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Long Non-Coding RNA (lncRNA) Urothelial Carcinoma-Associated 1 (UCA1) Enhances Tamoxifen Resistance in Breast Cancer Cells via Inhibiting mTOR Signaling Pathway

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Long non-coding RNA (lncRNA) UCA1 is an oncogene in breast cancer. The purpose of this study was to investigate the role of UCA1 in tamoxifen resistance of estrogen receptor positive breast cancer cells.

Material/Methods: Tamoxifen sensitive MCF-7 cells were transfected for UCA1 overexpression, while tamoxifen resistant LCC2 and LCC9 cells were transfected with UCA siRNA for UCA1 knockdown. qRT-PCR was performed to analyze UCA1 expression. CCK-8 assay, immunofluorescence staining of cleaved caspase-9, and flow cytometric analysis of Annexin V/PI staining were used to assess tamoxifen sensitivity. Western blot analysis was performed to detect p-AKT and p-mTOR expression.

Results: LncRNA UCA1 was significantly upregulated in tamoxifen resistant breast cancer cells compared to tamoxifen sensitive cells. LCC2 and LCC9 cells transfected with UCA1 siRNA had significantly higher ratio of apoptosis after tamoxifen treatment. UCA1 siRNA significantly decreased the protein levels of p-AKT and p-mTOR in LCC2 and LCC9 cells. Enforced UCA1 expression substantially reduced tamoxifen induced apoptosis in MCF-7 cells, while rapamycin treatment abrogated the protective effect of UCA1.

Conclusions: UCA1 upregulation was associated with tamoxifen resistance in breast cancer. Mechanistically, UCA1 confers tamoxifen resistance to breast cancer cells partly via activating the mTOR signaling pathway.

MeSH Keywords: Inflammatory Breast Neoplasms • RNA, Long Noncoding • Tamoxifen • TOR Serine-Threonine Kinases

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Background

Tamoxifen, an antagonist of the estrogen receptor (ER), is a therapeutic agent currently used for the breast cancer patients with ER positive tumors [1–3]. During the past decades, the use of tamoxifen has significantly improved disease free survival and overall survival of breast cancer patients [1–4]. However, intrinsic or acquired tamoxifen resistance is still a major cause of therapeutic failure, leading to cancer recurrence and cancer related death [1,5,6]. Therefore, investigation into the molecular mechanism of tamoxifen resistance is warranted.

Long non-coding RNAs (lncRNAs) are evolutionarily conserved non-protein coding RNAs greater than 200 nucleotides [7]. Recent studies suggest that dysregulated RNAs are also involved in regulation of tamoxifen sensitivity in breast cancer cells [8]. For example, lncRNA HOTAIR overexpression in breast cancer cells can activate the ER transcriptional program even under hormone-deprived conditions [9]. HOTAIR depletion can significantly impair cell growth and abolish tamoxifen-resistance [9].

Urothelial carcinoma-associated 1 (UCA1) is an lncRNA with three exons that encode a 1.4 kb isoform and a 2.2 kb isoform [10]. The oncogenic role of UCA1 was initially observed in bladder cancer [11]. In colorectal cancer, UCA1 can enhance cell proliferation and 5-fluorouracil resistance by inhibiting miR-204-5p [12]. Several recent studies found that UCA1 also has oncogenic effect in breast cancer [10,13]. For example, UCA1 can promote breast tumor growth by suppression of p27 [10]. Inhibition of UCA1 using shRNA significantly reduces the invasiveness of breast cancer cells [14]. In addition, UCA1 can also promote breast cancer cell growth and reduce cell apoptosis via decreasing tumor suppressive miR-143 [15]. Besides this oncogenic effect, previous studies also reported that UCA1 can induce acquired resistance to EGFR-TKIs in EGFR-mutant non-small cell lung cancer by activating the AKT/mTOR pathway [16]. UCA1 can activate Wnt signaling in a Wnt6-dependent manner, which leads to increased chemoresistance of bladder cancer cells [17]. In fact, activation of AKT/mTOR signaling pathway has been considered a contributor to tamoxifen resistance [18–21]. Therefore, we hypothesized that UCA1 upregulation might be related to enhanced tamoxifen resistance in ER positive breast cancer cells.

Material and Methods

Cell culture

The ER positive and tamoxifen-sensitive human breast cancer cell line MCF-7 cells were obtained from ATCC (Manassas, VA, USA). The MCF-7 derived tamoxifen-resistant LCC2 and LCC9 cells were obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). All of the cancer cells were grown in RPMI 1640 medium supplemented with 10% FBS, 2 mM glutamine, 100 U/mL penicillin and 100 μg/mL of streptomycin, and cultured in an incubator with humidified atmosphere and 5% CO_2 at 37°C.

Plasmid preparation and cell treatment

UCA1 siRNAs and the scramble negative controls were designed and synthesized by RiBoBio (Guangzhou, China). LCC2 and LCC9 cells were transfected with 100 nM UCA1 siRNAs using Hiperfect transfection reagent (QIAGEN, GmbH, Hilden, Germany) according to manufacturer's instruction. The LCC2 and LCC9 cells with or without UCA1 inhibition were further subjected to treatment with 20 μM tamoxifen for 72 hours.

The lentiviral vector expression the 1.4 kb isoform UCA1 was generated as described in a previous study [15]. The lentiviral particles for transfection were produced by co-transfection with pPACKH1 Lentivector Packaging Kit (System Biosciences, Mountain View, CA, USA) to HEK 293T cells according to manufacturer's instruction. MCF-7 cells were infected with the lentiviral particles for UCA1 overexpression.

For rapamycin (Rapa, Sigma-Aldrich, Saint Louis, MO, USA) treatment, MCF-7 cells with UCA1 overexpression were subjected to treatment with 1 μM tamoxifen with or without 10 nM rapamycin for 72 hours.

qRT-PCR

Total RNA in cell samples were extracted using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to manufacturer's instructions. cDNA was reversely transcribed using the PrimeScript® RT reagent kit (TaKaRa, Dalian, Liaoning, China). The UCA1 expression level was quantified using the following primers: forward: 5'-TTTGCCAGCCTCAGCTTAAT-3'; reverse: 5'-TTGTCCCCATTTTCCATCAT-3' and SYBR® Premix DimerEraser kit (TaKaRa, Dalian, Liaoning, China) in an ABI Prism 7500 (Applied Biosystems, Foster City, CA, USA). GAPDH was used as the endogenous control gene. The results of qRT-PCR analysis were calculated using the $2^{-\Delta\Delta CT}$ method.

CCK-8 assay of cell viability

MCF-7 cells infected with UCA1 lentiviral particles and LCC2 and LCC9 cells transfected with UCA1 siRNA were seeded in a 96-well plate (3,000 cells per well) for 24 hours and then replaced by 200 μL full growth medium with varying concentrations of tamoxifen (0.1, 0.5, 1, 5, 10, 15, 20 50 μmol/L) for three days. The MCF-7 cells with UCA1 overexpression were cultured with or without the presence of 10 nM rapamycin.

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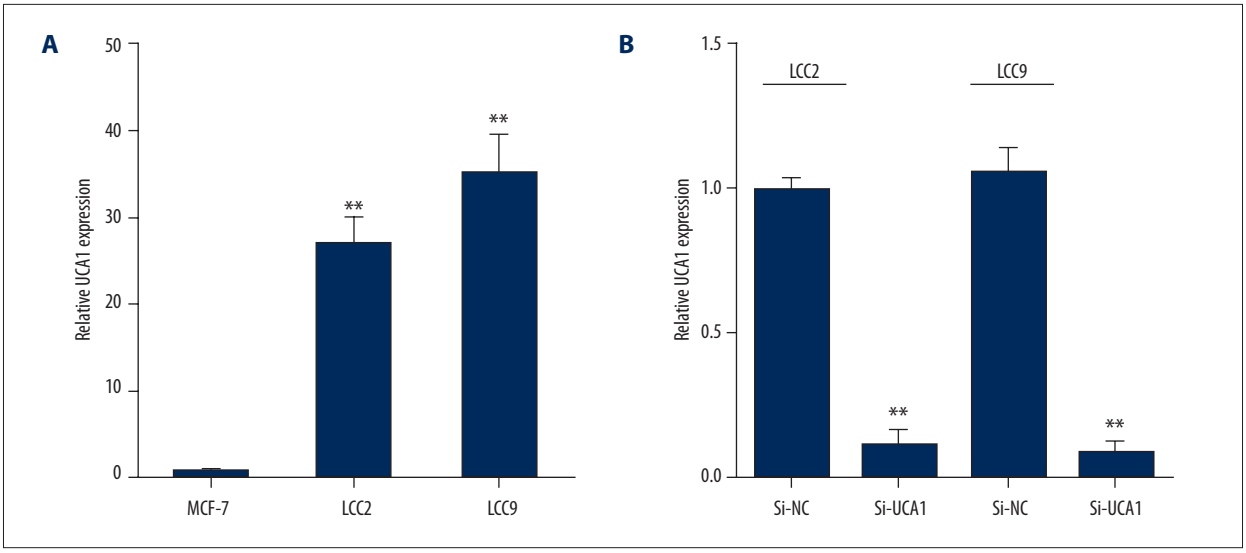

Figure 1. LncRNA UCA1 is significantly upregulated in tamoxifen resistant breast cancer cells. (**A**) qRT-PCR analysis of UCA1 expression in tamoxifen sensitive MCF-7 cells and in tamoxifen resistant LCC2 and LCC9 cells. (**B**) qRT-PCR analysis of UCA1 expression in LCC2 and LCC9 cells with or without transfection of UCA1 siRNA. ** $p<0.01$.

Then, cell viability was measured using WST-8 assay using Cell Counting Kit-8 (CCK-8, Dojindo, Tokyo, Japan) according to manufacturer's instruction.

Immunofluorescent staining

LCC2 and LCC9 cells after transfection were grown on coverslips (174950, Thermanox, Thermo Fisher) and were further treated with 10 μM tamoxifen for 72 hours. Then, the cells were fixed, permeabilized in 0.1% Triton X-100 and blocked in 1% BSA. Then, the cover slips were incubated with antibodies against cleaved caspase-9 at Asp315 (1: 500, PA5-17913, Thermo Fisher) at 4°C overnight. After washing, the coverslips were incubated in a secondary Alexa Fluor-555-labeled goat anti-rabbit IgG (#4413, Cell Signaling) for 30 minutes at room temperature in the dark. Cover slips were mounted with mounting media (ab104139, Abcam), which contained DAPI to stain the nuclei. The number of positive stained cells were scored by counting three sets of at least 100 cells under the microscope.

Flow cytometric analysis

Cell apoptosis was assessed using the Annexin V-FITC Apoptosis Detection Kit (JingMei Biotech, Beijing, China), according to the manufacturer's instructions. In brief, 100 μL cell suspension containing 1×10^5 cells were prepared. Then 5 μL Annexin V-FITC and 10 μL propidium iodide (PI) (20 μg/mL) were added and incubated in the dark for 15 minutes at room temperature. Then the ratio of apoptotic cells were analyzed using a FACSCaliber flow cytometry (BD Biosciences, Franklin Lakes, NJ, USA). Each test was performed with at least three repeats.

Western blot analysis

Cell samples were lysed using a lysis buffer (P0013, Beyotime, Shanghai, China). Then the protein concentration was quantified using a BCA protein assay kit (Beyotime). A conventional western blot was performed. Primary antibodies used included anti-phospho-AKT (1: 2,000, ab133458, Abcam, Cambridge, UK), anti-AKT (1: 1,000, EPR16798, Abcam), anti-phospho-mTOR (1: 2,000, ab109268, Abcam) and anti-mTOR (1: 2,000, ab2732, Abcam) and anti-β-actin (1: 2,000, ab8227, Abcam). After that, the membranes were incubated with corresponding HRP conjugated secondary anti-bodies.

The blot signals were visualized using the ECL Western blotting substrate (Promega, Madison, WI, USA). The relative gray scale of the bands were analyzed using ImageJ software.

Statistical analysis

Data are presented in the form of means ± standard deviation (SD) based on at least three repeats of three independent experiments. Comparison between groups was performed using the unpaired *t*-test. A two-sided *p* value of <0.05 was considered statistically significant.

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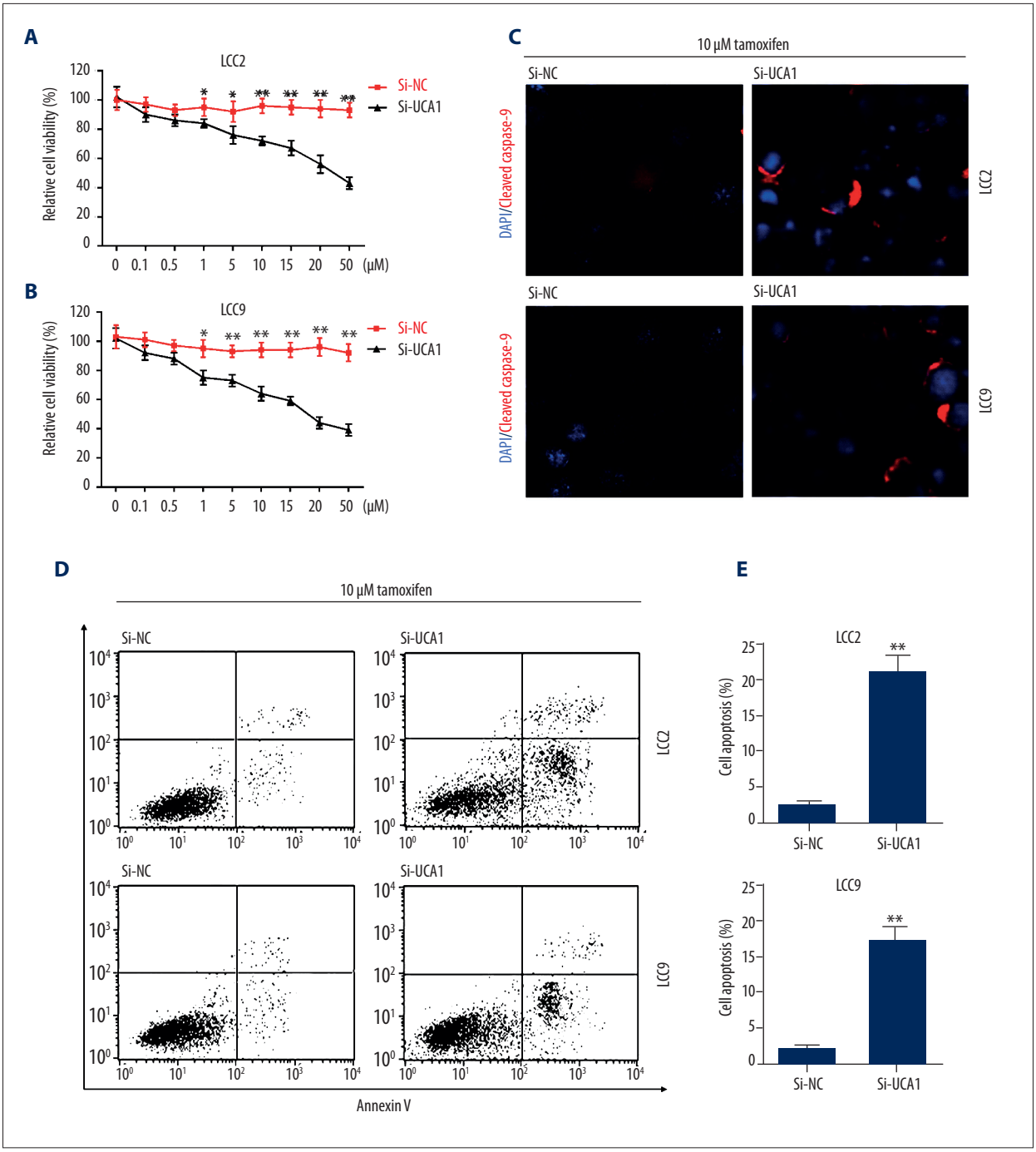

Figure 2. UCA1 knockdown sensitize breast cancer cells to tamoxifen. (**A, B**) CCK-8 assay of cell viability of LCC2 (**A**) and LCC9 (**B**) cells with or without UCA1 knockdown after treatment with varying concentrations of tamoxifen (0.1, 0.5, 1, 5, 10, 15, 20, and 50 μmol/L) for three days. (**C**) Typical images of the cleaved caspase-9 labeled by Alexa Fluor-555-labeled antibody (red color) and the nuclei stained by DAPI (blue color). (**D, E**) Representative images (**D**) and quantitation (**E**) of flow cytometric analysis of apoptotic LCC2 and LCC9 cells with or without UCA1 knockdown after treatment with 10 μM of tamoxifen for three days. * $p<0.05$; ** $p<0.01$.

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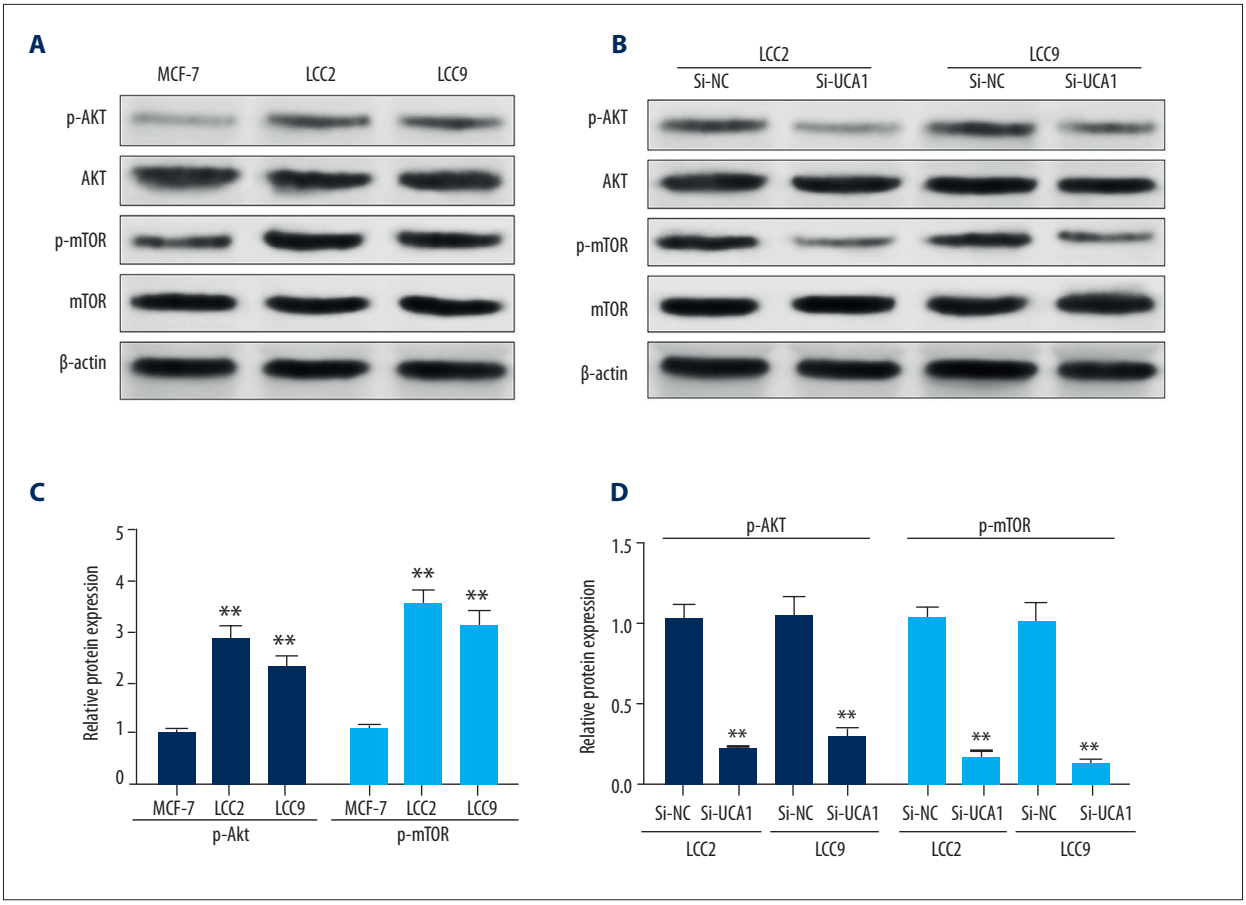

Figure 3. UCA1 activates mTOR signaling pathway in breast cancer cells. (**A–D**) Western blot analysis images (**A, B**) and quantitation of the relative gray scale (**C, D**) of the expression of p-AKT and p-mTOR in MCF-7, LCC2 and LCC9 cells (**A, C**) and in LCC2 and LCC9 cells with or without transfection of UCA1 siRNA (**B, D**). ** $p<0.01$.

Results

LncRNA UCA1 was significantly upregulated in tamoxifen resistant breast cancer cells

UCA1 has been reported as an oncogenic lnRNA in breast cancer [10,14] and can also enhance chemoresistance in some cancers [12,16]. However, whether UCA1 is involved in regulation of tamoxifen sensitivity in breast cancer cells is not clear. In this study, we first studied the expression of UCA1 in tamoxifen sensitive MCF-7 cells and in tamoxifen resistant LCC2 and LCC9 cells. The qRT-PCR results showed that LCC2 and LCC9 cells had a more than 20-fold increase in UCA1 expression compared to the precursor MCF-7 cells (Figure 1A). Transfection of UCA1 siRNA significantly decreased UCA1 level in LCC2 and LCC9 cells (Figure 1B).

UCA1 knockdown sensitized breast cancer cells to tamoxifen

By performing CCK-8 assays, we observed that both LCC-2 and LCC-9 cells with UCA1 knockdown had significantly decreased cell viability after tamoxifen treatment (Figure 2A, 2B). Immunofluorescent staining showed that UCA1 siRNA also significantly increased tamoxifen induced expression of cleaved caspase-9 in the cells (Figure 2C). To further verify the effect of UCA1 knockdown on tamoxifen sensitivity, the cells were subjected to flow cytometric analysis of Annexin V/PI staining. The results showed that LCC2 and LCC9 cells transfected with UCA1 siRNA had a significantly higher ratio of apoptosis after 10 μM tamoxifen treatment (Figure 2D, 2E).

UCA1 activated mTOR signaling pathway in breast cancer cells

By performing Western blot analysis, we confirmed substantially higher expression of p-AKT and p-mTOR in LCC2 and LCC9 cells than in MCF-7 cells (Figure 3A, 3C). UCA1 siRNA

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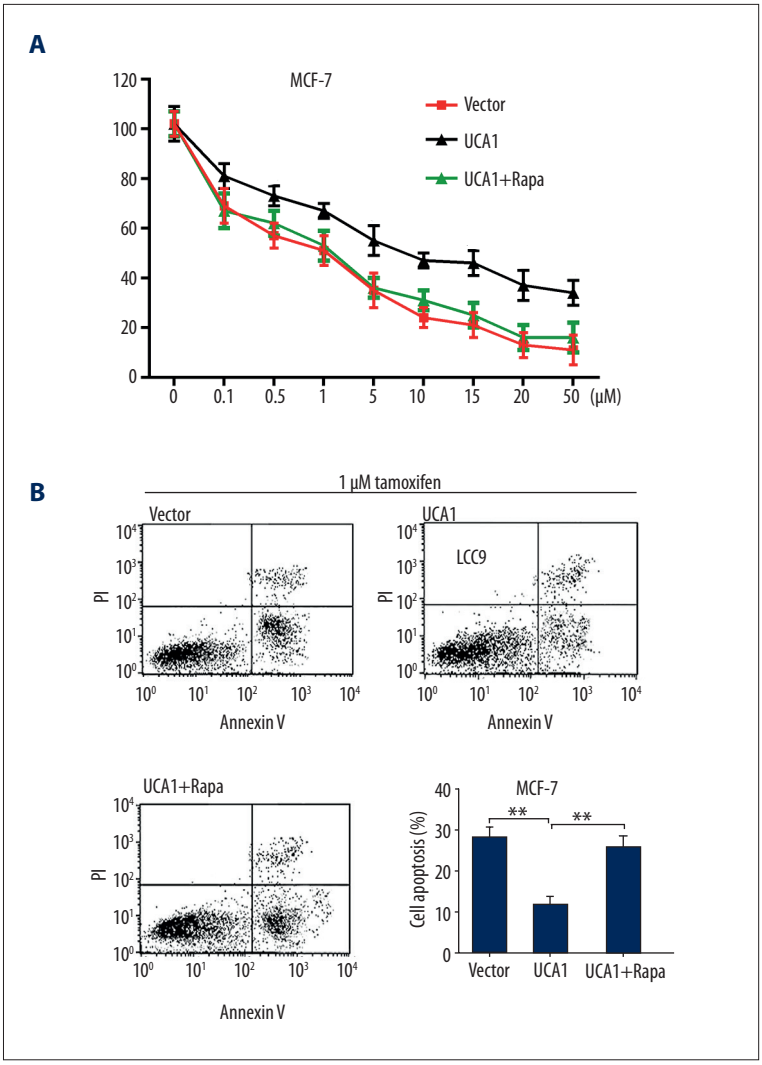

Figure 4. UCA1 reduces tamoxifen sensitivity of breast cancer cells partly via activating mTOR signaling. (**A, B**). CCK-8 assay of cell viability of MCF-7 cells with or without UCA1 overexpression after treatment with varying concentrations of tamoxifen (0.1, 0.5, 1, 5, 10, 15, 20, and 50 μmol/L) for three days. Comparison of cell viability was performed between UCA1 and UCA1+Rapa groups. (**B**) Representative images and quantitation of flow cytometric analysis of apoptotic MCF-7 cells with or without UCA1 overexpression after treatment with 1 μM of tamoxifen for 3 days. * $p<0.05$; ** $p<0.01$

significantly decreased the expression of p-AKT and p-mTOR in LCC2 and LCC9 cells (Figure 3B, 3D).

UCA1 enhanced tamoxifen resistance of breast cancer cells partly via activating mTOR signaling

To further study the role of UCA1 in tamoxifen sensitivity of breast cancer cells, MCF-7 cells were infected with UCA1 expression lentiviral particles and then subjected to tamoxifen treatment with or without the presence of rapamycin. CCK-8 assays showed that UCA1 overexpression markedly reduced tamoxifen sensitivity of MCF-7 cells (Figure 4A). However, rapamycin treatment abrogated the protective effect of UCA1 overexpression (Figure 4A). By performing flow cytometric analysis, we also observed that enforced UCA1 expression substantially reduced tamoxifen induced apoptotic MCF-7 cells (Figure 4B), while rapamycin treatment canceled the protective effect of UCA1 (Figure 4B).

Discussion

UCA1 is an lncRNA involved in modulation of drug sensitivity in multiple types of cancer. For example, UCA1 can induce acquired resistance to EGFR-TKIs in EGFR-mutant non-small cell lung cancer by activating the AKT/mTOR pathway [16]. It can also increase chemoresistance of bladder cancer cells via activating the Wnt signaling pathway in a Wnt6-dependent manner [17]. Knockdown of UCA1 in Adriamycin resistant SGC7901/ADR cells can significantly decrease the resistance [22]. These findings suggest that UCA1 might be an important lncRNA modulating drug sensitivity. However, the underlying mechanisms are largely unknown. In this study, we first compared the expression of UCA1 between tamoxifen resistant and sensitive breast cancer cells. The results showed that the tamoxifen resistant LCC2 and LCC9 cells had significantly higher expression of UCA1 than the parent MCF-7 cells. Then, we further investigated the effect of UCA1 on tamoxifen resistance in the cells. Our data showed that both LCC-2 and LCC-9 cells with

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UCA1 knockdown had significantly decreased cell viability, increased expression of cleaved caspase-9, and higher ratio of apoptosis after tamoxifen treatment. Therefore, we decided to further investigate the underlying mechanism.

Recent studies revealed dysregulated lncRNAs are involved in modulation of drug sensitivity in breast cancer via multiple mechanisms. For example, the lncRNA ATB is positively correlated with trastuzumab resistance of breast cancer patients [23]. Functionally, it can competitively bind with miR-200c and lead to upregulation of miR-200c target gene ZEB1 and ZNF-217, resulting in enhanced epithelial-to-mesenchymal transition [23]. GAS5 downregulation in HER2-positive SKBR-3 cells is associated with enhanced cell proliferation and trastuzumab-resistance [24]. Functionally, GAS5 can act as a molecular sponge for miR-21, leading to the decreased expression of phosphatase and tensin homologs (PTEN) [24]. HOTAIR overexpression in breast cancer cells is associated with enhanced cell proliferation, whereas HOTAIR depletion significantly reduces cell survival and abolishes tamoxifen-resistant cell growth [9]. Mechanistically, HOTAIR is a direct target of ER-mediated transcriptional repression [9]. Therefore, its expression is restored after tamoxifen induced blockade of the ER signaling [9].

Previous studies reported that UCA1 upregulation can lead activation of the AKT/mTOR pathway in multiple types of cancer cells [16,25]. In addition, mTOR inhibition can effectively restore the susceptibility of ER positive breast cancer cells to tamoxifen [20]. Inhibition of the AKT/mTOR signaling has been considered an effective strategy to overcome tamoxifen resistance in breast cancer cells [18,26]. Actually, some non-coding RNAs such as miRNAs with regulative effect on mTOR signaling pathway can modulate tamoxifen sensitivity of breast cancer cells. For example, miR-21 inhibition can enhance sensitivity of breast cancer cells to tamoxifen by enhancing autophagic cell death through inhibition of the PI3K-AKT-mTOR pathway [19]. Overexpression of miR-451a can increase sensitivity of breast cancer cells to tamoxifen by reducing the activation of p-AKT and p-mTOR [27]. Therefore, we hypothesized that UCA1 might regulate tamoxifen sensitivity via the AKT/mTOR signaling pathway. Our data showed that LCC2 and LCC9 had significantly higher basal expression of p-AKT and p-mTOR than MCF-7 cells. UCA1 siRNA significantly decreased the expression of p-AKT and p-mTOR in LCC2 and LCC9 cells. These results suggest that UCA1 can activate mTOR signaling pathway in breast cancer cells. The following functional study showed that rapamycin, an mTOR inhibitor significantly abrogated the protective effect of UCA1 on MCF-7 cells when treated with tamoxifen, suggesting that UCA1 reduces tamoxifen sensitivity of breast cancer cells partly via activating mTOR signaling pathway.

Conclusions

UCA1 upregulation was associated with tamoxifen resistance in breast cancer. Mechanistically, UCA1 confers tamoxifen resistance to breast cancer cells partly via activating the mTOR signaling pathway.

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