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ORIGINAL RESEARCH

Knockdown of IQGAP1 inhibits proliferation and epithelial–mesenchymal transition by Wnt/β-catenin pathway in thyroid cancer

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Background: Thyroid cancer is the most common endocrine malignant disease with a high incidence rate. The expression of IQGAP1 is upregulated in various cancers, including thyroid cancer. However, the role and underlying mechanism of IQGAP1 in thyroid cancer are still not clear.

Materials and methods: The expression of IQGAP1 in thyroid cancer tissues and cells was determined by reverse transcription polymerase chain reaction and Western blot analysis. Cells were transfected with different siRNAs using Lipofectamine 2000 or were treated with various concentrations of XAV939. The effects of IQGAP1 knockdown on proliferation and epithelial–mesenchymal transition (EMT) of thyroid cancer cells were determined by MTT assay and Western blot analysis. Animal experiments were performed to investigate the effects of IQGAP1 knockdown on the growth of tumors in vivo.

Results: High IQGAP1 expression is found in thyroid cancer tissues and cells. Knockdown of IQGAP1 had inhibitory effects on cell proliferation and EMT, as well as on the Wnt/β-catenin pathway. Additionally, inactivation of the Wnt/β-catenin pathway by XAV939 or si-β-catenin suppressed cell proliferation and EMT. Furthermore, suppression of the Wnt/β-catenin pathway reversed the positive effects of pcDNA-IQGAP1 on cell proliferation and EMT in vitro. Moreover, downregulation of IQGAP1 suppressed tumor growth and EMT in SW579 tumor xenografts through the Wnt/β-catenin pathway in vivo.

Conclusion: Our study demonstrated that knockdown of IQGAP1 inhibited cell proliferation and EMT through blocking the Wnt/β-catenin pathway in thyroid cancer.

Keywords: IQGAP1, thyroid cancer, proliferation, epithelial–mesenchymal transition, Wnt/β-catenin

Introduction

Thyroid cancers are tumors of the thyroid gland relevant to the endocrine system, ~90% of which are differentiated thyroid cancers, including papillary thyroid cancer (PTC) and follicular thyroid cancer, and the incidence of which is currently on the rise.[1] Thyroid cancers are usually induced by radiation exposure to form a nodule in the anterior region of the neck.[2] Thyroid cancer prognosis is closely related to the progression of local primary tumors to late stage, finally spreading to various organs.[3] Thus, the molecular mechanism of the epithelial–mesenchymal transition (EMT) phenomenon in thyroid carcinoma still needs to be clarified.

EMT occurs in pre-metastatic cancer cells and was first confirmed as a feature of embryogenesis and has also been found in the healing of wound, fibrosis of organ and the occurrence of metastasis.[4] EMT is considered to play a vital role in the initial

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stage of metastatic progression in most carcinomas.[5] During EMT process, epithelial cells separate from the strong structural constraints and change their morphology from pebble shape to fusiform fibroblast-like shape of mesenchymal cells, thereby losing epithelial differentiation capacity and enhancing the migration and invasion ability.[6,7] Moreover, the expressions of the EMT markers N-cadherin, E-cadherin and Vimentin were altered accompanying with the change in the cell phenotype.[8]

IQGAPs are evolutionary conserved multi-domain scaffold proteins, including IQGAP1, IQGAP2 and IQGAP3.[9] Among these, IQGAP1 has been proved to widely exist in human tissues and participate in many cellular processes, such as cell attachment, cell migration, extracellular signaling and division of cytoplasm.[10–12] Previous studies indicated that IQGAP1 promoted cell proliferation through interacting with the MAP kinase and PI3K/Akt pathways in thyroid cancer cells.[13,14] Moreover, IQGAP1 amplification was found to be associated with invasiveness of thyroid cancer cells, and coexistence of IQGAP1 copy-number gain and BRAF V600E mutation was particularly associated with a high tumor recurrence rate of 60% in PTC.[14]

A recent study showed that downregulation of IQGAP1 in thyroid cancer cells repressed cell proliferation and invasion.[15] Another study has indicated that constitutive activation of WNT/β-catenin pathway is often found in human cancers, and the WNT/β-catenin pathway is involved in cell growth, proliferation and stem cell differentiation.[16] Furthermore, it was also reported that the expression level of β-catenin was upregulated in anaplastic thyroid cancer compared with differentiated thyroid cancer.[17] Therefore, we speculated that the WNT/β-catenin pathway might have a vital role in thyroid cancer.

Here, we detected the expression level of IQGAP1 in thyroid cancer tissues and cells and performed loss-of-function study to clarify the role and underlying mechanism of IQGAP1 in cell proliferation and EMT of human thyroid cancer cells. Moreover, we observed the effects of knockdown of IQGAP1 on the growth of tumor in vivo.

Materials and methods

Tissue acquisition

This study was performed with the approval of the ethics committee of Huaihe Hospital of Henan University, and informed consent was obtained from all patients with PTC whose tissue specimens were used in this study. None of the patients included suffered from other concurrent malignancies or anaplastic or other poorly differentiated follicular carcinomas of the thyroid or underwent any treatment prior to surgery. Fresh-frozen biopsy tumor tissues (n=35) and adjacent normal tissues (n=35) were obtained from patients with PTC undergoing surgical resection at Huaihe Hospital of Henan University. The samples were stored at −70°C for further experiments.

Cell culture and transfection

Human thyroid squamous cell carcinoma cell line SW579, human PTC cell line TPC-1 and human thyroid cell line Nthy-ori 3-1 were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). The cells were incubated in Roswell Park Memorial Institute (RPMI) 1640 medium (Invitrogen, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, Carlsbad, CA, USA) in an incubator with 5% CO_2 at 37°C. After 24 h, the cells were transfected with si-IQGAP1-1, si-IQGAP1-2, si-β-catenin-1, si-β-catenin-2, pcDNA-IQGAP1, pcDNA-IQGAP1 + si-β-catenin-1 and si-control using Lipofectamine 2000 (Invitrogen) in accordance with the manufacturer's instructions. All the siRNA sequences are listed as follows: si-IQGAP1-1, 5′-UGCCAUGGAUGAGAUUGGA-3′; si-IQGAP1-2, 5′-UUAUCGCCCAGAAACAUCUU GUUGG-3′; si-β-catenin-1, 5′-GAATGCCGTTCGC CTTCATTA-3′; si-β-catenin-2, 5′-CACCTCCCAAGT CCTTTAT-3′ and si-control, 5′-UUCUCCGAACGUGU CACGU-3′.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA from tissues and cells was extracted by TRIzol reagent (Life Technologies, Gaithersburg, MD, USA) according to the manufacturer's instructions. The reverse transcription reaction was performed using the ABI7500 system (Applied Biosystems, Foster City, CA, USA) and QuantiTect SYBR Green PCR Master Mix (Qiagen, Valencia, CA, USA) following manufacturer's instructions. All samples were normalized to β-actin according to the $2^{-\Delta\Delta C_t}$ method.

Western blot analysis

The extracted total proteins from tissues and cells were quantified by Pierce BCA Protein Assay Kit (Amersham, Little Chalfont, UK). The protein specimens were then isolated by a 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes (EMD Millipore, Billerica, MA, USA). After blocking in Tris-buffered saline, 0.1% Tween 20 (TBST) buffer with 5% bovine serum albumin (BSA, Sigma-Aldrich,

St Louis, MO, USA) for 2 h at room temperature, the membranes were incubated with primary antibodies overnight at 4°C. Following washing twice in TBST, the membranes were further incubated with secondary antibody labeled with HRP for 1 h at 37°C. The antibodies used in this study were as follows: anti-IQGAP1 (1;1,000; Abcam, Cambridge, MA, USA), E-cadherin (1;1,000; GeneTex, San Antonio, TX, USA), N-cadherin (1;1,000; Abcam), Vimentin (1;1,000; Sigma-Aldrich, St Louis, MO, USA), Twist1 (1:1,000; Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA), β-catenin (1:10,000; CST, Inc., Danvers, MA, USA), c-myc (1:10,000; CST, Inc.), cyclin D1 (1:10,000; Abcam) and secondary antibody peroxidase-conjugated anti-IgG (1:5,000; Abcam). The signals and intensities of the proteins of interest were determined by a chemiluminescent detection system (Pierce ECL Substrate Western blot detection system; Thermo Fisher Scientific, Pittsburgh, PA, USA) and Quantity One 4.5.0 software (Bio-Rad Laboratories Inc., Hercules, CA, USA). All experiments were repeated three times.

MTT assay

Cells were plated in 96-well plates (Corning Costar, Corning, NY, USA) at 2×10^3 cells/well in 200 µL of RPMI 1640 medium and incubated for 24 h. At 48 h after transfection, 10 µL of MTT solution (Sigma-Aldrich) was added to the plated cells, and incubation was continued for a further 4 h at 37°C. After dissolving intracellular formazan crystals by the addition of 100 µL of dimethyl sulfoxide (DMSO; Sigma-Aldrich) to each well, the absorbance at 490 nm was measured using an Emax precision microplate reader (Molecular Devices, Sunnyvale, CA, USA).

Xenograft tumor nude mice model

All animal experiments were approved by the Ministry of Science and Technology of China and the committee on experimental animals of Huaihe Hospital of Henan University. The animal procedures were followed to the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and the guidelines of the Animal Welfare Act. Female athymic BALB/c nu/nu mice (4–5 weeks old, 15–20 g) were purchased from Shanghai Experimental Animal Center (Shanghai, China). All mice were housed in a pathogen-free barrier facility with access to food and water. Xenografts were established by subcutaneous injection of 5×10^6 SW579 cells in a volume of 100 µL into the right hind leg of mice. When the tumor volume reached the required size (50–100 mm^3), mice were randomly divided into the following groups (n=5): si-control and si-IQGAP1-2 (5 µg siRNA daily for 21 days by intratumoral injection). si-control and si-IQGAP1-2 were mixed with polyethylenimine (PEI; Sigma-Aldrich) in accordance with the manufacturer's instructions. Tumor size was measured with calipers once every 3 days, and volume was calculated using the formula $V=0.5236$ ($l\times w\times h$), where l, w and h represent length, width, and height. All mice were euthanized at day 21 following the treatment, and the tumors were removed for tumor weight measurement and Western blot analysis.

Statistical analysis

All data were presented as mean ± standard deviation. The statistical significance of difference between groups was determined by Student's two-tailed t-test, and one-way analysis of variance (ANOVA) was used to compare three or more groups using SAS 9.2 software (SAS Institute, Inc., Cary, NC, USA). $P<0.05$ was considered significant. Experiments were repeated at least three times.

Results

IQGAP1 was overexpressed in thyroid cancer tissues and cell lines

To explore the effects of IQGAP1 on thyroid cancer, we first detected the expression levels of IQGAP1 mRNA and protein in the tumor tissues and adjacent normal tissues from 35 thyroid cancer patients as well as in normal thyroid cell Nthy-ori 3-1 and thyroid cancer cell lines SW579 and TPC-1 by qRT-PCR and Western blot analysis, respectively. The data presented that the expression levels of both IQGAP1 mRNA and protein in the tumor tissues were significantly increased in comparison with the normal tissues (Figure 1A and B). Moreover, the mRNA and protein levels of IQGAP1 in both thyroid cancer cell lines were drastically higher than that in the normal thyroid cell (Figure 1C and D). Taken together, these results indicated that IQGAP1 upregulation may take part in the progression of thyroid cancer.

Knockdown of IQGAP1 inhibited cell proliferation and EMT of thyroid cancer cells

To investigate whether knockdown of IQGAP1 could affect cell proliferation and EMT of thyroid cancer cells, we first transfected si-IQGAP1-1 or si-IQGAP1-2 into SW579 and TPC-1 cells. The results of qRT-PCR and Western blot analysis showed that IQGAP1 mRNA (Figure 2A) and protein (Figure 2B) expressions were dramatically downregulated by the siRNAs transfection in both SW579 and TPC-1 cells, suggesting an effective IQGAP1 knockdown. MTT assay

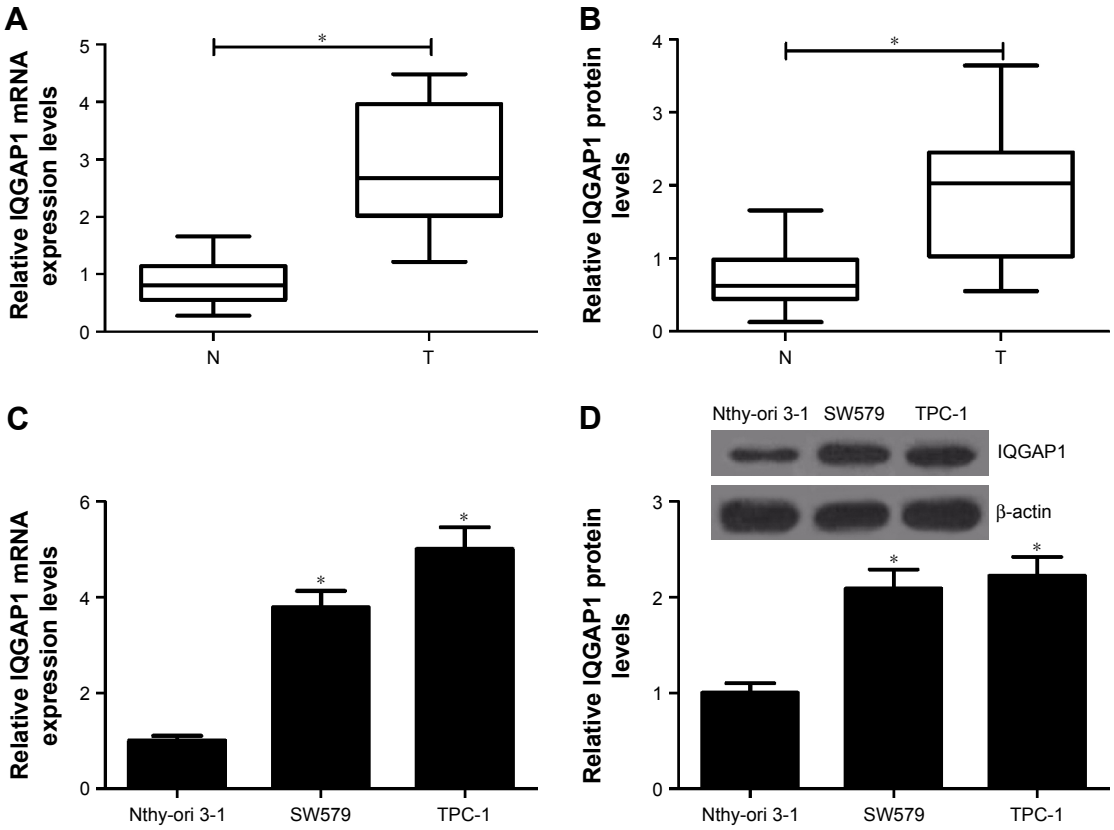

Figure 1 mRNA and protein levels of IQGAP1 expression are significantly upregulated in thyroid cancer tissues (n=35) and thyroid cancer cell lines.
Notes: (**A**) qRT-PCR analysis of IQGAP1 mRNA level in thyroid cancer tissues. (**B**) Western blot analysis of IQGAP1 protein in thyroid cancer tissues. (**C**) qRT-PCR analysis of IQGAP1 mRNA level in SW579 and TPC-1 cells. (**D**) Western blot analysis of IQGAP1 protein level in SW579 and TPC-1 cells. *$P<0.05$.
Abbreviations: qRT-PCR, quantitative real-time polymerase chain reaction; N, normal; T, tumor.

revealed that knockdown of IQGAP1 significantly repressed cell viability of both cell lines (Figure 2C). In addition, Western blot analysis was performed to detect the expression levels of EMT-related proteins in both cell lines transfected with si-IQGAP1-1 and si-IQGAP1-2, respectively. The data showed that compared with the control group, si-IQGAP1-1 and si-IQGAP1-2 treatments significantly elevated the epithelial marker E-cadherin and decreased the mesenchymal markers (N-cadherin and Vimentin) and EMT-related protein Twist in both cell lines (Figure 2D and E). Overall, these results implied that IQGAP1 downregulation impeded proliferation and EMT in thyroid cancer cells.

Knockdown of IQGAP1 suppressed WNT/β-catenin pathway in thyroid cancer cells

To explore the potential mechanism of IQGAP1 in thyroid cancer cells, β-catenin and target genes (c-myc and cyclin D1) expression in the Wnt/β-catenin pathway were detected by Western blot analysis in both cell lines transfected with si-IQGAP1-1 and si-IQGAP1-2, respectively. The data showed that knockdown of IQGAP significantly decreased levels of these genes in SW579 (Figure 3A and B) and TPC-1 cells (Figure 3C and D), demonstrating that depletion of IQGAP1 repressed the Wnt/β-catenin pathway in thyroid cancer cells.

Inactivation of the Wnt/β-catenin pathway restrained EMT and proliferation in thyroid cancer cells

To further explore if the inactivity of the Wnt/β-catenin pathway repressed cell proliferation and EMT, SW579 cells were treated with different concentrations of Wnt/β-catenin signaling inhibitor XAV939 (5, 10 and 20 μM), and TPC-1 cells were transfected with si-β-catenin-1 or si-β-catenin-2. Western blot analysis showed that XAV939 significantly inhibited expressions of β-catenin and target genes (c-myc and cyclin D1) of Wnt/β-catenin pathway in SW579 cells in a dose-dependent manner (Figure 4A and B). Moreover, XAV939 significantly repressed expressions of N-cadherin, Vimentin and Twist, while promoted E-cadherin expression in SW579 cells in a dose-dependent

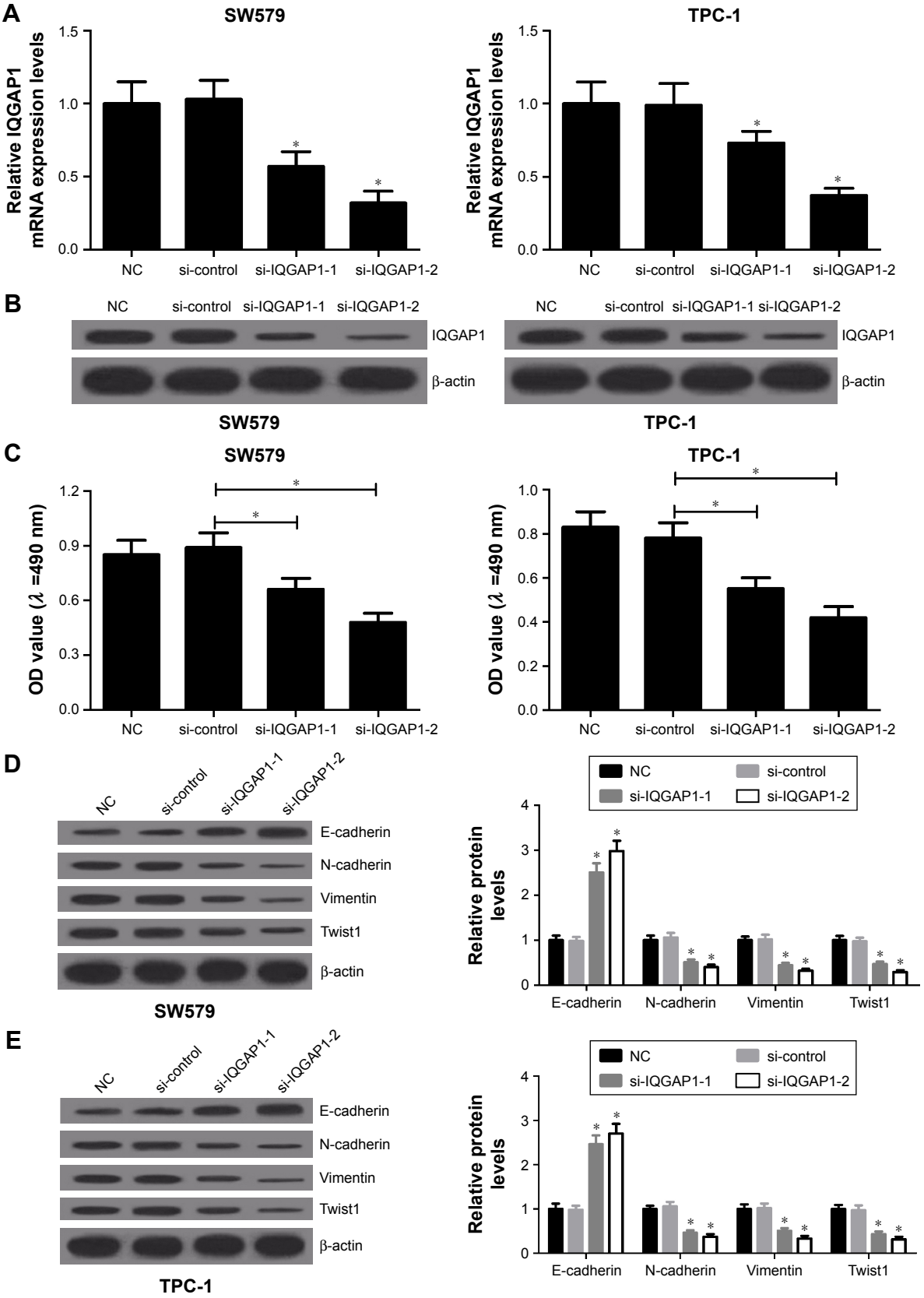

Figure 2 Knockdown of IQGAP1 inhibited proliferation and EMT of thyroid cancer cells.

Notes: SW579 and TPC-1 cells transfected with si-control, si-IQGAP1-1 or si-IQGAP1-2 were cultured for 48 h. (**A**) qRT-PCR analysis of IQGAP1 mRNA level in transfected cells. (**B**) Western blot analysis of IQGAP1 protein in transfected cells. (**C**) MTT assay was performed to detect viability in transfected cells. (**D** and **E**) Western blot analysis of E-cadherin, N-cadherin, Vimentin and Twist in transfected cells. *$P<0.05$.

Abbreviations: EMT, epithelial–mesenchymal transition; qRT-PCR, quantitative real-time polymerase chain reaction; OD, optical density.

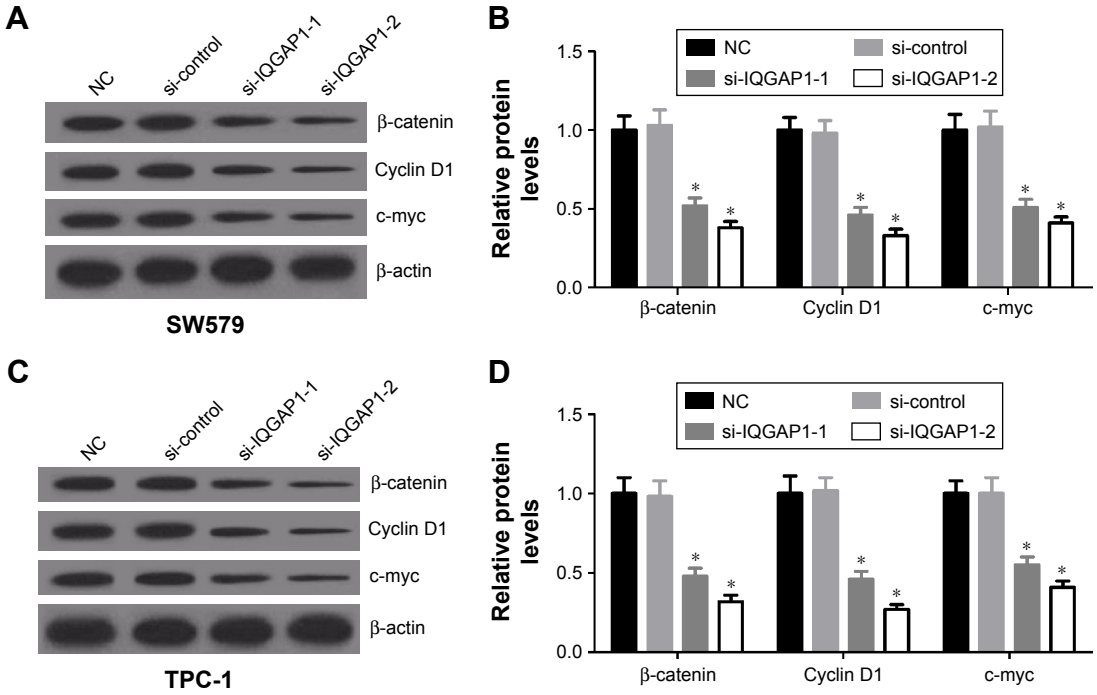

Figure 3 Knockdown of IQGAP1 suppressed activation of the Wnt/β-catenin pathway in thyroid cancer cells.
Notes: (**A** and **B**) Western blot analysis was used to detect β-catenin, cyclin D1 and c-myc in SW579 cells transfected with si-IQGAP1-1 or si-IQGAP1-2 at 48 h. (**C** and **D**) Western blot analysis was used to determine β-catenin, cyclin D1 and c-myc in TPC-1 cells transfected with si-IQGAP1-1 or si-IQGAP1-2 at 48 h. *$P<0.05$.
Abbreviation: NC, negative control.

manner (Figure 4C and D). Interestingly, si-β-catenin-1 and si-β-catenin-2 exerted similar effect on expressions of β-catenin, target genes of Wnt/β-catenin pathway and EMT-related proteins (Figure 4E–H). MTT assay revealed that XAV939 inhibited cell proliferation of SW579 cells in a concentration-dependent manner (Figure 4I), and siRNA-mediated knockdown of β-catenin repressed cell viability of TPC-1 cells (Figure 4J). Together, these results suggested

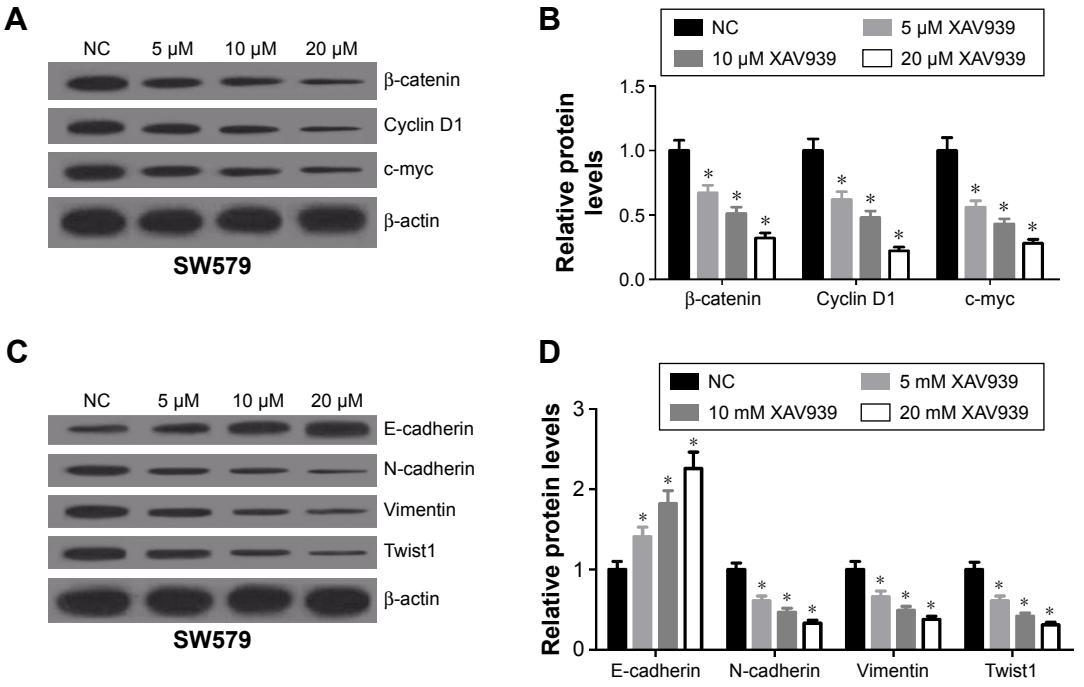

Figure 4 (*Continued*)

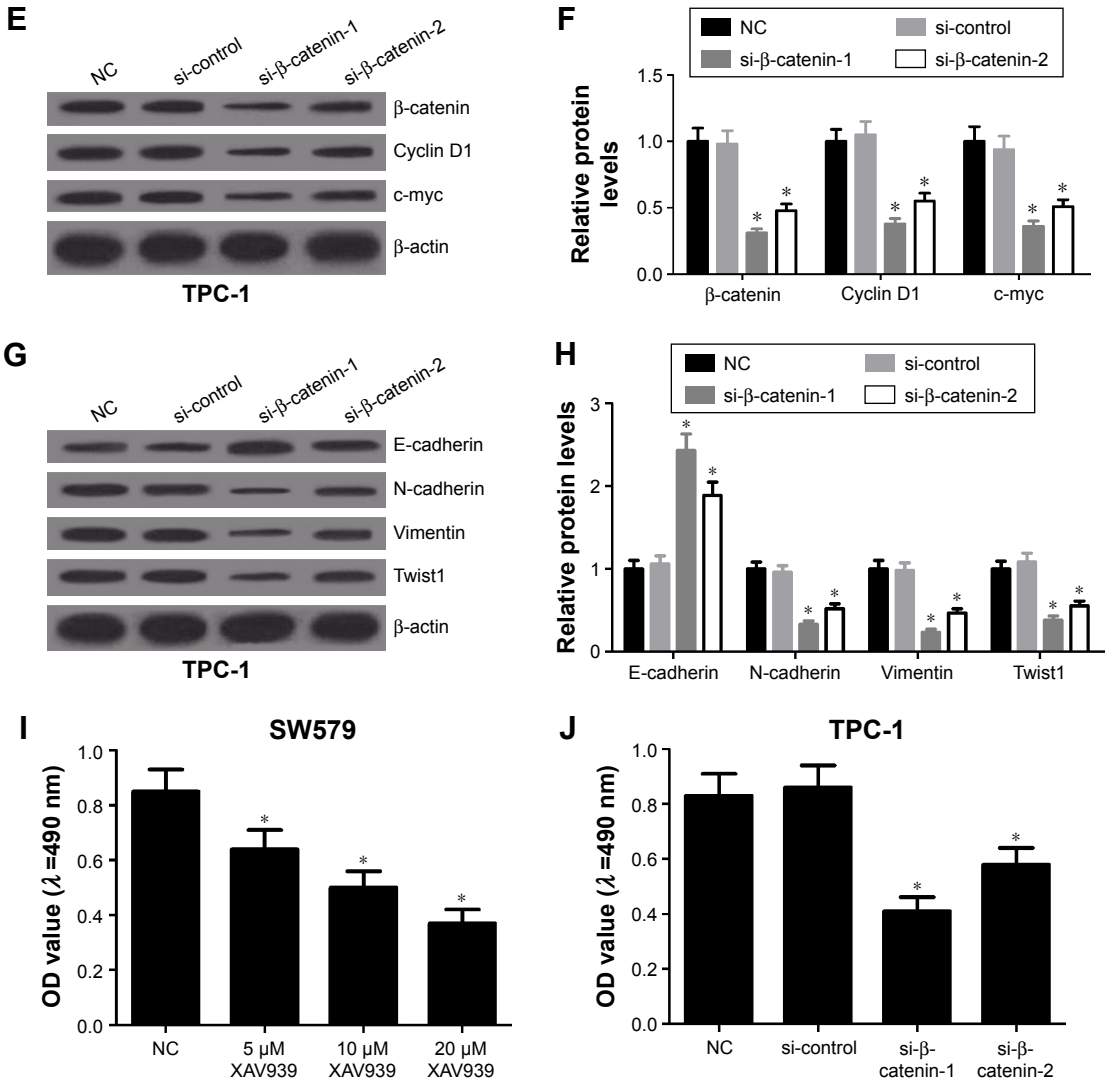

Figure 4 Inactivation of the Wnt/β-catenin pathway suppressed cell proliferation and EMT in thyroid cancer cells.
Notes: SW579 cells were treated with different concentrations of Wnt/β-catenin signaling inhibitor XAV939 (5, 10 and 20 μM), and TPC-1 cells were transfected with si-β-catenin-1 or si-β-catenin-2. (**A** and **B**) Western blot analysis of β-catenin, cyclin D1 and c-myc in SW579 cells at 48 h. (**C** and **D**) Western blot analysis of E-cadherin, N-cadherin, Vimentin and Twist in SW579 cells at 48 h. (**E** and **F**) Western blot analysis was performed to test the expression of β-catenin, cyclin D1 and c-myc in TPC-1 cells at 48 h. (**G** and **H**) Western blot analysis was applied to determine the level of E-cadherin, N-cadherin, Vimentin and Twist in TPC-1 cells at 48 h. (**I**) MTT assay was applied to examine the viability of SW579 cells at 48 h. (**J**) MTT assay was carried out to measure the viability of TPC-1 cells at 48 h. *$P<0.05$.
Abbreviations: EMT, epithelial–mesenchymal transition; OD, optical density; NC, negative control.

that blocking the Wnt/β-catenin pathway inhibited EMT and proliferation in thyroid cancer cells.

Inactivation of the Wnt/β-catenin pathway reversed the effects of IQGAP1 overexpression on EMT and proliferation in thyroid cancer cells

To further testify if IQGAP1 affects cell proliferation and EMT of SW579 and TPC-1 cells via the Wnt/β-catenin pathway, the cells were treated with pcDNA-control, pcDNA-IQGAP1, pcDNA-IQGAP1 + XAV939 or pcDNA-IQGAP1 + si-β-catenin-1 for Western blot analysis and MTT assay. The data presented that SW579 cells transfected with pcDNA-IQGAP1 had a significant increase in N-cadherin, Vimentin and Twist level and a significant decrease in E-cadherin expression, whereas XAV939 reversed the effects of pcDNA-IQGAP1 on expressions of EMT-associated proteins (Figure 5A and B). Moreover, IQGAP1 overexpression promoted cell proliferation of SW579 cells, while XAV939 weakened the positive effect of IQGAP1 overexpression on cell viability (Figure 5C). Similarly, si-β-catenin-1 notably relaxed the effects of IQGAP1 upregulation on EMT-associated proteins and cell viability of TPC-1 cells (Figure 5D–F). These results revealed that IQGAP1 regulated EMT and proliferation of thyroid cancer cells through the Wnt/β-catenin pathway.

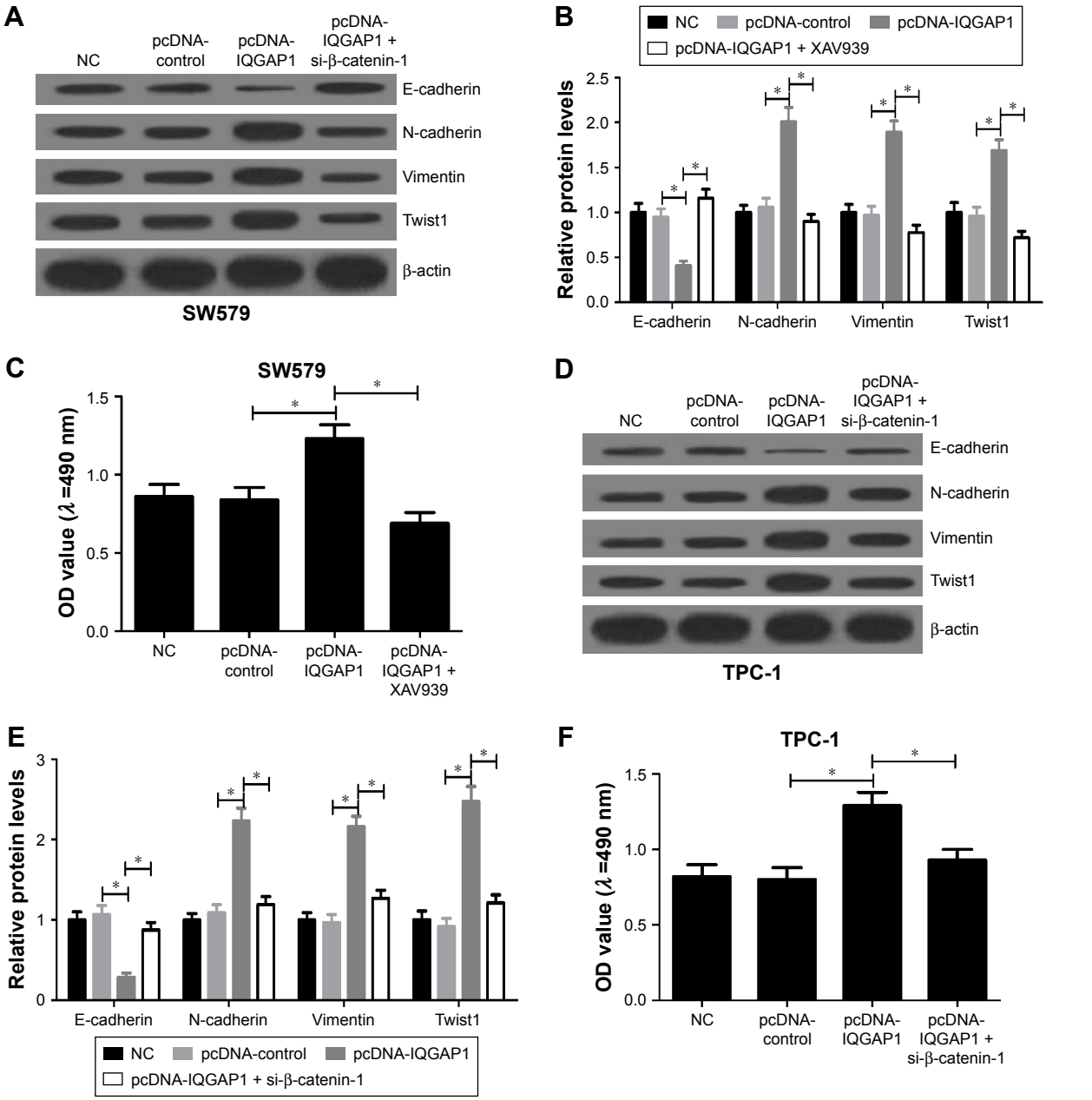

Figure 5 Inactivation of the Wnt/β-catenin pathway reversed the effects of IQGAP1 overexpression on thyroid cancer cells.
Notes: (**A** and **B**) Effects of combination of pcDNA-IQGAP1 and XAV939 on E-cadherin, N-cadherin, Vimentin and Twist in SW579 cells. (**C**) MTT assay was used to detect the effects of combination of pcDNA-IQGAP1 and XAV939 on proliferation in SW579 cells. (**D** and **E**) Effects of co-transfection with pcDNA-IQGAP1 and XAV939 on E-cadherin, N-cadherin, Vimentin and Twist in TCP-1 cells. (**F**) MTT assay was used to measure the effects of co-transfection with pcDNA-IQGAP1 and XAV939 on proliferation in TPC-1 cells. *$P<0.05$.
Abbreviations: OD, optical density; NC, negative control.

Knockdown of IQGAP1 suppressed the growth of SW579 tumor xenografts

We further explored the effects of knockdown of IQGAP1 on SW579 tumor xenografts in vivo. The data showed that si-IQGAP1-2 treatment (once daily) had a prominent inhibition on tumor growth compared with the control group (Figure 6A). Up to 21 days after the first si-IQGAP1-2 treatment, the mice were euthanized and weight measurement of SW579 tumor xenografts was also performed. As shown in Figure 6B, inhibition of IQGAP1 significantly reduced tumor weight. In addition, expressions of β-catenin and target genes (c-myc and cyclin D1) of the Wnt/β-catenin pathway and EMT-associated proteins in the excised SW579 xenograft were detected. The data presented that compared with

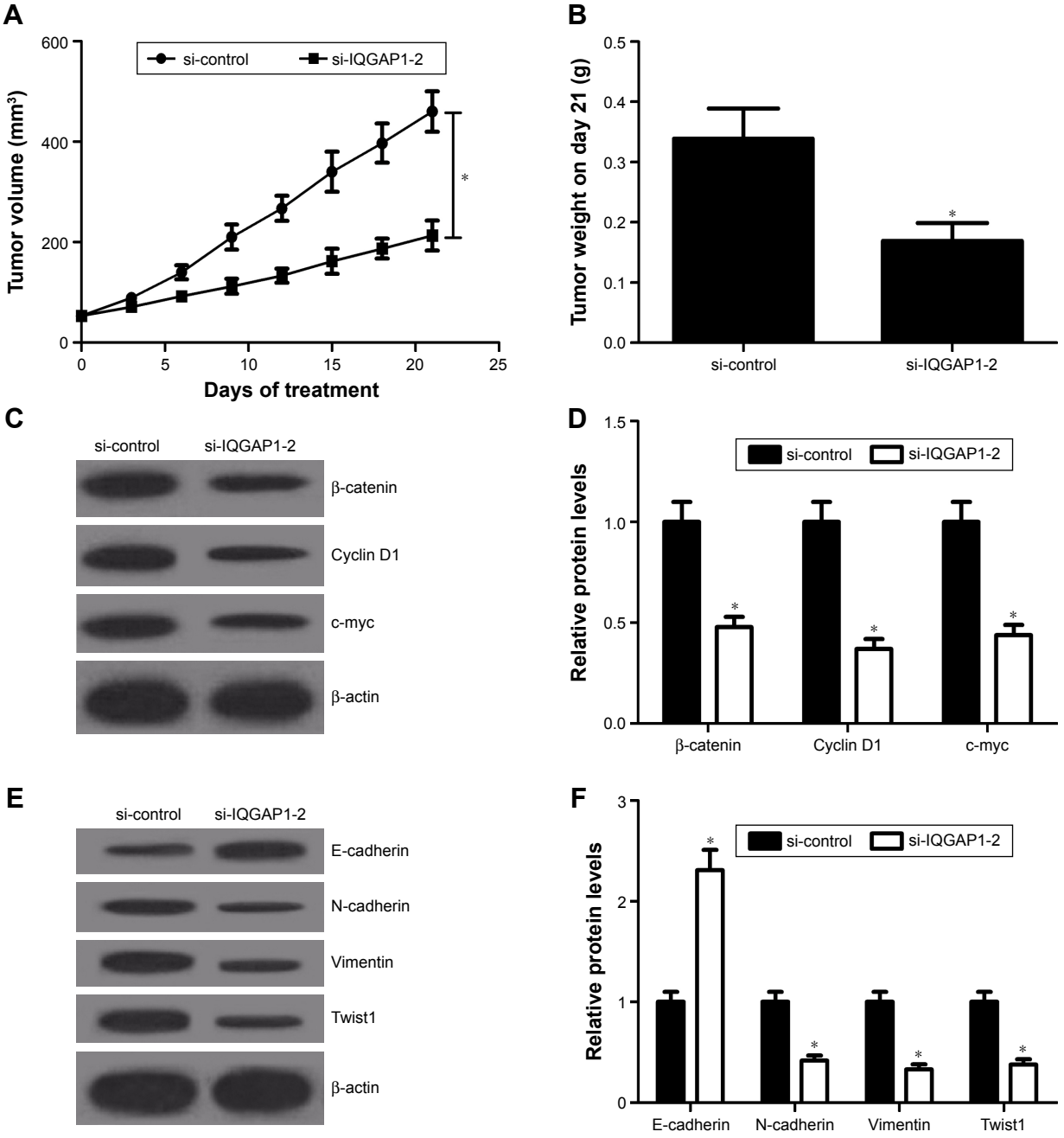

Figure 6 Downregulation of IQGAP1 suppressed the growth of SW579 tumor xenografts in vivo.

Notes: When the tumor volume reached the required size (50–100 mm^3), 5 μg siRNA (si-control or si-IQGAP1-2) was injected into tumor cavity daily for 21 days. The mice were euthanized at day 21. (**A**) Effects of IQGAP1 knockdown on the growth of SW579 xenografts. (**B**) Tumor weights were measured at day 21. (**C** and **D**) Western blot analysis of β-catenin, cyclin D1 and c-myc in resected tumor tissues. (**E** and **F**) Western blot analysis of E-cadherin, N-cadherin, Vimentin and Twist excised in tumor tissues. n=5 and *$P<0.05$.

the control group, si-IQGAP1-2 significantly inhibited the levels of β-catenin, c-myc and cyclin D1 in the Wnt/β-catenin pathway in the resected tumor (Figure 6C and D). Furthermore, si-IQGAP1-2-derived tumor presented a remarkable reduction in N-cadherin, Vimentin and Twist expression and an obvious increase in E-cadherin expression compared with the control group (Figure 6C–F).

Discussion

Thyroid cancers are tumors of the thyroid gland and originate from follicular or parafollicular cells. It is reported that the incidence of thyroid cancer has increased virtually in the majority of countries over the past few decades.[18] In addition, growing evidence has revealed the relationship between IQGAP1 expression and tumorigenesis.[9,15]

To explore the precise role and mechanism of IQGAP1 in the cancer progression, this study investigated the effects of knockdown of IQGAP1 in thyroid cancer.

Previous studies reveal that IQGAP1 may promote the progression of some cancers, including thyroid cancer.[19,20] Meng et al indicated that IQGAP1 is upregulated in thyroid cancer tissues and FTC133 cells.[15] Consistent with this, our study showed that IQGAP1 expression is upregulated in thyroid cancer tissues and SW579 and TPC-1 cell lines. A previous study showed that IQGAP1 knockdown results in a prominent reduction in cell proliferation and invasion in the FTC133 cells.[15] As is reported in some other types of cancers,[21,22] we also found that knockdown of IQGAP1 suppressed proliferation of SW579 and TPC-1 cell lines and reduced tumor growth in vivo. To explore how IQGAP1, as a multifunctional protein, regulates tumor proliferation and EMT in thyroid cancer, the regulation of IQGAP1 on the expressions of the EMT-related proteins E-cadherin, N-cadherin, Vimentin, Twist1, β-catenin and the Wnt/β-catenin targets c-myc and cyclin D1 in thyroid cancer were detected in vitro and in vivo.

EMT is a vital step in the initiation of the metastasis, during which the majority of tumor cells spread into distal organs.[6] Therefore, better understanding of the molecular mechanisms of thyroid cancer metastasis is important for developing new medical treatments for thyroid cancer. The loss or reduction of the expression of E-cadherin, a cell adhesion molecule, is a crucial event in the initiation of EMT.[23] In the current study, we also found that downregulation of IQGAP1 significantly augment epithelial marker E-cadherin expression. Moreover, mesenchymal markers (N-cadherin and Vimentin) and Twist (an EMT inducer in cancer) were downregulated in IQGAP1-knockdown thyroid cancer cells. These data suggested that IQGAP1 knockdown apparently suppressed EMT of cells, which was consistent with the recent study.[24]

When the Wnt/β-catenin pathway is activated, Wnt molecules bind to frizzled receptors and lead to destruction of the complex, and then β-catenin transfers into the nucleus and accumulate, finally inducing the loss of E-cadherin.[25,26] The Wnt/β-catenin signaling pathway is involved in EMT in gastrulation, cardiac valve formation and cancer.[27] Moreover, it has been showed that the activation of the Wnt/β-catenin pathway can promote EMT in various cancers.[23] Therefore, to clarify how IQGAP1 regulated the EMT in thyroid cancer, we detected the expressions of β-catenin and downstream target genes (c-myc and cyclin D1) of the Wnt/β-catenin pathway, and our data presented that significant reductions in β-catenin, c-myc and cyclin D1 were observed in IQGAP1-knockdown thyroid cancer cells. In addition, inactivation of the Wnt/β-catenin pathway inhibited EMT and reversed the positive effect of EMT and proliferation induced by the expression of IQGAP1. These data suggested that knockdown of IQGAP1 inhibited the proliferation and EMT of thyroid cancer cells through suppressing the Wnt/β-catenin pathway.

Conclusion

Our study demonstrated that IQGAP1 is upregulated in thyroid cancer tissues and cells. Knockdown of IQGAP1 exerted inhibitory effects on the cell proliferation and EMT of thyroid cancer cells via blocking the Wnt/β-catenin pathway. Moreover, knockdown of IQGAP1 suppressed the growth and EMT of SW579 tumor xenografts in vivo. Our study suggested that knockdown of IQGAP1 may be a potentially novel therapeutic method and provided a theoretical basis for therapeutic target for thyroid cancer.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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