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Long noncoding RNA UCA1 promotes proliferation and metastasis of thyroid cancer cells by sponging miR-497-3p

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Abstract. – OBJECTIVE: **Recently, long noncoding RNAs (lncRNAs) have attracted much attention for their roles in tumor progression. The aim of this study was to investigate the exact role of lncRNA UCA1 in the development of thyroid cancer (TC) and to explore the possible underlying mechanism.**

PATIENTS AND METHODS: **UCA1 expression in both TC cells and tissues was detected by quantitative Real Time-Polymerase Chai[illegible] Re-action (qRT-PCR). Colony formation ass[illegible] proliferation, and transwell assay were c[illegible]ed *in vitro*. Subsequent luciferase reporte[illegible]e assay was applied to investigate the under[illegible] mechanism. Furthermore, the function of U[illegible] *in vivo* was monitored as well.**

RESULTS: **UCA1 expression [illegible] TC sam[illegible]ples was significantly highe[illegible] of corresponding normal tissu[illegible]fter [illegible]1 was knocked down *in vitro* a[illegible] *vivo*, t[illegible]oliferation, migration, and in[illegible] of T[illegible] significantly inhibited. Mo[illegible]expression of miR-497-3p was [illegible]esse[illegible] the knockdown of UCA1. Fu[illegible]more, mi[illegible]p was directly targeted b[illegible]1.**

CONCLUSIO[illegible]kdown of U[illegible] could inhibit TC ce[illegible]olife[illegible] and metastasis via sponging [illegible]iR-497-3p. O[illegible]dings might offer a new the[illegible]utic interven[illegible] TC patients.

Key W[illegible]
Lo[illegible]oncodi[illegible]NA, UCA1, Thyroid cancer (TC), Mi[illegible]p.

[illegible]duction

T[illegible]id cancer (TC) is one of the most prevale[illegible]e world. Over the past decades, [illegible]morbidity of TC has greatly increased world[illegible][1]. Currently, TC remains the eighth most c[illegible]n cancer in China[2]. In recent years, a huge deve[illegible]ment has been made in the effective treatment of TC. Howeve[illegible]to its unsatisfied survi[illegible]rings a subs[illegible] burden to patients a[illegible]ociety[3]. Therefore, it is urgent to identify [illegible] biomarkers f[illegible] an early diagnosis of TC.

[illegible]ong non-co[illegible] RNAs (lncRNA) are a sub[illegible] of non-prote[illegible]oding RNAs with more than 2[illegible]leotide[illegible]ength. Authors have indicated that [illegible]ve as major contributors in carcinogene[illegible], including cell apoptosis, cell prolif[illegible]ation, and cell metastasis. LncRNA LINC01133 [illegible] colorectal cancer metastasis through [illegible] [illegible]ction of the epithelial-mesenchymal transition (EMT)[4]. By regulating vasculogenic angiogenesis, lncRNA MALAT1 is reported to promote tumorigenicity and cell metastasis in gastric cancer[5]. Meanwhile, lncRNA MALAT1 accelerates the migration and invasion of hepatocellular carcinoma cells *via* targeting miR-204[6]. Besides, lncRNA CRNDE-h[7] has been reported to be a novel serum biomarker for colorectal cancer. However, the clinical role and biological mechanism of lncRNA UCA1 in the development of TC have not been fully elucidated.

In this study, we found that the expression of UCA1 was remarkably up-regulated in TC tissues. The knockdown of UCA1 significantly inhibited the proliferation and metastasis of TC cells. Moreover, our further experiment explored the underlying mechanism of UCA1 function in TC development.

Patients and Methods

Cell Lines and Clinical Samples

54 paired TC tissues and adjacent non-tumor tissues were sequentially gathered from TC patients undergoing surgery in the Tumor Hos-

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pital of Jinlin Province from February 2017 to December 2018. Written informed consent was obtained from each patient before the operation. No radiotherapy or chemotherapy was applied for any patient before the operation. The tissues obtained from the surgery were stored immediately at –80°C for use. All collected tissues were analyzed by an experienced pathologist. This investigation was approved by the Ethics Committee of Tumor Hospital of Jinlin Province.

Cell Culture

K1, TPC-1, SW579 and Nthy-ori 3–1 (normal human thyroid cell line) cells were offered by the Chinese Academy of Science (Shanghai, China). All cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA) consisting of 10% of fetal bovine serum (FBS; Life Technologies, Gaithersburg, MD, USA) and penicillin. Besides, the cells were maintained in an incubator with 5% CO_2 at 37°C.

Cell Transfection

Lentiviral small hairpin RNA (shRNA) targeting UCA1 was synthesized and cloned into [illegible]ti-EF1a-EGFP-F2A-Puro vector (Bioset[illegible] San Diego, CA, USA). Subsequently, synth[illegible]ed shRNA was transfected into TPC-1 TC cel[illegible]cording to the instructions of Lipofectamine 2[illegible] (Invitrogen, Carlsbad, CA, USA).

Quantitative Real Time-[illegible]yme[illegible] Chain Reaction (qRT-P[illegible]

Total RNA in tissues [illegible]ells w[illegible] by using TRIzol Rea[illegible]t ([illegible], Carlsbad, CA, USA). Subsequ[illegible], the ex[illegible]d total RNA was reverse-trans[illegible]d into comp[illegible]tary deoxyribose nucle[illegible](cDNAs) thro[illegible] the reverse Transcr[illegible]n K[illegible]KaRa Biotechnology Co., Ltd., D[illegible]lian, China). [illegible]rs used for qRT-PCR wer[illegible] follows: UCA[illegible]rd 5′- TTTG-CCAG[illegible]CAGCTTAAT-3′, re[illegible]rse 5′- TTGTC-CCC[illegible]TTCC[illegible]AT-3′; glyceraldehyde 3-p[illegible]ate [illegible]drogen[illegible]e (GAPDH) forward 5′-CC[illegible]AGAT[illegible]GGCAATGCTGG-3′ [illegible] rev[illegible]′-TG[illegible]GCATGGACTGTGGT-[illegible]CA-3′. [illegible]mo-cycling condition was as f[illegible]s: 30 s [illegible]C, 5 s for 40 cycles at 95°C, and [illegible] at 60°C.

[illegible]ony Formation Assay

[illegible]PC-1 (1.5×10^3 cells/well) cells were first seede[illegible] 6-well plates. Ten days later, formed colo[illegible] were fixed with 10% of formaldehyde for 30 min and stained with 0.5% of crystal violet for 5 min. CANON camera w[illegible] photographs of colonies, and Imag[illegible] Plus [illegible] (Silver Springs, MD, USA) wa[illegible]d for data analysis.

Cell Proliferation Assa[illegible]

TC cells were first se[illegible] into 96-we[illegible] at a density of 1×10^3 c[illegible]well. S[illegible]sequent[illegible] µL Cell Counting K[illegible] (CCK[illegible]Dojindo, Kumamoto, Japan) wa[illegible]d i[illegible]ells at [illegible]rent time points, fol[illegible]ed [illegible]bation [illegible]2 h in the dark. Abs[illegible]nce at [illegible] w[illegible]easured by a microp[illegible]eader (Bio-R[illegible]cules, CA, USA).

Transwell Assay

F[illegible]cting the TC[illegible] migration, 2 ×10^5 t[illegible]ected cells in 100 µL serum-free DMEM [illegible]e transforme[illegible] into the upper chamber of [illegible]8-µm cultur[illegible]ert (Corning, Corning, NY, [illegible]). Meanwhil[illegible]0% of FBS-DMEM was added [illegible]e lower[illegible]mber of the insert. 24 h later, these[illegible]e treated with methanol for 30 min and [illegible]ed with hematoxylin for 20 min. The number of migrating cells was counted by an [illegible]icroscope (×20). The three fields were [illegible]ndo[illegible]y selected for each sample. For detecting the TC cell invasion, 2 ×10^5 transfected cells in 100 µL serum-free DMEM were transformed into the upper chamber of an 8-µm culture insert (Corning, Corning, NY, USA) coated with 50 µg of Matrigel (BD Biosciences, Franklin Lakes, NJ, USA). Meanwhile, 20% of FBS-DMEM was added to the lower chamber of the culture insert. 24 h later, these inserts were treated with methanol for 30 min and stained with hematoxylin for 20 min. The number of invaded cells was counted by an inverted microscope (×20). The three fields were randomly selected for each sample.

Xenograft Model

For the tumor formation assay, the transfected TPC-1 cells were subcutaneously injected into NOD/SCID mice (4-5 weeks old). Tumor diameters were detected every 5 days after inoculation. Tumor volume was calculated as the following formula: volume = length × width^2 × 1/2. The mice were sacrificed and tumors were extracted after 4 weeks. For the tumor metastasis assay, transfected TPC-1 cells were injected into the tail vein of NOD/SCID mice (4-5 weeks old). The mice were sacrificed and lung tissues were extracted after 4 weeks. The number of metastatic nodules in the lung was then counted. Animal experiments in this study were approved by the Animal Ethics Committee of the Tumor Hospital of Jinlin Province.

Luciferase Reporter Gene Assay

The 3′-UTR of UCA1 was first cloned into the pGL3 vector (Promega, Madison, WI, USA). Site-directed mutagenesis of the miR-497-3p binding site in UCA1 3′-UTR was performed using the QuickChange site-directed mutagenesis Kit (Stratagene, La Jolla, CA, USA). Subsequently, the cells were transfected with UCA1 WT-3′-UTR or UCA1 MUT-3′-UTR and miR-ctrl or miR-497-3p for 48 h. Finally, the dual-luciferase reporter assay system (Promega, Madison, WI, USA) was utilized to detect the luciferase activity.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 20.0 (SPSS, Chicago, IL, USA) was adopted for all statistical analysis. Data were presented as mean ± SD (Standard Deviation). Chi-square test and Student's *t*-test were se[illegible] when appropriate. $p<0.05$ was considered [illegible] cally significant.

Results

UCA1 Expression Level [illegible] C Ti[illegible] es and Cell Lines

First, the qRT-PCR [illegible] nduc[illegible] UCA1 expression in 5[illegible] TC p[illegible] ssues and 3 TC cell lines. As a r[illegible], UCA[illegible] ignificantly up-regulated in T[illegible] sues when c[illegible] ed with adjacent norma[illegible] (Figure 1). UC[illegible] expression in TC ce[illegible] as s[illegible] ntly higher than that of Nthy-ori[illegible]-1 cells as w[illegible] ure 2A).

Knoc[illegible] wn of UCA1 Inhib[illegible] ed Growth of T[illegible] ells

[illegible] ding [illegible] UCA1 [illegible] pression, TPC-1 TC cell [illegible] chose[illegible] the knockdown of UCA1. Q[illegible] CR w[illegible] sed to detect UCA1 ex[illegible] n in c[illegible] e 2B). Subsequent CCK-8 assa[illegible] evealed [illegible] after UCA1 was knocked dow[illegible] TC cells, the cell proliferation was re[illegible] pressed (Figure 2C). Further[illegible], the colony formation assay revealed that [illegible] UCA1 was knocked down, the number of [illegible] colonies of TC cells decreased significan[illegible] Figure 2D).

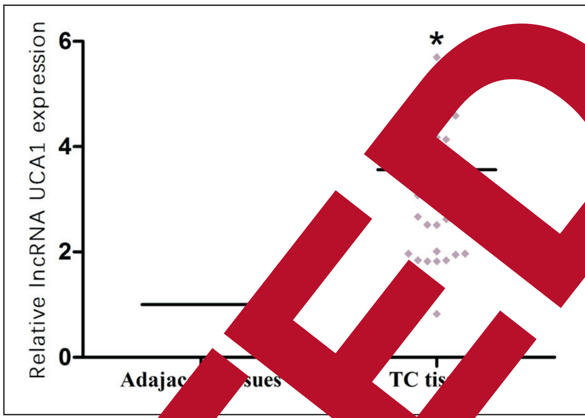


Figure 1. Ex[illegible] level of UCA1 [illegible] d significantly in TC tissu[illegible] ession marked[illegible] increased in TC tissues w[illegible] compa[illegible] h the corresponding normal tissues. Data were prese[illegible] ean ± standard error of the mean [illegible] 05.

[illegible] ockdown o[illegible] CA1 Inhibited Migration [illegible] Invasion [illegible] C Cells

[illegible] hen per[illegible] ed transwell assay and found that [illegible] wn of UCA1 significantly inhibited TC ce[illegible] migration (Figure 3A). Moreover, the [illegible] ults of transwell assay demonstrated that the [illegible] f TC cells was remarkably inhibited [illegible] A1 knock-down *in vitro* (Figure 3B).

UCA1 Promoted TC Tumorigenesis via miR-497-3p

Starbase v2.0 (http://starbase.sysu.edu.cn/mirLncRNA.php) was used to search for miRNAs that contained complementary bases with UCA1. Then, we selected miR-497-3p which contained the binding area of UCA1 (Figure 4A), as it was reported to suppress the tumorigenesis of various tumors. QRT-PCR results showed that significantly up-regulated miR-497-3p was observed in UCA1 shRNA group when compared with negative control group (Figure 4B). Furthermore, the luciferase reporter gene assay showed that the luciferase activity was significantly reduced after co-transfection of UCA1-WT and miR-497-3p. However, no significant changes were observed in luciferase activity after the co-transfection of UCA1-MUT and miR-497-3p (Figure 4C). All these data revealed that miR-497-3p was a direct target of UCA1.

UCA1 Knockdown Inhibited Tumor Formation and Metastasis In Vivo

The ability of UCA1 in tumor formation and metastasis was detected *in vivo*. Results indicated that tumor size in UCA1 shRNA group

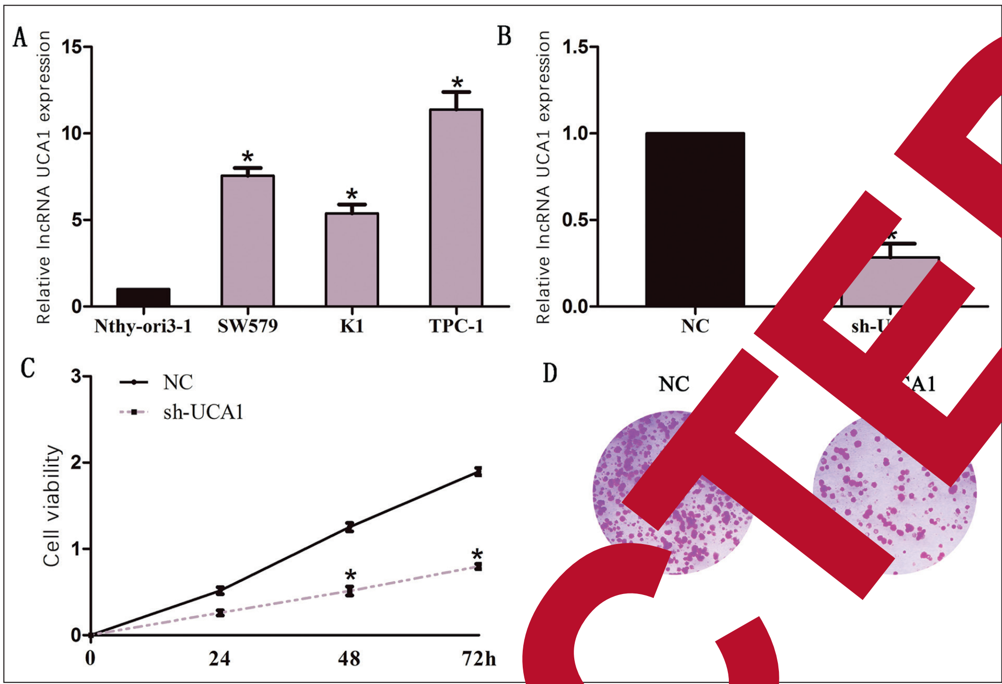
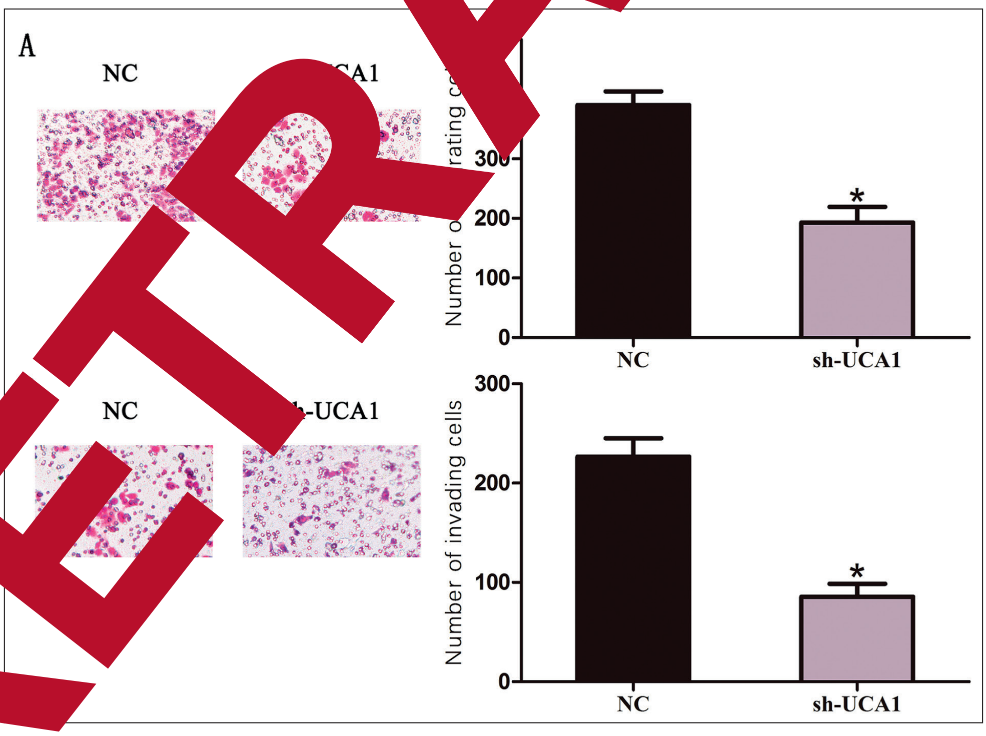


Figure 2. Knockdown of UCA1 inhibited TC cell proliferation. **A,** Ex[illegible]n levels of U[illegible] relative to GAPDH in human TC cell lines and Nthy-ori 3-1 (normal human thyroid cell line) were determined [illegible]PCR[illegible]CA1 expression in TC cells transduced with UCA1 shRNA (sh-UCA1) and negative control (NC) was detected by q[illegible]PDH was used as an internal control. **C,** CCK-8 assay showed that the proliferation of TC cell[illegible]nificantly inhibited *via* knockdown of UCA1. **D,** Colony formation assay showed that knockdown of UCA1 significantly [illegible]ber of formed colonies in TC cells (magnification: 10×). The results represented the average of three independent e[illegible]ments ([illegible]rd error of the mean). *$p<0.05$.



[illegible]re 3. Knockdown of UCA1 inhibited TPC-1 TC cell migration and invasion. **A,** Transwell assay showed that knockdown [illegible]A1 significantly repressed the migration of TPC-1 TC cells (magnification: 40×). **B,** Transwell assay showed that kn[illegible]n of UCA1 significantly repressed the invasion of TPC-1 TC cells (magnification: 40×). The results represented the av[illegible]e of three independent experiments (mean ± standard error of the mean). *$p<0.05$, as compared with control cells.

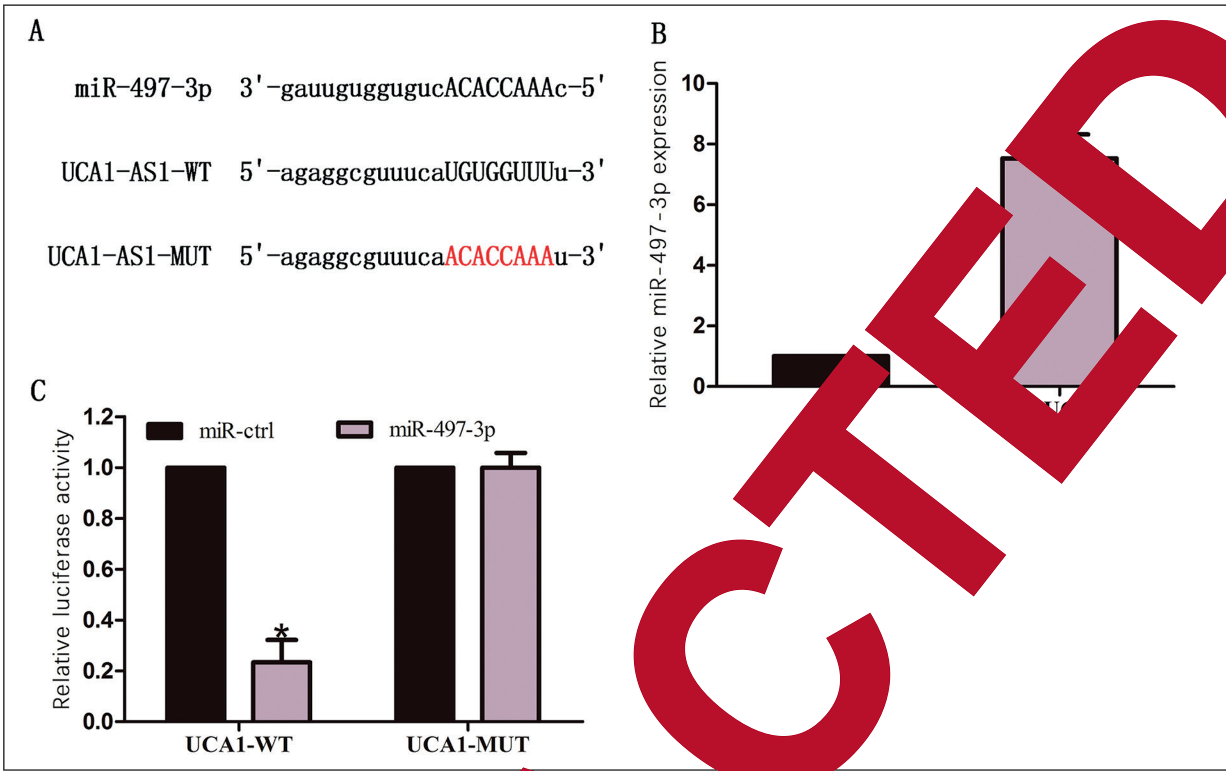


Figure 4. The association between UCA1 and miR-497-3p in TC. **A,** The binding sites of miR-497-3p on UCA1. **B,** MiR-497-3p expression increased significantly in sh-UCA1 group when compared with NC group. **C,** Co-transfection of miR-497-3p and UCA1-WT strongly decreased luciferase activity, while co-transfection of miR-control and UCA1-WT did not change luciferase activity. The results represented the average of three independent experiments. Data were presented as mean ± standard error of the mean. *$p<0.05$, as compared with [illegible] cells.

was significantly smaller than that of negative control group (Figure 5A). The weight of dissected tumors in UCA1 shRNA group was significantly less when compared with negative control group (Figure 5B). Meanwhile, the number of metastatic nodules in lung tissues of UCA1 shRNA group was significantly reduced when compared with negative control group (Figure 5C). Subsequently, the expression level of UCA1 in dissected tumor tissues was detected by qRT-PCR. Results showed that UCA1 was lowly expressed in UCA1shRNA group when compared with negative control group (Figure 5D). The above results suggested that UCA1 could reduce tumor formation and metastasis *in vivo*.

Discussion

LncRNAs have been reported to play crucial roles in oncogenesis and progression of TC, including cell proliferation, motility, invasion, and metastasis. Meanwhile, lncRNAs can be applied as potential biomarkers and therapeutic targets for TC[8-10].

Located on human chromosome 19p13.12 positive strand, urothelial cancer associated 1 (UCA1) was initially discovered and investigated in bladder cancer. Previous studies[11] have indicated that UCA1 functions as an oncogene in bladder cancer by promoting cell proliferation and metastasis. Recently, UCA1 has emerged as a novel regulator in the initiation and progression of various cancers. Through suppressing miR-204-5p expression, UCA1 promotes cell proliferation and drug resistance in colorectal cancer[12]. Induced by SP1, UCA1 facilitates the proliferation of gastric cancer cells through recruiting EZH2 and activating the AKT pathway[13]. Furthermore, UCA1 functions as an oncogene in pancreatic cancer *via* promoting tumor growth and cell metastasis by sponging miR-135a[14].

In this study, we found that UCA1 was significantly up-regulated in both TC tissues and cell lines. After UCA1 was knocked down, TC cell

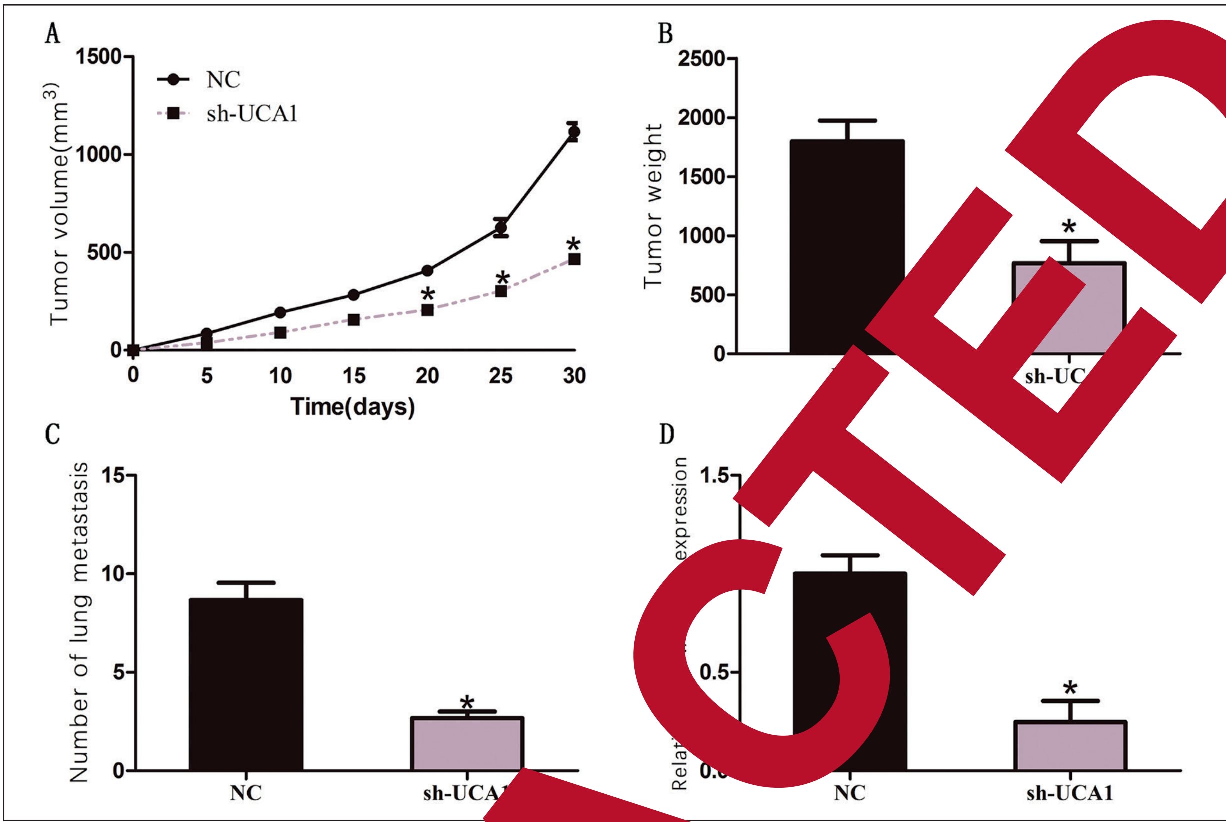


Figure 5. Knockdown of UCA1 inhibited tumor fo[illegible]n and [illegible]C *in vivo*. **A,** Tumor size in sh-UCA1 group was significantly smaller than that of NC group. **B,** The w[illegible]f d[illegible]ed tu[illegible]rs in sh-UCA1 group was markedly smaller when compared with NC group. **C,** The number of metastati[illegible]n lung tissues of sh-UCA1 group was significantly reduced when compared with NC group. **D,** UCA1 was lowly ex[illegible]d in dissected tumors of sh-UCA1 group compared with NC group. *p<0.05, as compared with co[illegible]

proliferation, migration, a[illegible]vasion [illegible]e markedly inhibited. The abo[illegible]lts i[illegible] UCA1 acted as an onc[illegible] promoted tumorigenesis of T[illegible]

In recent year[illegible]e interactio[illegible]een lncRNA/miRNA [illegible]l networks h[illegible]ttracted much attenti[illegible]hro[illegible]rgeting miR-20b, lncRNA CA[illegible]TA1 enhanc[illegible] proliferation and mobility i[illegible]east cancer[15]. B[illegible]ging miR-211-3p, lnc[illegible] SNHG15 enhances the proliferation, migr[illegible], and [illegible]sion of human breast cancer cel[illegible]y ne[illegible]vely re[illegible]lating the expression of mi[illegible]429, l[illegible]A ILF3-AS1 facilitates the [illegible]eratio[illegible]nvasion, and migration [illegible]noma[illegible] this study, bioinformatics soft[illegible] was us[illegible] predict the possible targeted [illegible]RNAs of UCA1. MiR-497-3p, a highly co[illegible]A on the human chromosome [illegible]3.1, was selected from predicted miRNAs [illegible]ts important role in various cancers[18-20]. Our re[illegible]ndicated that miR-497-3p expression was sig[illegible]ntly down-regulated after the knockdown of UCA1. Subsequent luciferase reporter gene assay showed that miR-497-3p could directly bind to UCA1. By conducting tumor formation and metastasis assays, we found that the knockdown of UCA1 also inhibited tumor formation and metastasis *in vivo*. All the above results suggested that UCA1 might promote tumorigenesis of TC *via* sponging miR-497-3p.

Conclusions

We identified that LncRNA UCA1 enhances TC cell proliferation and metastasis through sponging miR-497-3p. Our findings suggest that UCA1 may contribute to therapy for TC as a target candidate.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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