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UCA1 promotes papillary thyroid carcinoma development by stimulating cell proliferation via Wnt pathway

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Abstract. – OBJECTIVE: To explore whether lncRNA UCA1 (long non-coding RNA urothelial carcinoma associated 1) could promote the development of papillary thyroid carcinoma (PTC) via Wnt pathway and its underlying mechanism.

PATIENTS AND METHODS: UCA1 expression in PTC tissues, paracancerous tissues, and thyroid cancer cells were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). UCA1 lentivirus was then constructed for the following *in vitro* experiments. Proliferative ability of MTC and SW579 cells was detected by cell counting kit-8 (CCK-8) and colony formation assay. Cell apoptosis after altering UCA1 expression in MTC and SW579 cells was detected by flow cytometry and Western blot. Invasive ability of MTC and SW579 cells was detected by transwell and wound healing assay. Finally, protein expressions of Wnt pathway-related genes were detected by Western blot.

RESULTS: UCA1 was overexpressed in PTC tissues and thyroid cancer cells. UCA1 expression was positively correlated to tumor size, tumor stage, and metastasis of PTC. Overexpressed UCA1 promoted proliferation and invasion, whereas inhibited apoptosis of thyroid cancer cells via Wnt pathway.

CONCLUSIONS: Overexpressed UCA1 promotes PTC development by stimulating proliferation, migration, and anti-apoptosis of thyroid cancer cells via activating Wnt pathway.

Key Words
UCA1, Papillary thyroid carcinoma, Wnt, Cell proliferation.

Introduction

Thyroid cancer is the most common malignancy in thyroid tissue. Thyroid cancer is classified as papillary carcinoma, follicular carcinoma, medullary carcinoma, and undifferentiated carcinoma based on the pathological features[1,2]. Among them, papillary thyroid carcinoma (PTC) accounts for over 80% of thyroid cancer, reflecting their origin from thyroid follicular epithelial cells. In the past 20 years, the incidence of PTC has remarkably increased throughout the world. Current treatments of PTC mainly include surgical removal, radioactive iodine elimination, and postoperative chemotherapy. Although the treatments have been greatly advanced, the 10-year survival rate of PTC is only 67%. It is of great significance to explore the underlying mechanism involved in PTC development.

Wnt pathway is an extremely conservative pathway in the growth and development of organisms. Wnt pathway regulates the normal development and biological functions of organism embryonic tissues. Some studies[3,4] have found that multiple biological processes can be regulated by Wnt pathway, including EMT (epithelial-mesenchymal transition), cell proliferation, apoptosis, etc. Dysfunctional Wnt pathway probably leads to unrestricted cell proliferation, growth, and tumorigenesis[5]. It is reported that Wnt pathway exerts an essential role in the development of thyroid tissue. In normal thyroid tissue, Wnt pathway can promote the differentiation and proliferation of thyroid cells. It also stimulates synthesis of thyroid hormones *via* regulating thyroid peroxidase[6]. However, abnormal activation of the Wnt pathway may lead to thyroid cancer development. For example, studies have found that lithium stimulates proliferation of thyroid cells *via* Wnt pathway[7]. Upregulated β-catenin in the thyroid tissue is closely related to PTC occurrence[6]. Dickkopf-1 (DKK-1) can inhibit the survival and migration of thyroid cancer cells by inhibiting Wnt pathway[8]. These findings suggested that Wnt pathway is correlated to the occurrence and development of PTC, which provides new suggestions for improving clinical outcomes of PTC patients.

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LncRNA UCA1 (long non-coding RNA urothelial carcinoma associated 1) regulates Wnt pathway through interacting with DNA, mRNA, miRNA, and protein, thus affecting the biological activities of tumors[9]. UCA1 was first discovered in bladder cancer[10]. Many studies have shown that UCA1 is overexpressed in bladder cancer[11], osteosarcoma[12], cervical cancer[13], and gastric cancer[14]. UCA1 promotes the proliferation, metastasis, and invasion of various tumor cells, suggesting that UCA1 may serve as a diagnostic biomarker. Previous researches have shown that UCA1 promotes the development of oral mucosal squamous cell carcinoma *via* Wnt pathway[15]. It is also confirmed that UCA1 enhances the drug resistance of bladder cancer cells *via* Wnt pathway[16]. The specific role of UCA1 in PTC development, however, has been rarely studied.

Patients and Methods

Sample Collection

40 PTC patients treated in our hospital from the 2014 year to the 2016 year were enrolled. All patients were pathologically diagnosed as PTC. Basic characteristics of enrolled PTC patients were listed in Table I. The PTC tissues and paracancerous tissues were surgically resected and immediately preserved in liquid nitrogen. This study was approved by the Ethics Committee of Weifang People's Hospital and all patients signed the informed consent.

RNA Extraction and qRT-PCR (Quantitative Real Time-Polymerase Chain Reaction)

Total RNAs in PTC tissues and paracancerous tissues were extracted using TRIzol method (Invitrogen, Carlsbad, CA, USA) for reverse transcription according to the instructions of PrimeScript RT reagent Kit (TaKaRa, Otsu, Shiga, Japan). QRT-PCR was then performed based on the instructions of SYBR Premix Ex Taq TM (TaKaRa, Otsu, Shiga, Japan), with 3 replicates in each group. Primers used in the study were as follows: UCA1, F: CCACACCCAAAACAAAAAATCT, R: TCCCAAGCCTCTAACAACAA; GAPDH, F: TGTTCGTCATGGGTGTGAAC, R: ATGGCATGGACTGTGGTCAT.

Cell Culture

Human thyroid follicular epithelial cell lines and thyroid cancer cell lines (MTC, FTC-133, TPC-1, B-CPAP, SW579, and PDTC cells) were obtained from ATCC (American Type Culture Collection) (Manassas, VA, USA). Cells were cultured in DMEM (Dulbecco's Modified Eagle Medium) (Gibco, Rockville, MD, USA) containing 10% FBS (fetal bovine serum), 100 U/mL penicillin and 100 μg/mL streptomycin (Hyclone, South Logan, UT, USA), and incubated in a 5% CO_2 incubator at 37°C. Culture medium was replaced every 2 days.

Cell Transfection

Lentiviruses containing complementary Deoxyribose Nucleic Acid (cDNA) sequences of UCA1 and negative control were constructed. LV-UCA1 and LV-Vector were provided by Gene Pharma (Shanghai, China). MTC and SW579 cells were digested and seeded in the 6-well plates at a density of 2×10^5/mL. Culture medium containing 6 μg/mL Polybrene and the corresponding lentivirus were added in each well. After transfection for 48 h, its efficacy was verified by qRT-PCR.

Cell Counting Kit-8 (CCK-8) Assay

MTC and SW579 cells were seeded into 96-well plates at a density of 2×10^4/mL. 10 μL of a CCK-8 solution (Dojindo, Kumamoto, Japan) was added in each well after cell culture for 24, 48, 72, and 96 h, respectively. The absorbance at 450 nm of each sample was measured by a microplate reader (Bio-Rad, Hercules, CA, USA). Each group had 3 replicates.

Colony Formation Assay

MTC and SW579 cells were washed with PBS (phosphate-buffered saline), digested with trypsin, and centrifuged at 100 rpm/min for 3 min. After cell density was adjusted to 1×10^3/mL, cells were seeded in the 6-well plates. Subsequently, cells were fixed with 4% methanol for 30 min and stained with 0.1% crystal violet for another 30 min (Sigma-Aldrich, St. Louis, MO, USA), followed by the detection of colony formation.

Western Blot

Total protein was extracted from treated cells by RIPA (radioimmunoprecipitation assay) solution (Beyotime, Shanghai, China). The protein sample was separated by electrophoresis on 10% SDS-PAGE (sodium dodecyl sulphate-polyacrylamide gel electrophoresis). Samples were then transferred to PVDF (polyvinylidene difluoride) membrane (Millipore, Billerica, MA, USA). After membranes were blocked with skimmed milk,

Table I. Basic characteristics of enrolled PTC patients.

Clinicopathologic features	Number of cases	Expression of UCA1		*p*-value
		PTC tissues (Mean ± SD)	Paracancerous tissues (Mean ± SD)	
Age (years)				
≤40	19	10.31	1.34	0.5647
>40	21	10.09	1.15	
Tumor size				
>1 cm	15	10.47	1.62	0.0087*
≤1 cm	25	8.93	1.75	
Gender				
Male	12	10.54	1.23	0.2568
Female	28	10.02	1.34	
Invasion				
T0-T2	29	9.07	2.02	0.0151*
T3-T4	11	11.07	2.7	
TNM stage				
0-I	23	8.5	1.57	<0.0001*
II-IV	17	10.94	1.22	
Metastasis				
M0	30	8.97	2.02	0.0045*
M1	10	11.14	1.8	

*$p<0.05$

the membranes were incubated with primary antibodies (Cell Signaling Technology, Danvers, MA, USA) overnight at 4°C. The membranes were then washed with TBST (Tris-Buffered Saline with Tween-20) and followed by the incubation of secondary antibody at room temperature for 1 h. The protein blot on the membrane was exposed by enhanced chemiluminescence (ECL) method.

Cell Apoptosis Detection

MTC and SW579 cells were digested with 0.25% trypsin, centrifuged and fixed with 4% methanol for 20 min. Subsequently, cells were incubated with 500 µL of RNase (200 µg/mL) for 30 min, followed by incubation with 500 µL of propidium iodide (PI) for another 30 min. After cells were washed with PBS three times, cell apoptosis was detected using flow cytometry (Partec AG, Arlesheim, Switzerland).

Transwell Assay

MTC and SW579 cells were cultured with serum-free DMEM for 12 h and digested with 0.25% trypsin. 200 µL of cell suspension with the density of 2×10^5/mL and 600 µL of DMEM containing 10% FBS were added in the upper and lower chamber, respectively. After cell culture for 24 h, cells were fixed with 4% methanol for 30 min and stained with 0.1% crystal violet for 15 min. Images were observed and captured using a light microscope (Olympus, Tokyo, Japan).

Wound Healing Assay

MTC and SW579 cells were seeded into 6-well plates at a dose of 5×10^5/ml. When the cell confluence was up to 80%, a sterile 200 µL micropipette tip was used to vertically scratch the cell plate. Serum-free medium was replaced for 48 h-incubation. The cell migration was observed under an inverted microscope, and the width of the scratch was measured and photographed. Average width was calculated from 5 scratches.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 19.0 statistical software (IBM, Armonk, NY, USA) was used for data analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared using the *t*-test. $p<0.05$ considered the difference was statistically significant.

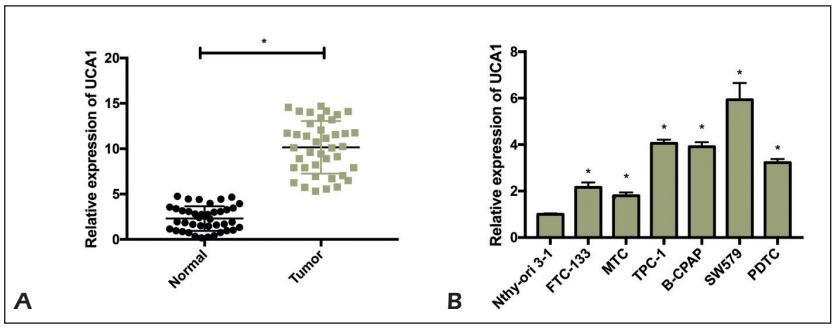

Figure 1. UCA1 was overexpressed in PTC. **A**, UCA1 was overexpressed in PTC tissues than that of paracancerous tissues. **B**, Compared with that of normal follicular epithelial cell line Nthy-ori 3-1, the mRNA level of UCA1 was remarkably elevated in thyroid cancer cell lines, including MTC, FTC-133, TPC-1, B-CPAP, SW579, and PDTC.

Results

UCA1 Was Overexpressed in PTC

UCA1 was overexpressed in PTC tissues than that of paracancerous tissues (Figure 1A). Besides, UCA1 expression was positively correlated to tumor size, tumor stage, and invasion of PTC (Table I). Furthermore, we detected UCA1 expression in thyroid tumor cell lines. Compared with that of normal follicular epithelial cell line Nthy-ori 3-1, the mRNA level of UCA1 was remarkably elevated in thyroid cancer cell lines, including MTC, FTC-133, TPC-1, B-CPAP, SW579, and PDTC (Figure 1B). Among them, SW579 cells expressed the highest level of UCA1 and MTC cells expressed the lowest level, which were selected for the following experiments.

Overexpressed UCA1 Promoted Proliferation of Thyroid Cancer Cells

To further explore the regulatory role of UCA1 in thyroid cancer cells, we constructed LV-UCA1 and LV-Vector, respectively. Transfection efficacy was verified by qRT-PCR (Figure 2A and 2B). Increased proliferation was observed in MTC and SW579 cells transfected with LV-UCA1 compared with those of controls (Figure 2C). Overexpressed UCA1 also increased colony formation ability of MTC and SW579 cells (Figure 2D).

Subsequently, Western blot was performed to verify whether UCA1 could regulate PTC development *via* Wnt pathway. GSK-3β is a multifunctional protein kinase participating in glycogen synthesis, cell proliferation, and other physiological processes. It is an important component of Wnt pathway, as well as β-catenin[17-19]. Our data revealed that protein expressions of GSK-3β and β-catenin were remarkably elevated after UCA1 overexpression (Figure 2E), indicating that UCA1 promotes cell proliferation *via* Wnt pathway.

Overexpressed UCA1 Inhibited Apoptosis of Thyroid Cancer Cells

The effect of UCA1 on apoptosis of thyroid cancer cells was detected by flow cytometry and Western blot. Apoptotic rate was lower in MTC and SW579 cells transfected with LV-UCA1 compared with that of controls (Figure 3A). Western blot results also showed that UCA1 overexpression upregulated anti-apoptosis gene Bcl-2[20] and downregulated pro-apoptosis gene Bax[21] in MTC and SW579 cells (Figure 3B).

Overexpressed UCA1 Promoted Invasion of Thyroid Cancer Cells

Transwell and wound healing assay were carried out to detect the invasive ability of thyroid cancer cells affected by UCA1. Transwell assay demonstrated that the amount of penetrating cells was remarkably larger in MTC and SW579 cells transfected with LV-UCA1 than those transfected with LV-Vector (Figure 4A). Besides, wound healing assay indicated that after cell culture with serum-free DMEM for 24 h, the migrated width in MTC and SW579 cells with UCA1 overexpression was larger than that of controls (Figure 4B).

Discussion

Current researches have demonstrated that lncRNA participates in various biological processes, including X chromosome silence, genome imprinting, chromatin modification, and transcriptional activation. LncRNA also regulates multiple cellular functions, such as proliferation, differentiation, apoptosis, and migration[22]. Differentially expressed lncRNAs in tumor tissues are closely related to the occurrence, progression, and metastasis of tumors[23]. LncRNA UCA1 has been well studied in different types of tumors. For instance, UCA1 promotes breast tumor development *via* inhibiting p27 (Kip1) pathway[24]. Upregulation of

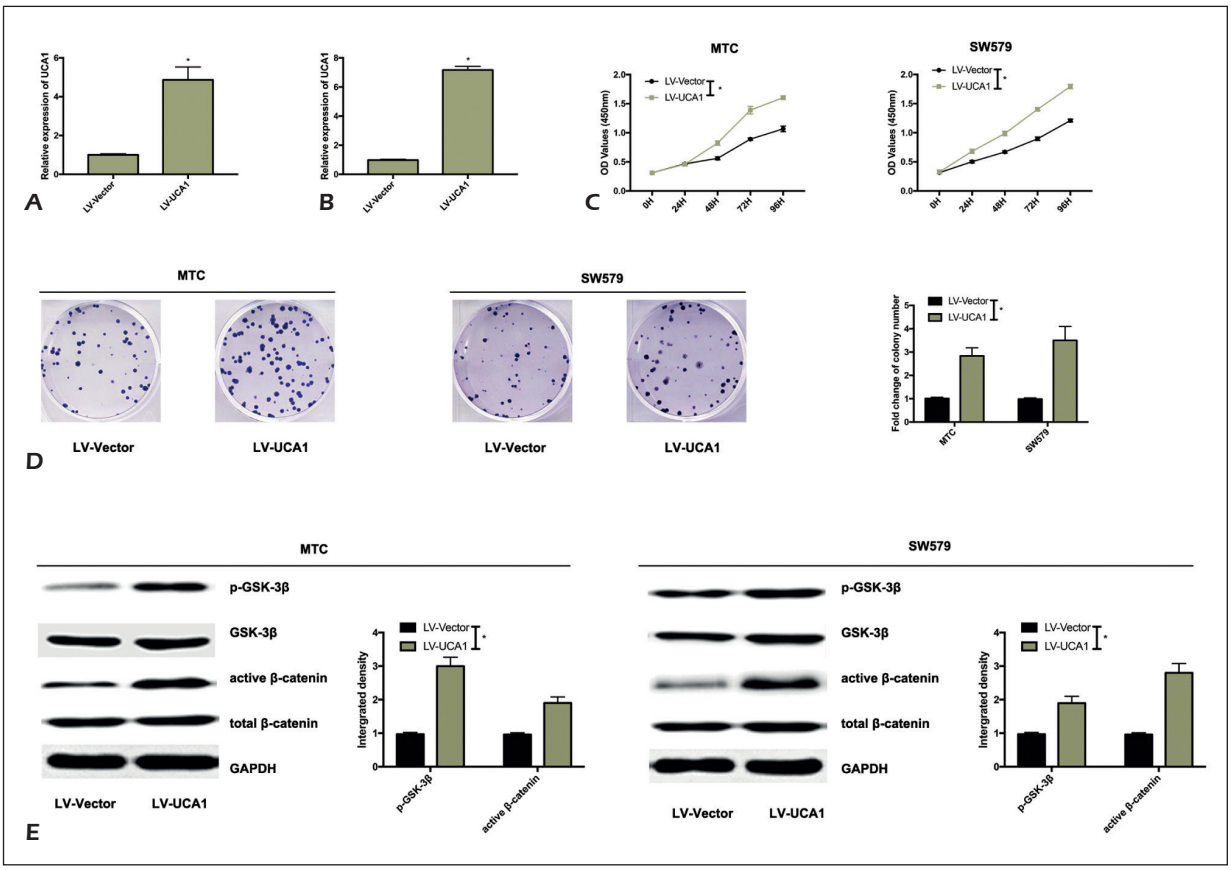

Figure 2. Overexpressed UCA1 promoted proliferation of thyroid cancer cells. **A**-**B**, Transfection efficacy of LV-UCA1 and LV-vector was verified by qRT-PCR. **C**, Proliferation in MTC and SW579 cells transfected with LV-UCA1 was increased compared with those of controls. **D**, Overexpressed UCA1 increased colony formation ability of MTC and SW579 cells (magnification 10×). **E**, Protein expressions of GSK-3β and β-catenin were remarkably elevated after UCA1 overexpression.

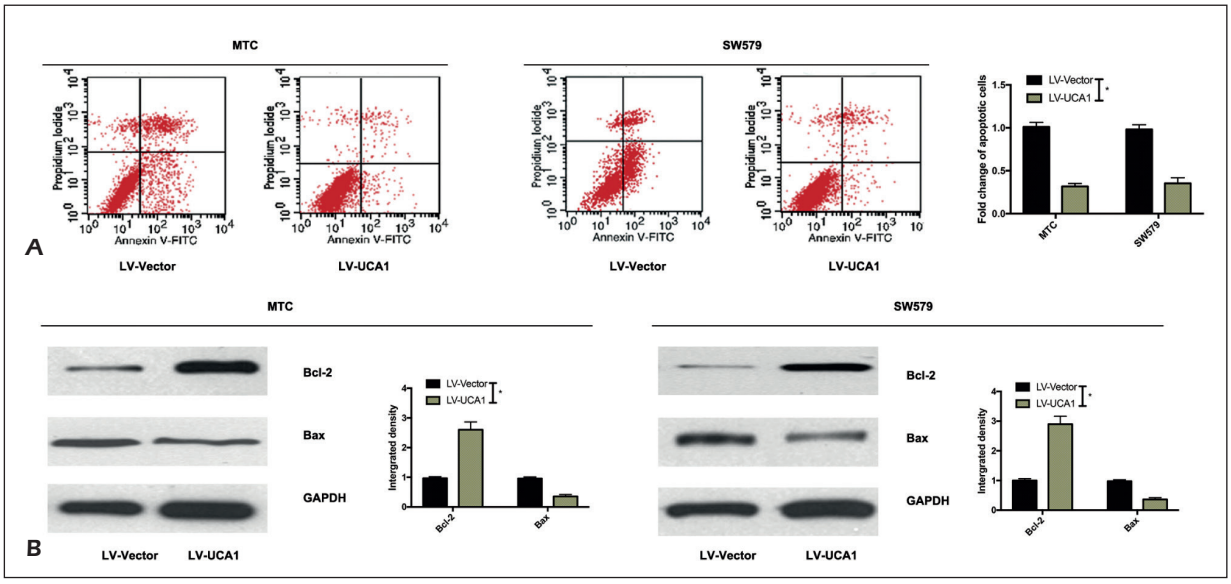

Figure 3. Overexpressed UCA1 inhibited apoptosis of thyroid cancer cells. A, Apoptotic rate of MTC and SW579 cells was lower after LV-UCA1 transfection compared with that of controls. B, UCA1 overexpression upregulated anti-apoptosis gene Bcl-2 and downregulated pro-apoptosis gene Bax in MTC and SW579 cells.

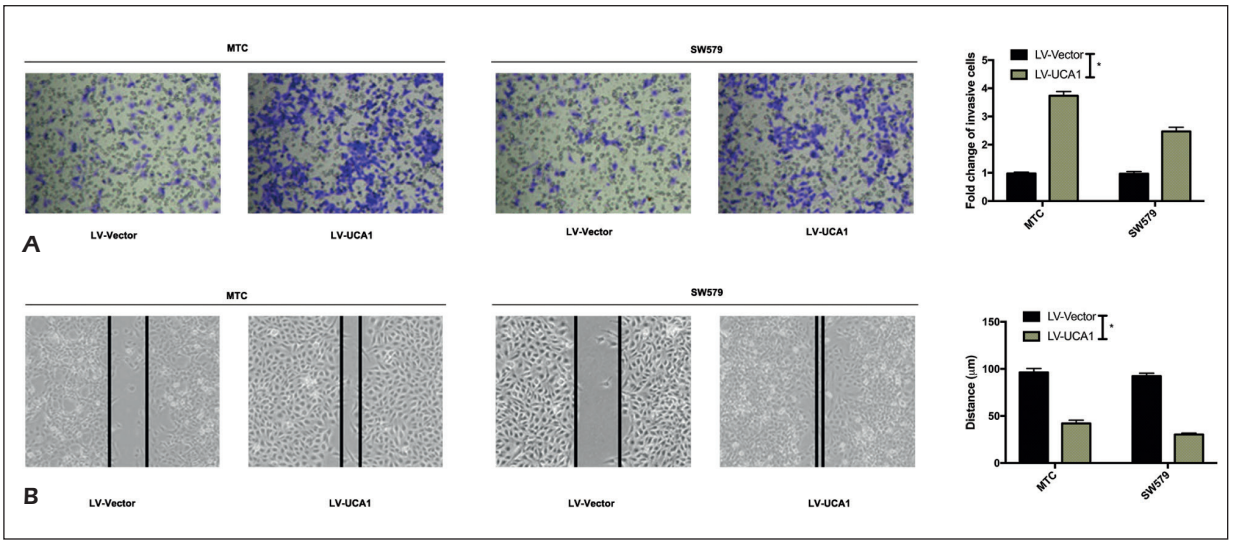

Figure 4. Overexpressed UCA1 promoted invasion of thyroid cancer cells. **A**, The amount of penetrating cells was remarkably larger in MTC and SW579 cells transfected with LV-UCA1 than those transfected with LV-Vector. **B**, The migrated width in MTC and SW579 cells with UCA1 overexpression was larger than that of controls (magnification 20×).

UCA1 in colorectal cancer affects cell proliferation, apoptosis, and cell cycle[25]. UCA1-induced GRK2 degradation promotes tumor metastasis in gastric cancer[26]. Li et al[27] demonstrated that upregulated UCA1 induced by HIF-1α promotes the growth of osteosarcoma cells *via* inhibiting PTEN/AKT pathway. UCA1 acts as an oncogene in non-small cell lung cancer through regulating microRNA-193a-3p[28]. In the present study, we aim to explore the potential role of UCA1 in PTC.

Wnt pathway, known as a classical signaling pathway, influences tumorigenesis at the transcriptional level *via* inhibiting or reducing protein translation and synthesis[29,30]. Studies have shown that Wnt signaling pathway is closely related to the proliferation, invasion, and metastasis of thyroid cells. Abnormal Wnt/β-catenin pathway leads to the occurrence and development of thyroid cancers[31,32]. Hence, we hypothesized whether UCA1 could regulate PTC development *via* Wnt pathway.

In our study, UCA1 was overexpressed in PTC tissues and cell lines. Further *in vitro* experiments were carried out after lentivirus construction. Overexpressed UCA1 in MTC and SW579 cells remarkably increased proliferative ability. Protein expressions of GSK-3β and β-catenin were upregulated in MTC and SW579 cells transfected with LV-UCA1, indicating UCA1 activates Wnt pathway. Flow cytometry and Western blot results elucidated that cell apoptosis was inhibited by UCA1 overexpression. Meanwhile, migration and invasion abilities of PTC cells were elevated after UCA1 overexpression. The above data demonstrated that overexpressed UCA1 promotes PTC development *via* Wnt pathway.

Conclusions

We showed that the overexpressed UCA1 promotes PTC development by stimulating proliferation, migration, and anti-apoptosis of thyroid cancer cells *via* activating Wnt pathway.

Conflict of Interests:

The authors declare they have no conflict of interest.

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