development, differentiation, and metastasis. Previous studies have revealed that ITGA7 is significantly associated with various cancers. It has been found that ITGA7 is expressed in many cancers, including malignant melanoma, prostate and liver carcinomas, and glioblastoma [12,13]. Barry *et al.* [14] found that upregulation of ITGA7 could reduce melanoma cell tumor growth, motility, and metastasis. Knocking down ITGA7 expression could increase the rate of migration in lung cancer cells [13]. Low level of ITGA7 could mediate cell adhesion migration on specific laminin isoforms and influence tumor growth and motility [14]. Zhang *et al.* [15] discovered that knocking down the chemokine receptor CXCR7 gene could decrease ITGA7 in PTC. Bhandari *et al.* [16] found that ITGA7 functions as a tumor suppressor and regulates migration and invasion in breast cancer. However, the relationship between ITGA7 and PTC is still unclear.

In the present study, the real-time quantitative polymerase chain reaction (RT-qPCR) assay was conducted in 19 pairs of tumor tissues and paired adjacent non-tumor tissues to validate the abnormal expression of ITGA7 in PTC. In addition, the function of ITGA7 was characterized in PTC cell lines to demonstrate the exact role of ITGA7 in PTC.

Materials and Methods

Patients and thyroid tissue samples

In this study, 19 pairs of PTC tissues and paired adjacent non-tumor tissues were obtained between 2016 and 2017 from the Department of Thyroid & Breast Surgery of the First Affiliated Hospital of Wenzhou Medical University. Major inclusion criteria were: (i) patients with pathologically confirmed thyroid cancer in the primary tumor but without any severe diseases in other organs, (ii) patients that had received total/near total thyroidectomy but had not received any radiotherapy, and (iii) patients with a negative history of any other malignant tumors. Major exclusion criteria were: (a) patients with a positive history of other malignant tumors, (b) patients with severe diseases such as heart failure, stroke, and chronic renal failure, and (c) patients with a history of ^{131}I therapy. Information about 19 patients used for the study is shown in Table 1. All patient-derived specimens and information were collected with written consents and recorded under the protocols approved by and conducted under the ethical standards of the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Fresh PTC tissues and normal tissues were snap-frozen in liquid nitrogen immediately after resection and stored at −80°C before RNA extraction.

Table 1. Clinicopathologic characteristics of the patients

Clinicopathologic characteristics	Number (%)
Age	
≤45	8 (42.1)
>45	11 (57.9)
Gender	
Female	5 (26.3)
Male	14 (73.7)
Tumor size	
≤10 mm	7 (36.8)
>10 mm	12 (63.2)
Unilateral or Bilateral	
Unilateral	14 (73.7)
Bilateral	5 (26.3)
Extrathyroidal invasion	
Yes	1 (5.3)
No	18 (94.7)
Lymph node metastasis	
Yes	7 (36.8)
No	12 (63.2)
AJCC	
I	15 (78.9)
II	0 (0)
III	3 (15.8)
IV	1 (5.3)

AJCC: American Joint Committee on Cancer.

Cell cultures and growth conditions

Three PTC cell lines (TPC1, KTC-1, and BCPAP) were provided by Professor Mingzhao Xing of the Johns Hopkins University School of Medicine (Baltimore, USA). The normal thyroid cell line (Htori-3) was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK). TPC1, KTC-1, and BCPAP cells were cultured in RPMI1640 medium (Invitrogen, Carlsbad, USA) supplemented with 10% fetal bovine serum (FBS; Invitrogen). All cells were incubated in a standard cell culture incubator (Thermo Fisher Scientific, Waltham, USA) at 37°C with 5% CO_2.

Cell transfection

TPC1 (6×10^4 cells/well) and KTC-1 (1×10^5 cells/well) were plated in six-well plates and cultured for 24 h. Then cells were transfected with small interfering RNA (siRNA) using Lipofectamine RNAiMAX transfection reagent (Invitrogen) following the manufacturer's protocol. For the transfection of TPC1 cells, 100 nM of siRNA was used; and for the transfection of KTC-1 cells, 75 nM of siRNA was used. After 48 h of transfection, the corresponding transfection efficiency was evaluated by RT-qPCR. The siRNAs used in the study were synthesized by GenePharma (Shanghai, China) and the sequences are as follows: ITGA7

siRNA-1, forward 5′-GCAUCAAGAGCUUCGGCUATT-3′ and reverse 5′-UAGCCGAAGCUCUUGAUGCTT-3′; ITGA7 siRNA-2, forward 5′-GCUGCCCACUCUACAGCUUTT-3′ and reverse 5′-AAGCUGUAGAGUGGGCAGCTT-3′; scrambled siRNA (NC), forward 5′-UUCUCCGAACGUGUCACGUTT-3′ and reverse 5′-ACGUGACACGUUCGGAGAATT-3′.

Real-time quantitative PCR

Total RNA was isolated from cells using TRIZOL reagent (Invitrogen) according to the manufacturer's instructions. The purity of the isolated RNA was measured at 260/280 nm by spectrophotometry (Thermo Fisher Scientific, San Jose, USA). All RNA samples were reverse transcribed into complementary DNA using THUNDERBIRD SYBR qPCR Mix (Toyobo, Osaka, Japan) according to the User Guide's protocol. Then RT-PCR was run and analyzed on a 7500 RT-PCR system (Applied Biosystems, Foster City, USA) according to the manufacturer's recommendations (stage 1: 95°C, 60 s; stage 2: 95°C, 15 s; then 60°C, 45 s, 40 cycles; stage 3: 95°C, 15 s; followed by 60°C, 15 s; then 95°C, 15 s again). The sequences of the primers used are as follows: *ITGA7*, forward 5′-GCTGTGAAGTCCCTGGAAGTGATT-3′ and reverse 5′-GCATCTCGGAGCATCAAGTTCTT-3′; *GAPDH*, forward 5′-GTCTCCTCTGACTTCAACAGCG-3′ and reverse 5′-ACCACCCTGTTGCTGTAGCCAA-3′.

The relative expression of genes was normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) expression and calculated according to the $2^{-\Delta\Delta Cq}$ method described by Livak and Schmittgen [17].

Invasion and migration assays

Cell migration and invasion abilities were measured by transwell assays (Corning, New York, USA). Briefly transfected cells and control cells were first digested with trypsin. Then, cells (migration assay: 3×10^4 cells for TPC1 and 5×10^4 for KTC-1; invasion assay: 6×10^4 cells for TPC1, 8×10^4 cells for KTC-1) were put into the upper chamber with 300 µl RPMI 1640 medium containing 10% FBS. And 600 µl medium containing 20% FBS was filled in the lower chamber. Then the 24-well plate was put into the incubator at 37°C with 5% CO_2. After 24 h, the membrane was fixed with 4% paraformaldehyde for 10 min and stained with 0.4% crystal violet solution for 10 min. Cell migration or invasion ability was evaluated by counting the cells that had migrated or invaded through the membrane. Five random fields of view were selected and images were captured under a microscope (DMi1; Leica, Bannockburn, USA) at a magnification of ×20.

Colony formation assay

For the colony formation assay, the transfected cells were digested and exposed to the indicated treatments. Then TPC1 cells (2×10^3 cells/well) and KTC-1 cells (3×10^3 cells/well) were placed into 6-well plates, maintained in RPMI 1640 containing 10% FBS for 6–8 days, and then fixed by 4% paraformaldehyde and stained with 0.4% crystal violet solution for 15 min at room temperature. These images were captured by the C1si camera (Nikon Instruments Inc., Melville, USA). All assays were performed in triplicate.

Cell proliferation assay

Cell proliferation was evaluated using the cell counting kit-8 (CCK-8; Beyotime, Haimen, China) assay according to the manufacturer's protocol. Briefly, 1000 cells/well for TPC1 and KTC-1 and 2000 cells/well for BCPAP were seeded into 96-well plates and cultured for 24, 48, 72, or 96 h. An aliquot of 10 µl CCK-8 solution was added to each well. After 4 h of incubation at 37°C and 5% CO_2, the absorbance was measured at 450 nm using a spectrophotometer (DS-11 FX; DeNovix, Wilmington, USA). For each group, data from five wells were pooled. All assays were performed in triplicate.

Apoptosis detection analysis

An Annexin V/propidium iodide (PI) apoptosis kit (Nanjing KeyGen Biotech, Nanjing, China) was used to determine the apoptotic rate according to the manufacturer's instruction. The cells were collected, rinsed three times with phosphate-buffered saline, and suspended in 1× binding buffer (Beyotime) at a concentration of 1×10^6 cells/ml. Cell suspensions (300 µl) were stained with 5 µl of Annexin V-fluorescein isothiocyanate (Nanjing KeyGen Biotech, Nanjing, China) and 5 µl of PI at room temperature for 15 min in the dark. Finally, cells were analyzed by flow cytometry on a BD FACS Aria Flow Cytometer (BD Biosciences, Franklin Lakes, USA).

Western blot analysis

The protein of transfected cells lysates was lysed in cell lysis buffer (Beyotime). Protein concentrations were measured using a bicinchoninic acid assay. Total protein lysates were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (Bio-Rad, Berkeley, USA) and electrophoretically transferred to polyvinylidene difluoride membranes (Millipore, Billerica, USA). The membranes were blocked with 5% non-fat milk in Tris-buffered saline supplemented with Tween 20 (TBST) for 2 h at room temperature, and incubated by primary antibodies overnight at 4°C, then washed three times with TBST and probed with the following antibodies: anti-ITGA7 antibody (ab203254; Abcam, Cambridge, USA), anti-N-cadherin antibody (13116; Cell Signaling Technology, Danvers, USA), anti-vimentin antibody (5741; Cell Signaling Technology), anti-E-cadherin antibody (3195; Cell Signaling Technology), and anti-human β-actin antibody (4970; Cell Signaling Technology). After three times wash with TBST, the membranes were then incubated with the horseradish peroxidase-conjugated anti-mouse IgG or anti-rabbit IgG as secondary antibody (Abcam) for 1 h at room temperature. All band intensities were quantified by Image Lab software.

Statistical analysis

All statistical analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, USA); data were presented as the mean ± standard deviation. Differences were considered to be statistically significant at $P < 0.05$. The Student's *t*-test (two-tailed) was used to determine the statistical significance of differences between groups.

Results

ITGA7 is downregulated in PTC

The whole-transcriptome resequencing of 19 paired PTC tissue samples (unpublished data) revealed that ITGA7 was downregulated in tumor tissues. To confirm the results of whole-transcriptome resequencing, we detected the mRNA expression level of *ITGA7* gene in 19 paired PTC patients by RT-qPCR. As shown in Fig. 1A, the expression of ITGA7 in tumor tissues was lower than in adjacent

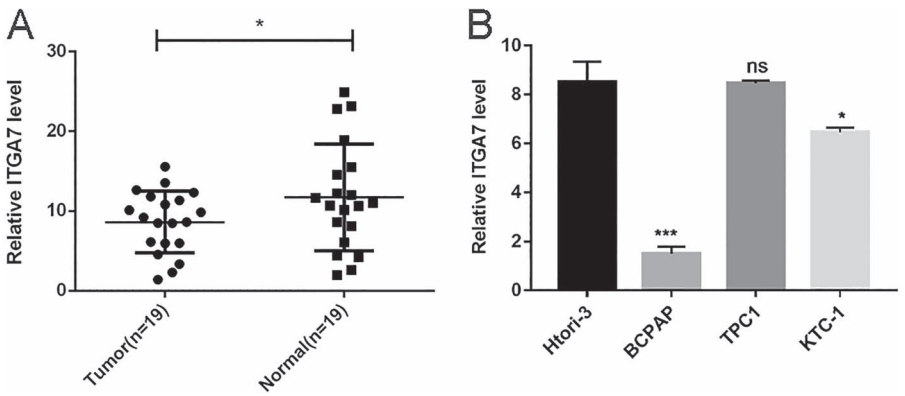

Figure 1. ITGA7 expression in PTC tissues and cell lines (A) The mRNA expression level of *ITGA7* in human PTC tissues compared with that in the paired adjacent normal tissues. (B) The relative mRNA expression levels of *ITGA7* in three PTC cell lines (TPC1, KTC-1, and BCPAP) compared with that in the normal thyroid cell line (Htori-3). $^{*}P < 0.05$, $^{***}P < 0.001$. ns, no significance.

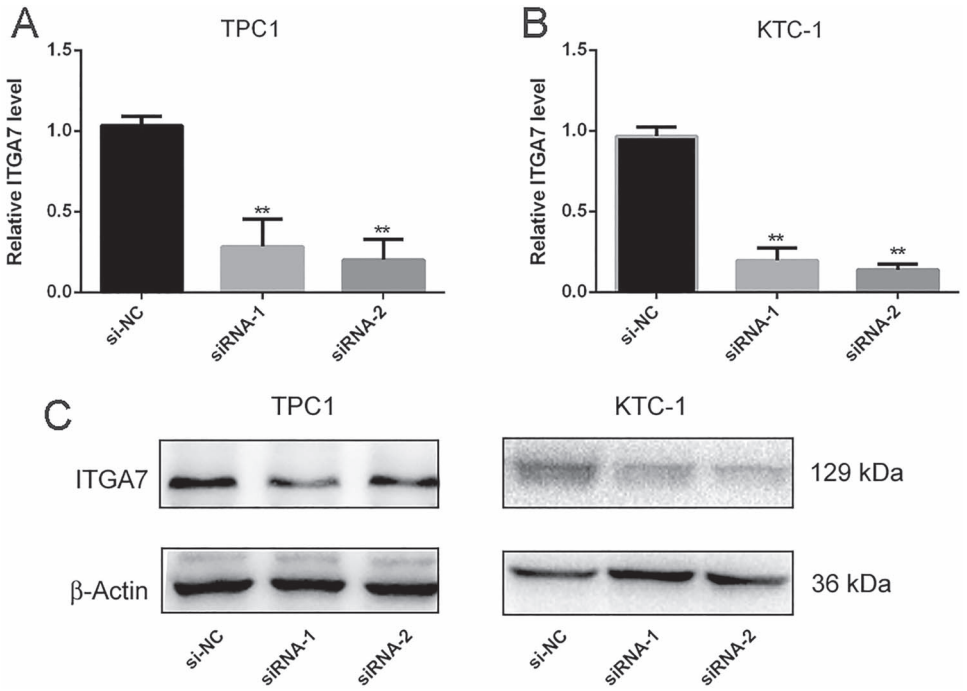

Figure 2. Downregulation of ITGA7 expression by siRNA in PTC cell lines at mRNA level and protein level TPC-1 and KTC-1 cells were transfected with siRNA-1 or siRNA-2 or si-NC. After 48 h, the mRNA and protein levels of ITGA7 were detected by RT-qPCR (A,B) and western blot (C) analysis, respectively. $^{**}P < 0.01$ compared with si-NC.

non-cancerous tissues (T:$N = 8.49$:12.87, $P = 0.0238$), suggesting that ITGA7 was downregulated in PTC tissues. To further validate the relationship between ITGA7 and PTC, we evaluated the expression level of ITGA7 in three PTC cell lines by RT-qPCR (Fig. 1B). The results showed that the expressions of ITGA7 were significantly reduced in PTC cell lines BCPAP and KTC-1. In further experiments we choose TPC1 and KTC-1 cells, which expressed relatively high levels of ITGA7 among the three PTC cell lines, to knock down ITGA7 expression using siRNA. As shown in Fig. 2A–C, both the protein and mRNA levels of ITGA7 were significantly reduced in these two cell lines after transfection with siRNA, when compared with cells transfected with the negative control siRNA. These results suggest that ITGA7 may act as an oncogene involved in PTC tumorigenesis.

ITGA7 regulates proliferation and colony formation of PTC cells

Rapid growth is a major feature of the tumor, so we wonder if ITGA7 could influence the proliferation of PTC cells. Knockdown of ITGA7 resulted in enhanced cell proliferation in TPC1 and KTC-1 cells, as determined by the cell viability assay (Fig. 3A,C). Further, the colony forming assay indicated that downregulated ITGA7 could increase the ability of proliferation in TPC1 and KTC-1 cells (Fig. 3B,D).

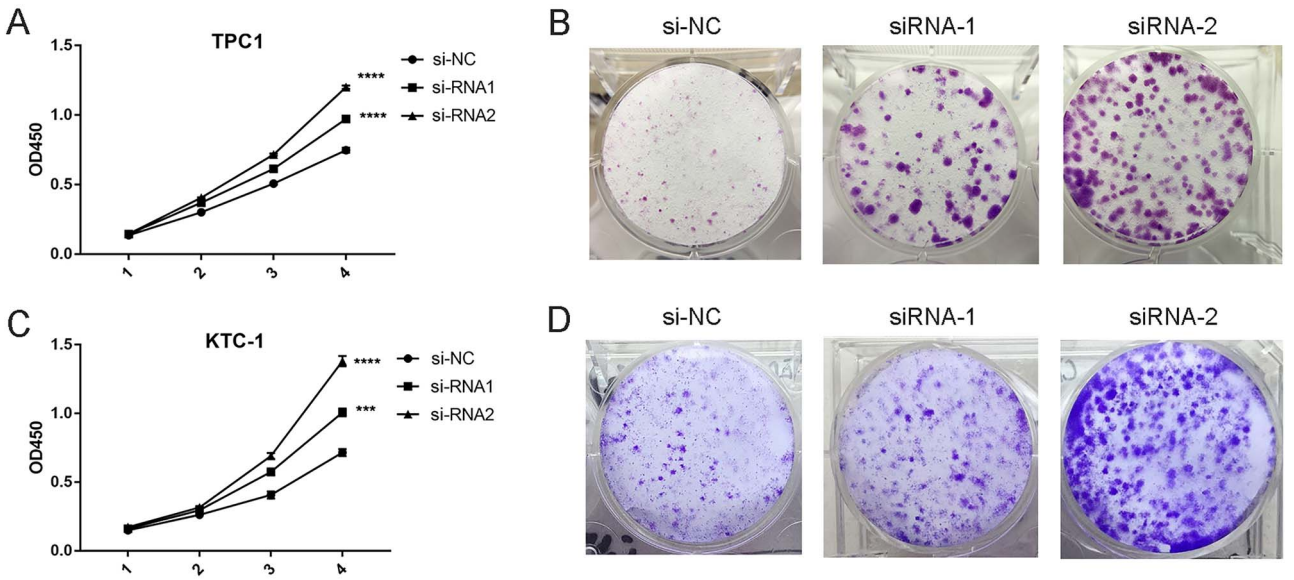

Figure 3. Knockdown of ITGA7 expression induces proliferation and colony formation of PTC cell lines (A,C) Cell viability assay of siRNA-1- or siRNA-2-transfected cells (TPC1 and KTC-1) compared to si-NC-transfected cells. (B,D) Cell colony formation assay of siRNA-1- or siRNA-2-transfected cells and si-NC-transfected cells. The relative quantification of the colony number. *** $P < 0.001$, **** $P < 0.0001$ compared with the si-NC group.

These results showed that downregulated ITGA7 could enhance the proliferation of PTC cells.

ITGA7 regulates migration and invasion of PTC cells

To further explore the relationship between ITGA7 and PTC, we continued to investigate the role of ITGA7 in the migratory and invasive abilities of PTC cells. In the migration assay, TPC1 and KTC-1 cells transfected with siRNA migrated much more than cells tranfected with the negative control siRNA (Fig. 4). It seems that siRNA-2 was more effective than siRNA-1. As shown in Fig. 5, knockdown of ITGA7 could enhance the invasive capacity of TPC1 and KTC-1 cells. These results indicated that ITGA7 may act as a tumor suppressor to influence metastasis in PTC.

Knockdown of ITGA7 decreases apoptotic cell death in PTC cells

The alterations of the decrease of ITGA7 in cancer cells lead to inhibited apoptotic signaling, which induces tumor development and

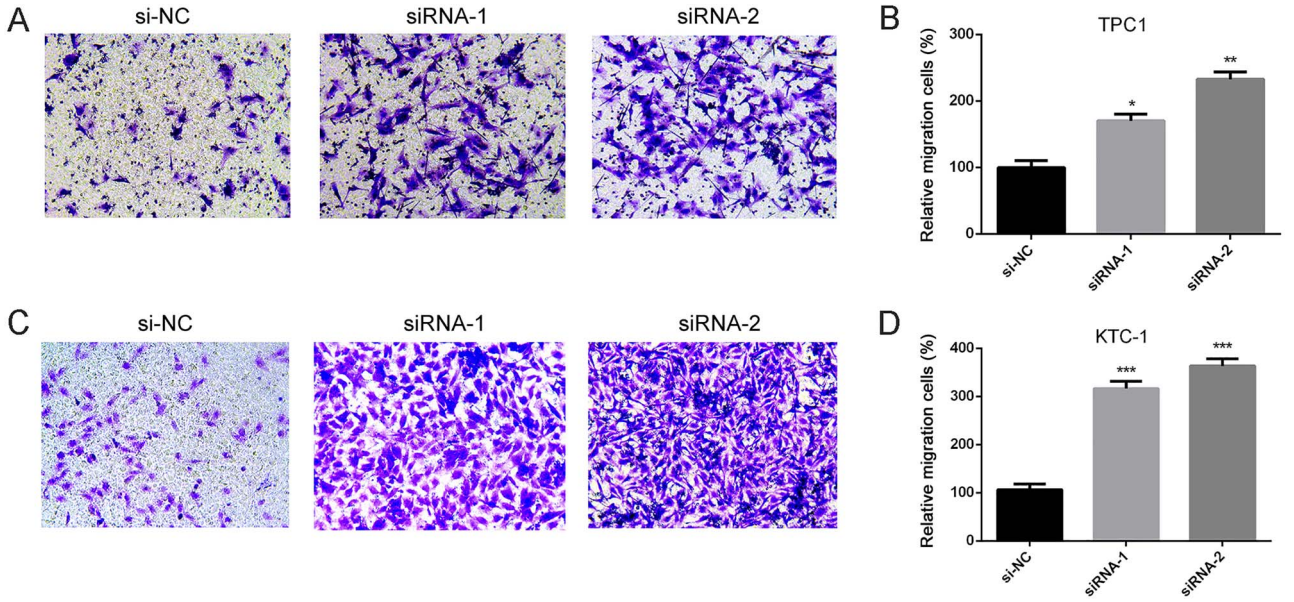

Figure 4. Downregulation of ITGA7 gene expression promotes cell migration of PTC cells (A,C) Cell migration assays in ITGA7-knockdown cells and their corresponding control cells. (B,D) Quantitative results of migration assays. The stained cells were manually counted from five randomly selected fields. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with the si-NC group.

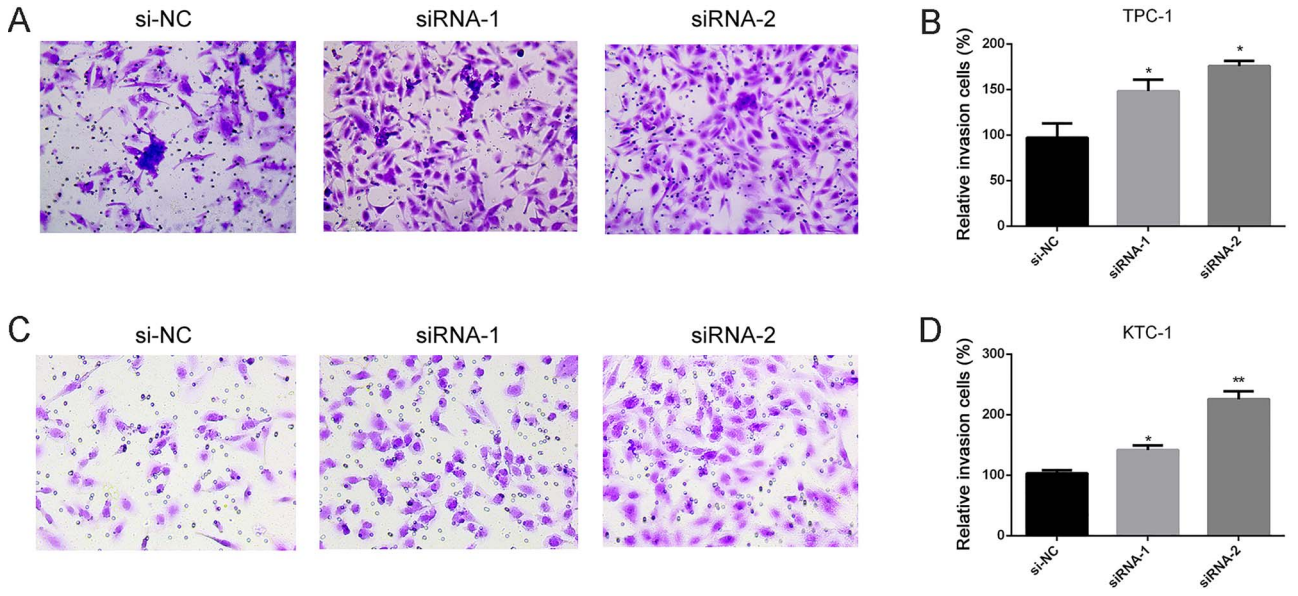

Figure 5. Downregulation of ITGA7 gene expression promotes cell invasion in PTC cells (A,C) Invasion assays in ITGA7-knowdown cells and their corresponding control cells. (B,D) Quantitative results of invasion assays. The stained cells were manually counted from five randomly selected fields. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the si-NC group.

metastasis [18,19]. To explore the underlying molecular mechanisms, the Annexin V/PI assay was used to analyze cells transfected with siRNA compared with the control cells. Our results suggested that knockdown of ITGA7 had a distinct impact on apoptosis in TPC1 and KTC-1 cells (Fig. 6). The portion of apoptosis was considerably reduced after downregulating ITGA7. These data showed that knockdown of ITGA7 could decrease apoptotic cell death in thyroid cancer cell lines.

ITGA7 influences cancer migration and invasion through EMT

Epithelial-to-mesenchymal transition (EMT) is a common morphologic transformation process, which induces tumor cells to leave the primary tumor site and establish metastases [20,21]. To explain the molecular mechanisms of metastases, we tested the protein expression level of epithelial markers and mesenchymal markers in thyroid cell lines. As shown in Fig. 7, knockdown of ITGA7 led to

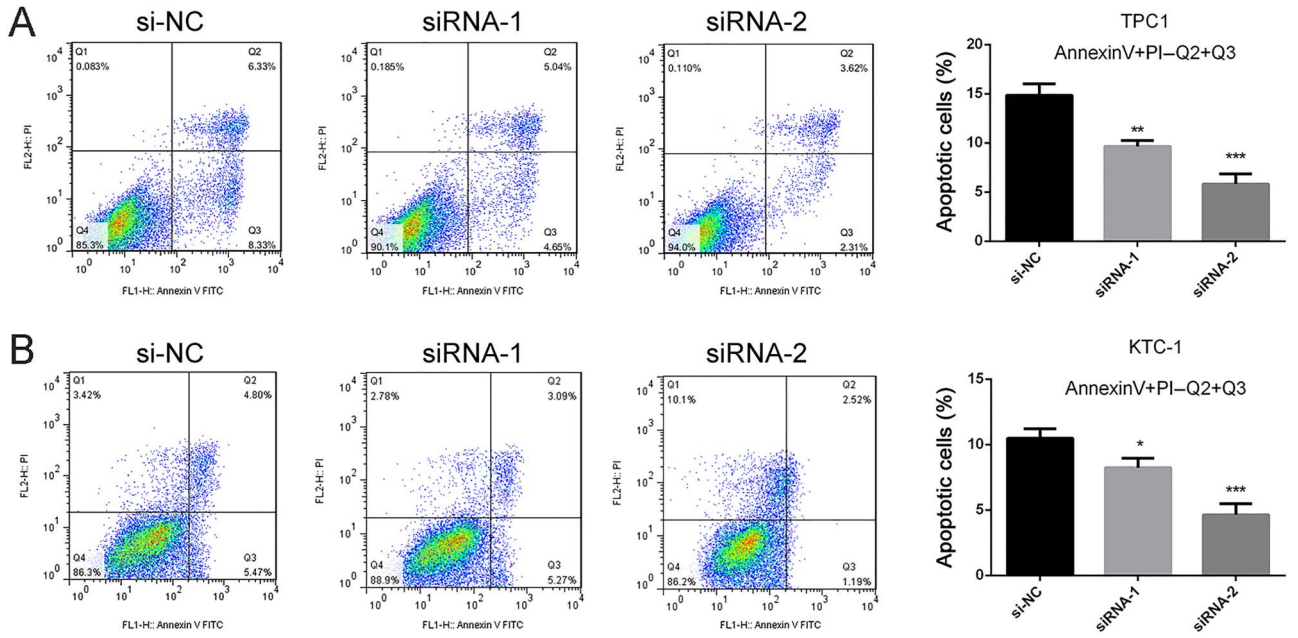

Figure 6. Downregulation of ITGA7 decreases the apoptosis of PTC cells Annexin V/PI assay was applied to analyze the siRNA-1- or siRNA-2-transfected TPC1 (A) cells and KTC-1 cells (B), and compared with the negative control cells (transfection with si-NC). Q2 + Q3 was regarded as a set of standards to measure the cell apoptosis. Downregulation of ITGA7 could significantly decrease apoptosis in thyroid cancer cells. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with the si-NC group.

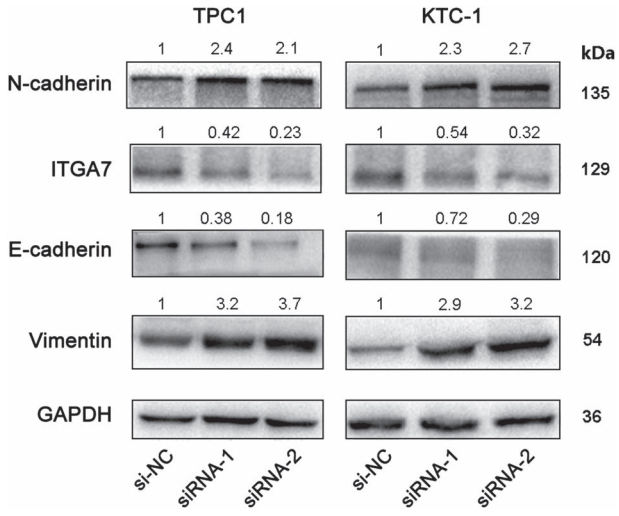

Figure 7. ITGA7 promotes metastasis by activating the EMT signaling pathway The impact of ITGA7 expression on EMT factor in PTC cell lines. The protein expressions of N-cadherin, E-cadherin, and vimentin were detected by western blot analysis. GAPDH was used as a loading control.

significantly lower E-cadherin expression level but higher N-cadherin and vimentin expression levels in PTC cells, suggesting that ITGA7 may regulate migration and invasion by modulating the expressions of E-cadherin, N-cadherin, and vimentin.

Discussion

The number of thyroid cancers is constantly increasing at a rate of 4% per year and some reports indicated that thyroid cancer will become the fourth prevalent cancer diagnosed by 2030 [2,22,23]. Although much progress has been made in medical research, the underlying molecular mechanisms of PTC remain unknown. PTC is highly inclined to lymph node metastasis, with over one-third patients having clinically detectable lymph node involvement on initial presentation [24,25]. Although there is no detectable lymph nodal disease during the preoperative examination, many patients have micrometastatic lymph node disease in postoperative pathological examination [26]. A lot of researchers have put their effort into revealing the molecular mechanisms of thyroid carcinoma pathogenesis, but the oncogenic drivers and epigenetic alterations about this disease are insufficiently known.

With the improvement of economic conditions and living standards, people become more and more concerned about their health. With the popularization of physical examination and deeper recognition of the thyroid carcinoma, the occurrence of thyroid cancer tends to increase in recent years. The technology of fine-needle aspiration cytology (FNAC) is the most reliable process to biopsy thyroid nodules, but 10%–40% of samples' results were still indeterminate. [27,28]. Meanwhile, the thyroid microcarcinoma still has a high risk of false negatives on diagnosis by sole FNAC [28,29]. With the development and application of genomics technologies, detecting puncture specimen at gene level can help improve the accuracy of diagnosis [30,31]. To find the biomarkers that can distinguish between malignant tumors and benign nodules is needed.

As we all known, *BRAF* V600E is the most common oncogenic mutation in thyroid cancer [32], which is highly specific for PTC. The test of *BRAF* V600E mutation can effectively increase the diagnostic accuracy of FNAC [33,34]. It is almost 100% specific for PTC that makes it a potentially accurate marker for the diagnosis of the indeterminate thyroid in histology by FNAC [33,35,36].

Previously, we detected 19 pairs of PTC tumors and adjacent normal tissues by whole-transcriptome resequencing, and the results showed that the ITGA7 expression was downregulated in thyroid tumor tissues than in adjacent normal thyroid tissues. Some studies have demonstrated that ITGA7 gene was associated with malignant melanoma, prostate and liver carcinomas, and glioblastoma [12].

In this study, we detected the expression of ITGA7 in 19 matched thyroid tumor tissues and adjacent normal tissues. The results validated that ITGA7 was significantly downregulated in PTC tissues compared with that in adjacent normal tissue in 19 PTC patients. ITGA7 is famous for its influence on the metastasis ability of tumor cells [12,14,16]. However, the function of ITGA7 in PTC is still not clear. Here, we examined the expression of ITGA7 in three PTC cell lines (TPC1, KTC-1, and BCPAP). ITGA7 downregulation was found to lead to the rise of the ability of cell migration and cell invasion, which is consistent with the notion that ITGA7 is a tumor suppressor in thyroid cancer. Previous studies showed that dysregulation of the apoptotic pathways could enhance tumorigenesis [37]. Our Annexin V/PI assay results indicated that knockdown of ITGA7 resulted in decreased apoptotic cell death in thyroid cancer cells.

EMT was first found by Greenberg and Hay and it may play a fundamental role in the initial step of invasion and metastasis of cancer cells [38]. EMT has been increasingly recognized to play pivotal roles in promoting tumor process [39,40]. Shen *et al.* [41] found that paclitaxel could upregulate miR-375 and overexpressed miR-375 could induce EMT process via directly targeting E-cadherin in cervical cancer. The ectopic SCUBE2 expression could inhibit cell migration and invasion through the reversal of EMT in breast cancer [42]. High expression of ITGA7 has been proved to correlate with worse outcome in glioblastoma and ITGA7 has been proposed as a downstream target of FOXC1 in the regulation of colorectal cancer metastasis [43,44]. ITGA7 has also been reported as a potential cancer stem cell marker in oesophageal squamous cell carcinoma. $ITGA7^+$ cells were found to have enhanced migration and invasion abilities, which may be induced by EMT, and ITGA7 can activate FAK and enhance the phosphorylation of FAK to drive the cancer stem cell features. Meanwhile, $ITGA7^+$ cells inhibit apoptosis via the FAK/PI3K/Akt signaling pathway.

In our research, we found that when ITGA7 was downregulated, the protein levels of N-cadherin and vimentin were increased, whereas that of E-cadherin was decreased, which is consistent with the result that knockdown of ITGA7 promoted the metastasis of PTC cells. The function of ITGA7 in PTC seems to be different from its function in other cancers. It should be noted that there are still some limitations in our study. On one hand, although we found that EMT was involved in the effect of ITGA7, the exact underlying mechanisms of ITGA7 in regulating the proliferation and apoptosis of thyroid cancer cells are yet to be determined by further experiments. On the other hand, because of the limited number of samples available for this study, a larger sample size is needed to confirm the results of this study and more detailed mechanisms would be worthy to explore.

In summary, we found that ITGA7 is one of the downregulated genes in PTC. Its dysregulation can induce proliferation, migration, and invasion in PTC through EMT. The results of this study may provide a target for gene therapy in the treatment of PTC.

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