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Long non-coding RNA UCA1 regulates the proliferation, migration and invasion of human lung cancer cells by modulating the expression of microRNA-143

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Abstract. – OBJECTIVE: Accounting for 25% of all the cancers and 20% of the cancer-related mortality, lung cancer is one of the devastating types of cancers. Due to an increase in the incidence of lung cancer and limited treatment options, there is a pressing need to look for novel drug options and to identify potential therapeutic targets. Long non-coding RNAs (LncRNAs) have been considered to be important therapeutic targets due to their plethora of cellular roles. Herein, we investigated the therapeutic potential of UCA1 in lung cancer and also attempted to examine the underlying mechanism through UCA1 exerts its growth inhibitory effects on cancer cells.

MATERIALS AND METHODS: The quantitative Reverse-Transcriptase Polymerase Chain Reaction (qRT-PCR) was used to perform the expression analysis. The CCK-8 assay was used to monitor the growth of the cells. The AO/EB assay was used to check apoptosis and flow cytometry was used for cell cycle distribution. The wound heal and transwell assays were used to monitor the cell migration and invasion.

RESULTS: It was found that the lncRNA UCA was significantly ($p < 0.05$) upregulated in the lung cancer cells and silencing of UCA1 could inhibit the proliferation of the SK-MES-1 lung cancer cells via induction of G2/M cell cycle arrest and apoptosis. Moreover, UCA1 silencing could also suppress the migration and invasion of the SK-MES-1 cells. The LncRNA UCA1 was also found to upregulate the expression of miR-143, and overexpression of miR-143 could also suppress the proliferation, migration, and invasion of the SK-MES-1 lung cancer cells. Both UCA1 silencing and miR-143 overexpression could cause a significant decrease in the expression of mitogen-activated protein kinase 1 (MAPK1). Therefore, it is concluded that UCA1 regulates the growth of the SK-MES-1 lung cancer by inhibition of MAPK1 via miR-143 upregulation.

CONCLUSIONS: UCA1, as well as miR-143, may be essential therapeutic targets for the management of lung cancer and warrant further investigations.

Key Words:
Lung cancer, Migration, Long non-coding RNAs, microRNA, Apoptosis.

Introduction

Long non-coding RNAs include >200 base pair long RNA molecules that do not code for any `protein[1]. Accumulating evidence has indicated that lncRNAs play a plerotha of roles in human cells[2]. Further, lncRNAs have also been implicated in the onset and development of several dreadful diseases such as cancer[3]. The expression of lncRNAs has been reported to be dysregulated in cancer cells[4]. Owing to the role of lncRNAs in the regulation of gene expression at transcriptional, post-transcriptional and via epigenetic mechanisms, they have been shown to be involved in the development and tumorigenesis of several cancer types[4]. LncRNAs have been reported to act as both as oncogenes and tumor-suppressors[5]. Among lncRNAs, UCA1 has been shown to be overexpressed in cancer cells and has been found to regulate the growth of breast and gastric cancer to name a few[6,7]. Further, UCA1 has been shown to regulate the proliferation and migration of the lung cancer cells[8]. However, the exact mechanism is yet to be explored. Herein, the role and therapeutic potential of lncRNA UCA1 were examined in the lung cancer cells and the underlying mechanism

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by which UCA1 regulates the growth of lung cancer cells was also investigated. Lung cancer causes significant mortality and morbidity across the globe[9]. It has been reported that more than one and a half million people died of lung cancer across the world in 2012[10]. The incidence of lung cancer is increasing at an alarming rate and it has been estimated that lung cancer associated deaths will increase to 3 million in 2035[11]. The lack of potent chemotherapy, therapeutic targets, and late diagnosis are the major obstacles in the treatment of lung cancer[12]. Herein, we found that the expression of lncRNA UCA1 was significantly ($p < 0.05$) upregulated in human lung cancer cells. Silencing of lncRNA UCA1 expression caused inhibition of the SK-MES-1 lung cancer cells via induction of apoptotic cell death and G_2/M cell cycle arrest. Further, silencing of UCA1 also caused considerable suppression of the migration and invasion of the lncRNA UCA1 in the SK-MES-1 cells. The exploration of the underlying mechanism revealed that UCA1 suppression causes enhancement in the expression of the microRNA (miR)-143. Further, ectopic expression of miR-143 resulted in the inhibition of the growth, migration, and invasion of the SK-MES-1 cells, similar to that of lncRNA UCA1. Finally, miR-143 overexpression also caused inhibition of the MAPK1 expression. It can be concluded that lncRNA UCA1 regulates the proliferation, migration, and invasion of lung cancer cells by suppressing the expression of MAPK1 via upregulation of miR-143 expression.

Materials and Methods

Cell Lines and Culture Conditions

The lung cancer cell lines (SK-MES-1, DMS-79, DMS-53, SHP-77, A549, A427, LA-4) and normal cell line (MRC5) were purchased from the Cell Bank of Type Culture Collection of Chinese Academy of Sciences (CBTCCCAS, Shanghai, China). The cells were cultured using Dulbecco's Modified Eagle Medium (DMEM) composed of 10% fetal bovine serum (FBS), 1 mM L-glutamine, 1% HEPES buffer, 1 U/mL penicillin-streptomycin (all obtained from Gibco Laboratories, Grand Island, NY, USA) at a temperature of 37°C under 5% CO_2 The percentage of passage cells were maintained at a confluence of 80-85% and the cell culture medium was changed every 24 h. The Ethics Committee of Shengjing Hospital of China Medical University approved the investigation under approval number CHM/A27C523/2018.

Expression Analysis

The total RNA was extracted from the primary lung cancer cell lines and normal cell line with the assistance of RNeasy kits (Qiagen Inc., Hilden, Germany). To reverse transcribe the cDNA, the Omniscript RT (Qiagen Inc.) was employed using 1 µg of the extracted RNA. The cDNA was then used as a template for qRT-PCR analysis with the assistance of the Taq PCR Master Mix kit (Qiagen Inc.) according to the manufacturer's protocol. The reaction mixture consisted of 20 µl containing 1.5 mM $MgCl_2$, 2.5 units *Taq* DNA Polymerase, 200 µM dNTP, 0.2 µM of each primer and 0.5 µg DNA. The cycling conditions were as follows: 95°C for 20 sec, followed by 40 cycles of 95°C for 15 sec, and 58°C for 1 min. GAPDH (glyceraldehyde 3-phosphate dehydrogenase) was used as an internal control and the relative quantification ($2^{-\Delta\Delta Cq}$) method was used to evaluate the quantitative variation between the samples as described previously[13].

Cell Transfection

When the lung SK-MES-1 cancer cells reached 80% confluence, they were transfected with mimics-negative control (NC), Si-UCA1 or miR-143 mimics obtained from Shanghai GenePharma (Shanghai, China; 10 pmol), with Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific Inc. Waltham, MA, USA) as per the manufacturer's protocol.

Cell Counting Kit-8 (CCK-8) Assay

After 48 h of transfection, the lung cancer SK-MES-1 cells were grown in 96-well plates in three replicates at the density of 1.0×10^3 cells/well. The viability of the SK-MES-1 cells was determined by Cell Counting Kit-8 (Sigma-Aldich, Hong Kong, China) following the guidelines of the manufacturer. Around 10 µL CCK-8 reagent was added into the wells at specific time intervals (0, 12, 24, 48, and 96 h) and the plates were then subjected to incubation for about 2 h at 37°C. The cell viability was then measured by taking the absorbance at 450 nm.

Acridine Orange/Ethidium Bromide (AO/EB) Staining

For AO/EB staining, the transfected lung cancer SK-MES-1 (0.6×10^6) were grown in 6 well

plates. Following an incubation period of around 12 hours, the SK-MES-1 cells were subjected to incubation for 24 h at 37°C. As the cells sloughed off, 25 µl cell cultures were put onto glass slides and subjected to staining with a solution (1 µl) of AO and EB. The slides were covered with coverslips and examined with a fluorescent microscope.

Cell Cycle Analysis

After transfection, the SK-MES-1 cells were incubated at 37°C for 24 h. The cells were subjected to washing with phosphate buffered saline (PBS). Afterwards, the SK-MES-1 cells were stained with Propidium Iodide (PI) and the distribution of the cells in cell cycle phases was assessed by FACS flow cytometer.

Cell Invasion and Wound Heal Assays

The invasion abilities of the transfected SK-MES-1 lung cancer cells were examined by transwell chamber assay. In brief, 1×10^4 SK-MES-1 cells were seeded in the upper chamber of the transwell 8 µm pore size polycarbonate filters. This was followed by the placement of the chambers into 24-well plates and subjected to incubation at 37°C for 48 h. The inserts were coated with extracellular matrix gel (50 µl) (ECM, Sigma-Aldrich, Hong Kong, China). Swabbing was performed to remove the non-invaded cells from the upper surface. However, the invaded cells on the lower surface were subjected to fixation with methanol (70%) for about 35 min and followed by staining with crystal violet (0.5%) for about 50 min, subjected to washing with PBS and finally counted under a light microscope (5 fields). Wound heal assay was employed to investigate the migration of the SK-MES-1 cells as described previously[14].

Statistical Analysis

The experiments were repeated thrice and the values are mean +SD. Significance was tested at $p < 0.05$. One-way ANOVA followed by Tukey's post-hoc test was used for statistical analysis with the help of GraphPad Prism 7 software (La Jolla, CA, USA).

Results

LncRNA UCA1 is Aberrantly Upregulated in Lung Cancer Cell Lines

The expression profile of miRNA-143 was investigated in normal and lung cancer cell lines by qRT-PCR (Figure 1A). It was found that UCA1 exhibited aberrant expression and was significantly upregulated ($p < 0.05$) in all the lung cancer cell lines. It was revealed that UCA1 was upregulated in lung cancer lines by up to 3.8 fold relative to the normal cell line. The highest upregulation was found in case of the SK-MES-1 cell line.

Silencing of LncRNA UCA1 in SK-MES-1 Triggers Apoptosis and Cell Cycle Arrest

Next, we sought to understand the role of UCA1 in lung cancer and for that the SK-MES-1 cells were transfected with either the Si-UCA1 mimics or NC (negative control). The silencing of UCA1 in SK-MES-1 cells was confirmed by the qRT-PCR which showed that transfection of the SK-MES-1 cells with Si-UCA1 caused around 9 fold decrease in the expression of UCA1 relative to NC transfected cells (Figure 1B). Next, the proliferation rate of the NC and Si-UCA1 SK-MES-1 transfected cells was determined by CCK-8 assay and it was found that that the transfection of Si-UCA1 in the SK-MES-1 cells caused a significant decline in the proliferation rate (Figure 1C). AO/EB of the NC and Si-UCA1 transfected cells were performed to unveil the underlying mechanism for the decrease in the proliferation rate of the Si-UCA1 transfected cells. The AO/EB staining results showed that Si-UCA1 transfection (i.e., UCA1 silencing) activated apoptotic cell death of the SK-MES-1 cells (Figure 1D). Further, the cell cycle analysis of the NC or Si-UCA1 transfected SK-MES-1 lung cancer cells was also performed and it was found that the UCA1 silencing caused the arrest of the SK-MES-1 cells at the G_2/M checkpoint of the cell cycle. These experiments indicate that lncRNA UCA1 acts a tumor suppressor in lung cancer cells and the UCA1 silencing induced inhibition of SK-MES-1 cell proliferation via apoptotic cell death and cell cycle arrest.

Silencing of LncRNA UCA1 Inhibits the Migration and Invasion of the SK-MES-1 Cells

The effects of UCA1 silencing were also examined on the migration and invasion of the SK-MES-1 lung cancer cells by wound heal and transwell chamber assays respectively. The results showed that the migration of the SK-MES-1 lung cancer was significantly ($p < 0.05$) reduced in the Si-UCA1 transfected cells as indicated by the wound heal assay (Figure 2A). The results of the transwell assay showed that the invasion

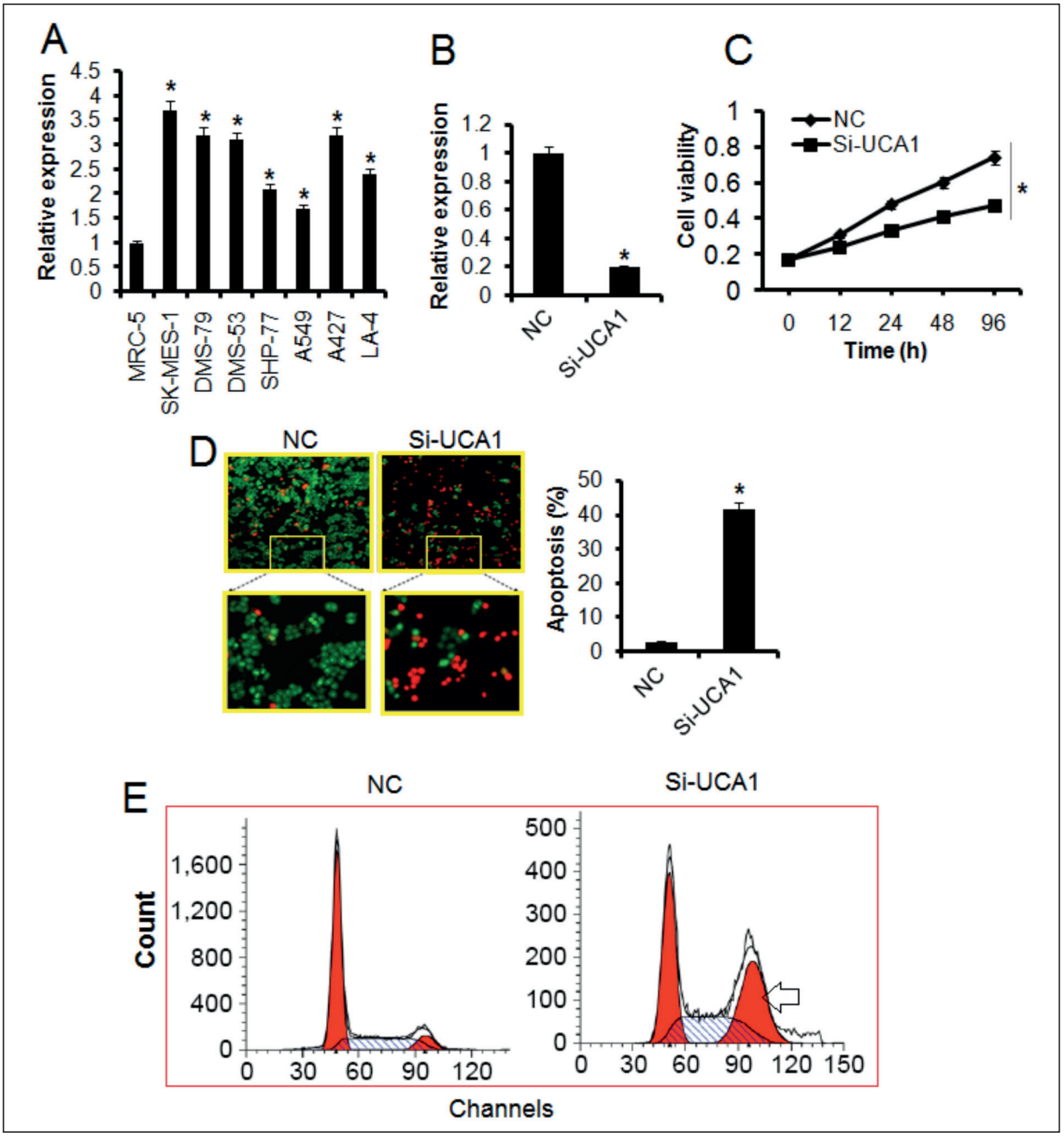

Figure 1. LncRNA UCA-1 silencing inhibits the proliferation of lung cancer cells. **A,** Expression of lncRNA UCA1 in different lung cancer cell lines and one normal cell line. **B,** Expression of UCA 1 in NC or Si-UCA1 transfected SK-MES-1 lung cancer cells. **C,** CCK-8 assay showing the % viability of the NC or Si-UCA1 transfected SK-MES-1 cells. **D,** AO/EB staining for detection of apoptosis in NC or Si-UCA1 transfected cells. **E,** Cell cycle distribution of the NC or Si-UCA1 transfected SK-MES-1 cells (Arrow depicts G_2/M phase cells) The experiments were performed in triplicate and expressed as mean ± SD (*$p < 0.05$).

of the SK-MES-1 cells was inhibited by around 60% upon silencing of UCA1 (Figure 2B). These results show that UCA1 silencing results in the inhibition of migration and invasion of the SK-MES-1 lung cancer cells.

LncRNA UCA1 Modulates the Expression of MiR-143 in SK-MES-1 Cells

The previous study[15] indicated that UCA1 regulates the proliferation and invasion of bladder cancer cells by modulating the expression

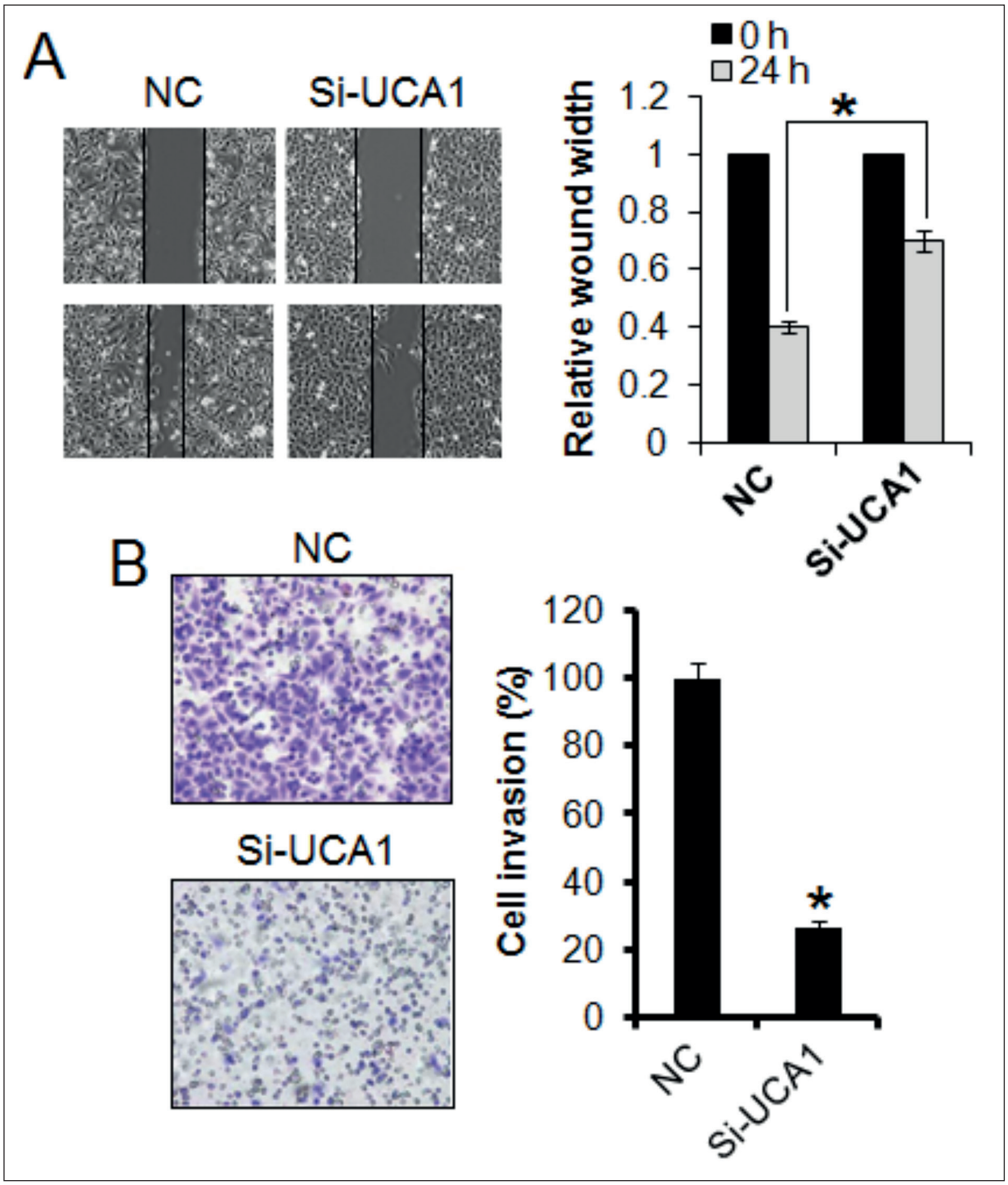

Figure 2. LncRNA UCA-1 silencing inhibits the migration and invasion of lung cancer cells. **A,** Wound heal assay showing migration of NC or Si-UCA1 transfected SK-MES-1 lung cancer cells. **B,** Transwell assay showing the invasion of NC or Si-UCA1 transfected SK-MES-1 lung cancer cells. The experiments were performed in triplicate and expressed as mean ± SD (*$p < 0.05$).

of miR-143. Therefore, the expression of miR-143 was also investigated in all the lung cancer cell lines as well as in the normal cell line. It was found that the expression of miR-143 is significantly ($p < 0.05$) upregulated in all the lung cancer cell lines (Figure 3A). However,

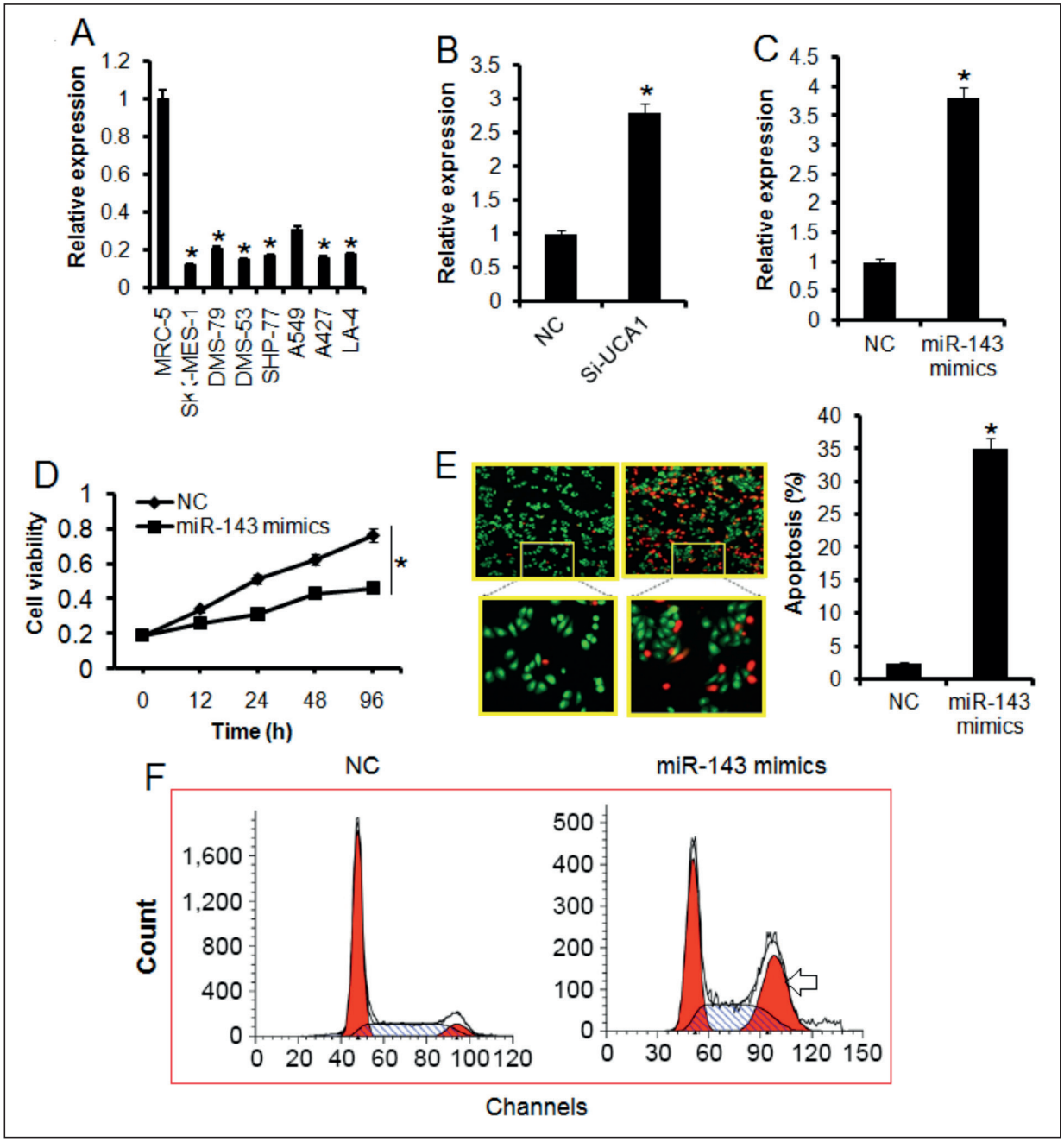

Figure 3. MiR-143 overexpression inhibits the proliferation of lung cancer cells. **A,** Expression of miR-143 in different lung cancer cell lines and one normal cell line. **B,** Expression of miR-143 in NC or miR-143 mimics transfected SK-MES-1 lung cancer cells. **C,** Expression of miR-143 in NC or miR-143 mimics transfected SK-MES-1 lung cancer cells. **D,** CCK-8 assay showing the % viability of the NC or miR-143 mimics transfected SK-MES-1 cells. **E,** AO/EB staining for detection of apoptosis in NC or miR-143 mimics transfected cells. **F,** Cell cycle distribution of the NC or miR-143 mimics transfected SK-MES-1 cells (*arrow* depicts G_2/M phase cells). The experiments were performed in triplicate and expressed as mean ± SD (*$p < 0.05$).

silencing of UCA1 expression in the SK-MES-1 lung cancer cell line caused considerable enhancement in the expression of the miR-143 (Figure 3B). Next, we overexpressed miR-143 in SK-MES-1 lung cancer cells (Figure 3C) and it was found that overexpression of miR-143 in the SK-MES-1 cells inhibited their proliferation by triggering apoptosis and G_2/M cell cycle arrest (Figure 3D-F). Further, miR-143 overexpression also suppressed the migration and

invasion of the SK-MES-1 cells (Figure 4A and B). These growth inhibitory effects of miR-143 overexpression were similar to that of UCA1 silencing. Further miR-143 has been reported[16] to modulate the expression of MAPK1. Herein, we observed that MAPK1 expression was significantly ($p < 0.05$) upregulated in all the lung cancer cells (Figure 5A). UCA1 silencing, as well as the miR-143 overexpression, caused inhibition of the MAPK1 expression in the

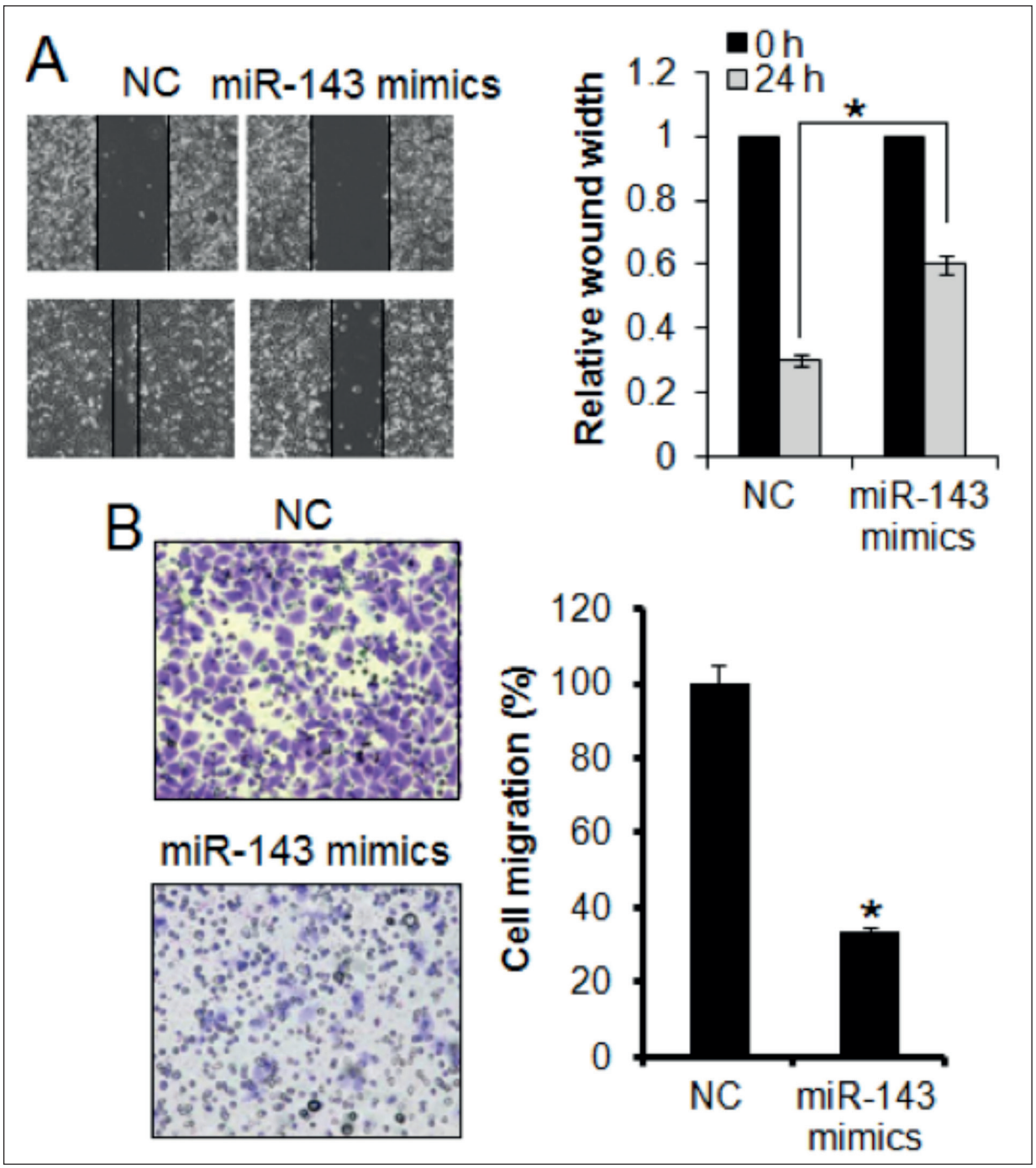

Figure 4. MiR-143 overexpression inhibits the migration and invasion of lung cancer cells. **A,** Wound heal assay showing migration of NC or miR-143 mimics transfected SK-MES-1 lung cancer cells. **B,** Transwell assay showing the invasion of NC or miR-143 mimics transfected SK-MES-1 lung cancer cells. The experiments were performed in triplicate and expressed as mean ± SD (*$p < 0.05$).

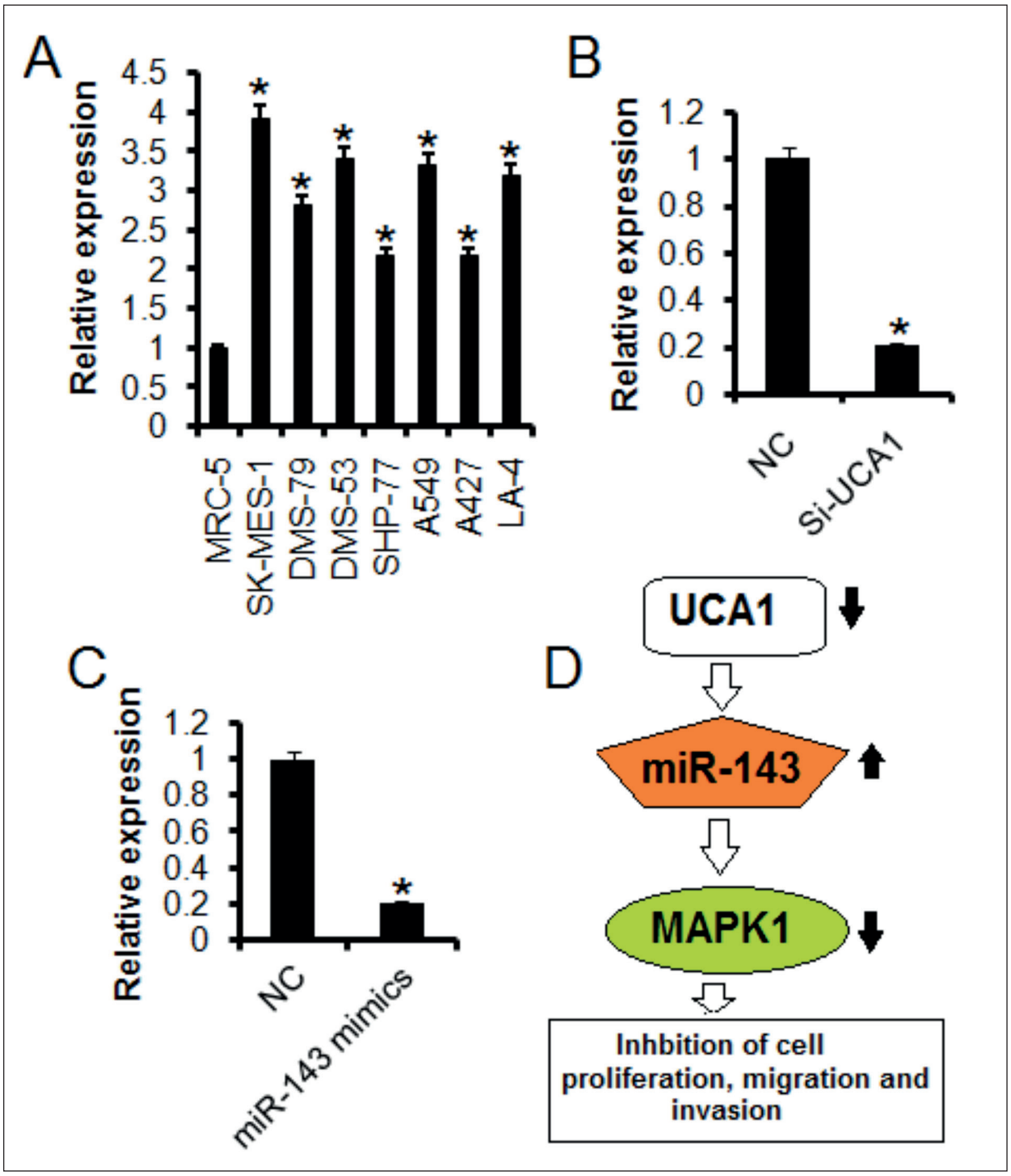

Figure 5. LncRNA UCA1 modulates the expression of MAPK1 via miR-143. **A,** Expression of MAPK1 in normal and lung cancer cell lines. **B,** Expression of MAPK1 in NC or Si-UCA1 transfected SK-MES-1 cells. **C,** Expression of MAPK1 in NC or miR-143 mimics transfected SK-MES-1 cells. **D,** Proposed model for the effects of UCA1 on SK-MES-1 lung cancer cells. The experiments were performed in triplicate and expressed as mean ± SD (*$p < 0.05$).

SK-MES-1 lung cancer cells (Figure 5B and C). These results indicate that UCA1 regulates the proliferation, migration, and invasion of the lung cancer cells by modulating the expression of MAPK1 by enhancing the expression of miR-143 (Figure 5D).

Discussion

Lung cancer is one of the devastating cancers that impose a huge disease burden on the world. Accounting for about for about 25% of all the cancers, lung cancer is the most prevalently detected cancer across the world and is responsible for about 20% of cancer-related mortality[9]. Herein, we explored the role of UCA1 in lung cancer and attempted to understand the underlying mechanism for the effects of UCA1 on the proliferation, migration and invasion of lung cancer cells. The expression of UCA1 was found to be aberrantly overexpressed in the lung cancer cells. Previous studies[17] revealed also that UCA1 is aberrantly overexpressed in bladder cancer. The suppression of UCA1 in SK-MES-1 lung cancer cells caused inhibition of their proliferation via induction of apoptotic cell death and G_2/M cell cycle arrest. These results are also in agreement with previous studies[18] wherein UCA1 has been shown to regulate the proliferation of gastric cancer cells by triggering apoptotic cell death. Further, UCA1 silencing also decreased the potential of the SK-MES-1 cells to migrate and invade. These results are similar to a previous study[19] which revealed that UCA1 could control the migration and invasion of esophageal squamous cell carcinoma. An earlier study[15] indicated that UCA1 targets miR-143 in bladder cancer cells. Therefore, we investigated the expression of miR-143 in all the lung cancer cell lines and it was found that the expression of miR-143 was significantly ($p < 0.05$) downregulated in all the lung cancer cells. However, silencing of UCA1 could enhance the expression of miR-143 in SK-MES-1 cells. Consistently, ectopic expression of miR-143 could inhibit the proliferation, migration, and invasion of the lung cancer similar to that of UAC1 silencing. These results are also supported by previous studies[20,21] wherein miR-143 has been reported to regulate the proliferation and migration of pancreatic cancer and osteosarcoma cells. The miR-143 overexpression has been reported to cause inhibition of the MAPK1 expression. Therefore, the qRT-PCR analysis was carried out which revealed MAPK1 to be upregulated in all the lung cancer cells. However, silencing of UCA1 or the overexpression of miR-143 could inhibit the expression of the MAPK1 in SK-MES-1 cells. The inhibition of the MAPK1 expression has also been shown to inhibit the growth of several cancers such as gastric cancer[22].

Conclusions

We revealed that lncRNA UCA1 is aberrantly overexpressed in the lung cancer cells. Silencing of UCA1 could suppress the proliferation, migration, and invasion of lung cancer cells by modulating the expression of MAPK1 via miR-143 upregulation. The results of the present work revealed that lncRNA could be a potential candidate for the management of lung cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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