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CircABCB10 promotes the proliferation and migration of lung cancer cells through down-regulating microRNA-217 expression

T.-Y. HU, Q.-X. ZHU, Q.-Y. DUAN, X.-Y. JIN, R. WU

Department of Clinical Oncology, Shengjing Hospital of China Medical University, Shenyang, China

Abstract. – OBJECTIVE: We aimed at studying the role and molecular mechanism of circular RNA circABCB10 in the progression of lung cancer (LCa).

PATIENTS AND METHODS: We collected LCa tissues using quantitative real-time polymerase chain reaction (qRT-PCR) technology to determine circABCB10 expression and performed survival analysis based on the clinical data of LCa patients. At the same time, the specific effects of circABCB10 on the biological function of LCa cell lines were determined by certain cell function experiments, including cell counting kit-8 (CCK-8) test, plate cloning experiment, transwell and cell wound healing assays. The downstream key gene microRNA-217 of circABCB10 was predicted through bioinformatics analysis and the potential regulation between them was confirmed by luciferase assay. microRNA-217 was knocked down in LCa cell lines to verify its important role in the progression of LCa.

RESULTS: CircABCB10 showed abnormally high expression in LCa tissues and cell lines and was related to the poor prognosis of patients. In vitro cell experiments demonstrated that knocking down circABCB10 remarkably suppressed the proliferation and migration ability of LCa cells. In addition, circABCB10 can specifically bind to microRNA-217 and negatively regulate its expression of microRNA-217 in LCa cells. Finally, cell functional experiments showed that microRNA-217 is a key downstream gene that mediates the regulation of circABCB10 on LCa cell function.

CONCLUSIONS: CircABCB10, abnormally highly expressed in LCa tissues, is able to induce the malignant progression of this cancer.

Key Words:
CircABCB10, Lung cancer, MicroRNA-217, Cell proliferation, Cell migration.

Introduction

Lung cancer (LCa) as one of the most common tumors ranks the third in the world, among which non-small cell lung cancer (NSCLC) is the most common one, accounting for about 80% of all cases[1]. At present, LCa has become the most common cause of cancer-related deaths worldwide, with approximately 1.8 million new cases and 1.59 million deaths each year[2]. The changes of many tumor suppressor genes and oncogenes are involved in the incidence of LCa, but the molecular and genetic basis of LCa still remains unclear[3-5]. Despite the emergence of new adjuvant chemotherapy regimens and targeted biologics, the prognosis of NSCLC patients is still unsatisfactory, with a low 5-year survival rate and a high recurrence rate. There is no doubt that a better understanding of its pathologic mechanisms will contribute to the development of new LCa therapy strategies.

CircRNAs (circRNAs) were originally referred to as a splicing error, which is a non-coding RNA that does not have the function of translating proteins[6,7]. Their covalent closed-loop structure is shorter than the linear 3 'and 5' terminal structure[8]. CircRNAs have been reported to affect tumor-related cellular activities, such as cell proliferation, invasion, and epithelial-mesenchymal transformation (EMT) processes[9,10]. CircRNAs play an essential part in the regulation of tumorigenesis through interaction with tumor-related microRNAs. CircRNAs can be used as regulators of microRNA sponges, splicing and transcription, and modifiers of parental gene expression[11]. Hsa_circ_001653 was found to be engaged in the progression of pancreatic cholangiocarcinoma through microRNA-377 /HOXC6 axis[12]. CircGNB1 accelerated the progress of triple negative breast cancer through the downstream microRNA-141-5p /IGF1R signal axis[13]. In gliomas, circPITX1 inhibits the glucose metabolism pathway of tumor cells and enhance[13] the sensitivity of radiotherapy through the regulation of microRNA-329-3p /NEK2 axis[14]. A new circRNA, circABCB10, has been extensively studied in var-

Corresponding Author: Rong Wu, MD; e-mail: wur@sj-hospital.org

ious human tumors, including pituitary tumor[15], liver cancer[16] and ovarian cancer[17]. CircABCB10 is considered to be a key oncogene in tumors progression and is involved in the regulation of a large number of miRNAs with tumor suppressive effects. However, no study has revealed its specific effect and detailed mechanism in LCa.

In this study, we tested the circABCB10 expression in LCa tissues and explored the impact of circABCB10 on LCa cell functions. We aim to look for target genes of circABCB10 related to LCa, and to study their biological functions and their correlation with the prognosis of LCa patients. We characterize a novel axis involving circABCB10 and microRNA-217 that governs the progression of LCa, thus provide a new molecular target for diagnosis and treatment of LCa.

Patients and Methods

Patient and Specimens

From June 2017 to March 2019, with the written consent of Shengjing Hospital of China Medical University, 23 matched NSCLC tumor specimens and corresponding adjacent non-cancer tissues were obtained. Fresh specimens were placed in liquid nitrogen immediately after excision and stored at 80°C. None of the patients received chemotherapy or radiotherapy before surgery. The plan was approved by the Ethics Committee of Shengjing Hospital of China Medical University. Tumor pathological classification and staging standards are implemented in accordance with the staging standards of the Union for International Cancer Control (UICC). Inclusion criteria: patients with no severe diseases in other organs, those undergoing no post-operative radiotherapy and those with normal lung function before operation. Exclusion criteria: patients with distant metastasis or metastasis of tumors, those complicated with other malignancies, those with mental disease, those complicated with myocardial infarction, heart failure or other chronic diseases, those with abnormal lung function prior to operation, or those previously exposed to radioactive rays.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from frozen tissues or cell lines using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and then reverse transcribed into cDNA. qPCR was performed on a TP800 real-time PCR instrument (TaKaRa, Kusatsu, Otsu, Japan), with a two-step standard PCR amplification procedure: the first step (pre-denaturation) 95°C, 30 seconds, 1 cycle; the second step (PCR reaction), 95°C reaction for 5 seconds, 60°C reaction for 30 seconds, 72°C reaction for 30 seconds, with a total of 40 cycles. Primer sequences used in qPCR detection: circ-ABCB10: forward 5'-CTAAGGAGTCACAGGAAGACATC-3'; Reverse: 5'-GTAGAATCTCTCAGACTCAAGGTTG-3'; miR-217: forward: 5'-TACTCAACTCACTACTGCATCAGGA-3', reverse: 5'-TATGGTTGTTCTGCTCTCTGTGTC-3'; U6: forward: 5'-AGCCCGCACTCAGAACATC-3', reverse: 5'-GCCACCAAGACAATCATCC-3'; glyceraldehyde 3-phosphate dehydrogenase (GAPDH): forward: 5'-GGGAGCCAAAAGGGTCAT-3', reverse: 5'-GAGTCCTTCCACGATACCAA-3'.

Cell Culture

Human lung bronchial epithelial cells (BEAS-2B) (as a control) and NSCLC cells (SPC-A1, A549, HCC827, H1299) provided by the Cell Bank of the Chinese Academy of Sciences (Shanghai, China) were cultured in 1640 medium (Youkang, Beijing, China) supplemented with 10% fetal bovine serum (FBS) (Hyclone, Hunan, China) at 37°C with 5% CO_2.

Cell Transfection

Both small interfering RNA (si-circABCB10) and small interfering RNA (si-control) were provided by Invitrogen (Carlsbad, CA, USA). miR-149 mimics and miR-149 inhibitors were synthesized from RiboBio (Guangzhou, Guangdong, China). The transfection was implemented by using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

Cell Counting Kit-8 (CCK-8) Test

CCK-8 assay (Dojindo Molecular Technologies, Kumamoto, Japan) was conducted to evaluate cell proliferation based on manufacturer's instructions.

5-Ethynyl-2'- Deoxyuridine (EdU) Assay

Cell proliferation was measured using EdU kit (Tenghui, Jinan, China) according to the instructions.

Plate Cloning Experiment

After continuous culture at 37°C for 14 days, cells were stained with crystal violet, and colonies were counted in each dish to estimate the cloning efficiency between different groups. Visible colo-

nies formed by more than 50 cells under the light microscope were included in the statistics.

Transwell Assay

The transwell chamber (8-μm pore membrane filter) was purchased from Corning Corporation (Corning, NY, USA) and used to determine the cell migration ability. Cells were prepared into cell suspensions and seeded in upper chamber (50,000 cells/well) supplemented with serum-free medium, and then 10% FBS medium was added to the lower compartment.

Cell Wound Healing Assay

The cell monolayer membrane was scratched with a 200 μL pipette tip after cells were fully adhered. The healing distance of the injured area at 48 hours was normalized by 0 hours as the control variable and was expressed as relative mobility (%).

Dual-Luciferase Assay

Promega luciferase detection kit (Promega, Madison, WI, USA) was used to measure luciferase activity according to the kit instructions. Wild type (WT) or mutant (MUT) predicted microRNA-217 binding sites of circABCB10 were cloned into pGL3 vector (circABCB10 wt, circABCB10 mut) respectively. These structures were cloned and synthesized by China Ribobio (Guangzhou, China).

Statistical Analysis

GraphPad Prism v7.0 software (La Jolla, CA, USA) was used for data analysis, and the data were expressed as x ± SD (standard deviation). The *t*-test was used to evaluate the significance between the two groups. The statistical significance was set as $p<0.05$.

Results

CircABCB10 Is Abnormally Highly Expressed In LCa

We performed real-time quantitative PCR analysis and found that circABCB10 expression in LCa tissue samples or LCa cell lines was remarkably higher than that in normal ones (Figure 1A, 1B). According to the follow-up information, we performed a gene-related survival analysis of LCa patients. K-M method survival analysis revealed that the prognosis of LCa patients in circABCB10 high expression group was poor in comparison to those in circABCB10 low expression group (Figure 1C). The above observations show that circABCB10 is remarkably overexpressed in LCa and is closely relevant to the poor prognosis of patients.

CircABCB10 Promotes the Proliferation of LCa Cells

To further confirm the effect of circABCB10 on the progression of LCa, we transfected si-circABCB10 and corresponding negative controls in LCa cell lines and used real-time quantitative PCR to verify the efficiency of transfection. Figure 2A shows that si-circABCB10 remarkably down-regulated circABCB10 expression in LCa cells. Subsequently, we detected the proliferation of cells by using CCK-8 experiment, EDU assay and cell colony forma-

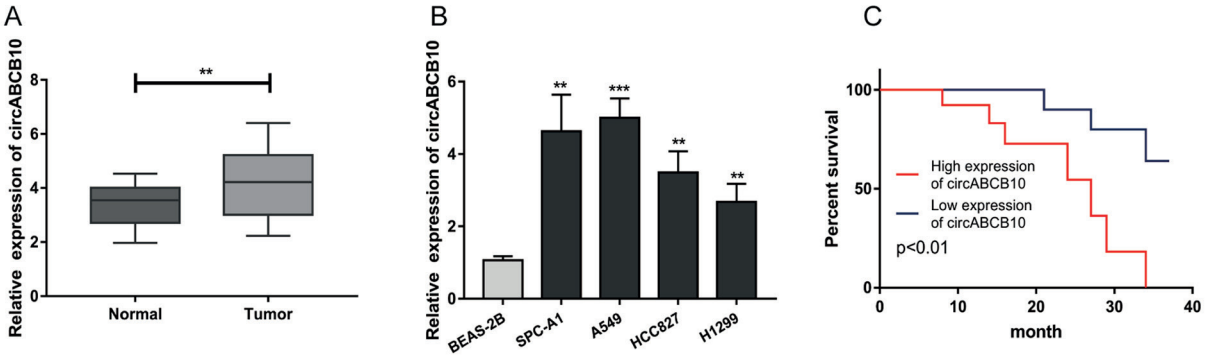

Figure 1. A, qRT-PCR results show that the expression level of circABCB10 in lung cancer tissue is significantly higher than that in normal lung tissue; **B,** qRT-PCR results show that the expression level of circABCB10 in lung cancer cell lines is significantly higher than that in normal lung cell lines; **C,** Survival analysis shows that the survival prognosis of patients with high expression of circABCB10 in lung cancer patients is worse than those with lower expression ** $p<0.01$, *** $p<0.001$.

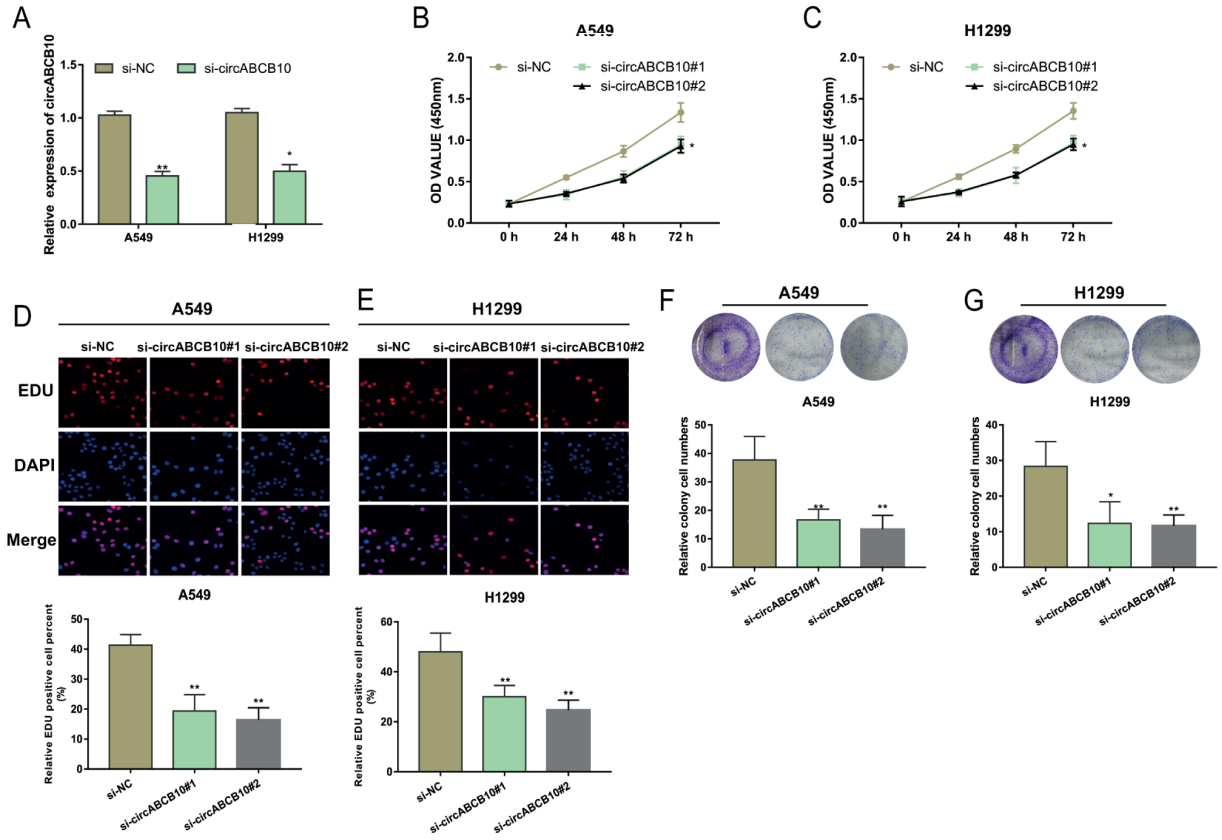

Figure 2. A, Transfection of si-circABCB10 significantly down-regulates the expression of circABCB10 gene in A549 and H1299 cell lines; **B-C,** CCK-8 experiment results show that after knocking down circABCB10 in lung cancer cells, the proliferation ability of A549 and H1299 cell lines appears to be significantly inhibited; **D-E,** EdU experiment results show that after knocking down circABCB10 in lung cancer cells, the proliferation ability of A549 and H1299 cell lines is significantly inhibited, (magnification: 20×). **F-G,** Cell plate cloning experiment results show that after knocking down circABCB10 in lung cancer cells, the proliferation ability of A549 and H1299 cell lines is significantly inhibited, (magnification: 20×). * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

tion assay. As a result, CCK8 results revealed that the cell proliferative ability was inhibited after transfection with si-circABCB10 (Figure 2B-2C). Figure 2D and 2E indicate that si-circABCB10 significant attenuated the growth activity of LCa cells; consistently, cell plate cloning experiment also revealed a reduction in cell colony formation capacity after knockdown of si-circABCB10 (Figure 2F, 2G). Taken together, the above results detect that circABCB10 can enhance the proliferation ability of LCa cells.

CircABCB10 Promotes the Migration Ability of LCa Cells

We then explored the effect of circABCB10 on LCa cell migration. Transwell test indicated that transfection of si-circABCB10 down-regulated the migration ability of LCa cells (Figure 3A-3B); consistently, the migration distance of LCa cell lines was reduced after transfection of si-circABCB10 (Figure 3C-3D). Thus, it can be concluded that circABCB10 is capable of enhancing the migratory ability of LCa cells.

CircABCB10 Binds to MicroRNA-217 and Downregulates Its Expression In LCa

To explore the mechanism by which circABCB10 regulates LCa cell functions, we predicted its downstream potential target genes through bioinformatics analysis and found that the 3'UTR region of circABCB10 has a binding site with microRNA-217 (Figure 4A). We found that the expression level of microRNA-217 was up-regulated after knockdown of circABCB10 in LCa cells (Figure 4B). Subsequently, we found a negative correlation between circABCB10 and mi-

croRNA-217 in 23 cases of LCa tissue samples by using Pearson algorithm analysis (Figure 4C). Meanwhile, Luciferase assay further proved that circABCB10 do bind to microRNA-217 in A549 and H1299 cell lines (Figure 4D-4E). These results demonstrate that circABCB10 may regulate the expression of microRNA-217 through ceRNA mechanism and thus participate in the development of LCa.

MicroRNA-217 Is a Key Downstream Gene of CircABCB10

Functional recovery experiments in cell biology research are often used to verify the critical role of signaling pathways. Therefore, to further understand the regulatory role of microRNA-217 in the circABCB10 signaling pathway in LCa, we co-transfected si-circABCB10 and microRNA-217 inhibitors in A549 and H1299 cell lines, and then observed the cell proliferation or migration ability. As expected, it was found that transfection of microRNA-217 inhibitor partially restored the inhibited impact of si-circABCB10 on proliferation rate (Figure 5A-5B), clonal reproduction activity (Figure 5C-5D), migration activity (Figure 5G-5H) and migration distance of LCa cells (Figure 5I-5J). These observations further confirm that circABCB10 may play a role in promoting LCa progression *via* inhibiting microRNA-217 expression.

Discussion

In 2018, there were 20, 93, 876 new cases of LCa and 176,1007 deaths, accounting for 11.6% and 18.4% of all cancers, respectively[18]. CircRNAs, highly conserved and widely distributed, play an essential regulatory role in tumors and are considered to have the potential to become important molecular markers for tumor diagnosis and treatment[19]. They have been extensively reported to be associated with the progression of LCa, and their dysregulation in tumors is often involved in tumor progression[20]. Currently, molecular therapy has gradually become the treatment choice for solid tumors, and the discovery of more effective molecular targets has become the focus of tumor research[21].

A newly discovered circRNA, circABCB10, has previously been found to be able to act as an oncogene in a variety of tumors but has not been studied in LCa[22]. By collecting and measuring circABCB10 expression in LCa tissue samples, we found an abnormally high expression of circABCB10 in LCa, which can predict poor prognosis of LCa patients. To further investigate the role of circABCB10 in LCa, we designed a series of functional experiments *in vitro*. We demonstrate that circABCB10 remarkably attenuated the migration and proliferation capacity of LCa cells, indicating that this

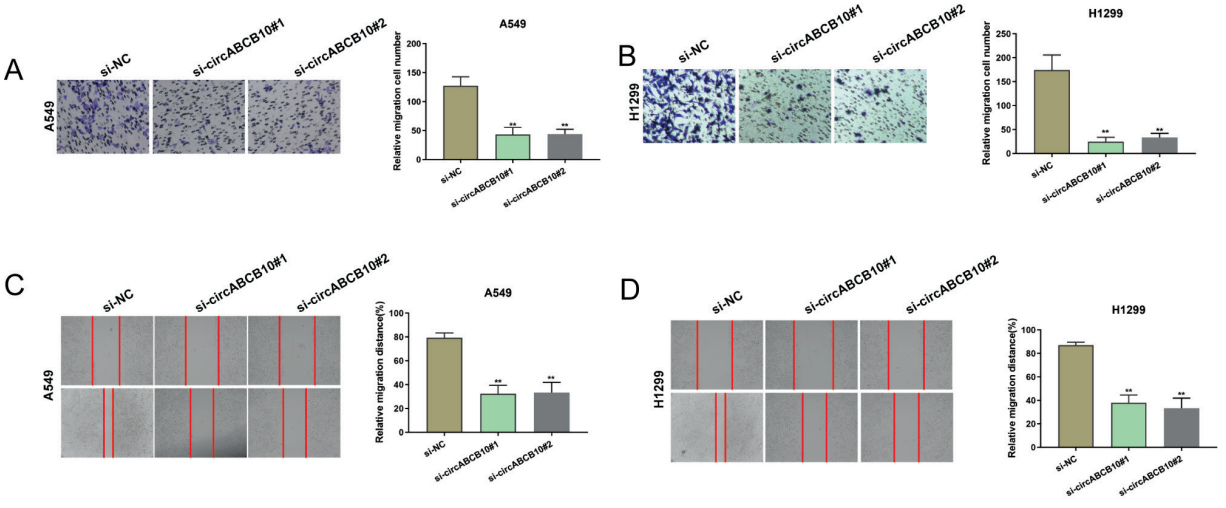

Figure 3. A-B, Transwell experimental results show that after knocking down circABCB10 in lung cancer cells, the migration ability of A549 and H1299 cell lines is significantly inhibited, (magnification: 20×). **C-D,** Cell wound healing test results show that after knocking down circABCB10 in lung cancer cells, the migration ability of A549 and H1299 cell lines is significantly inhibited, (magnification: 20×). ** $p<0.01$.

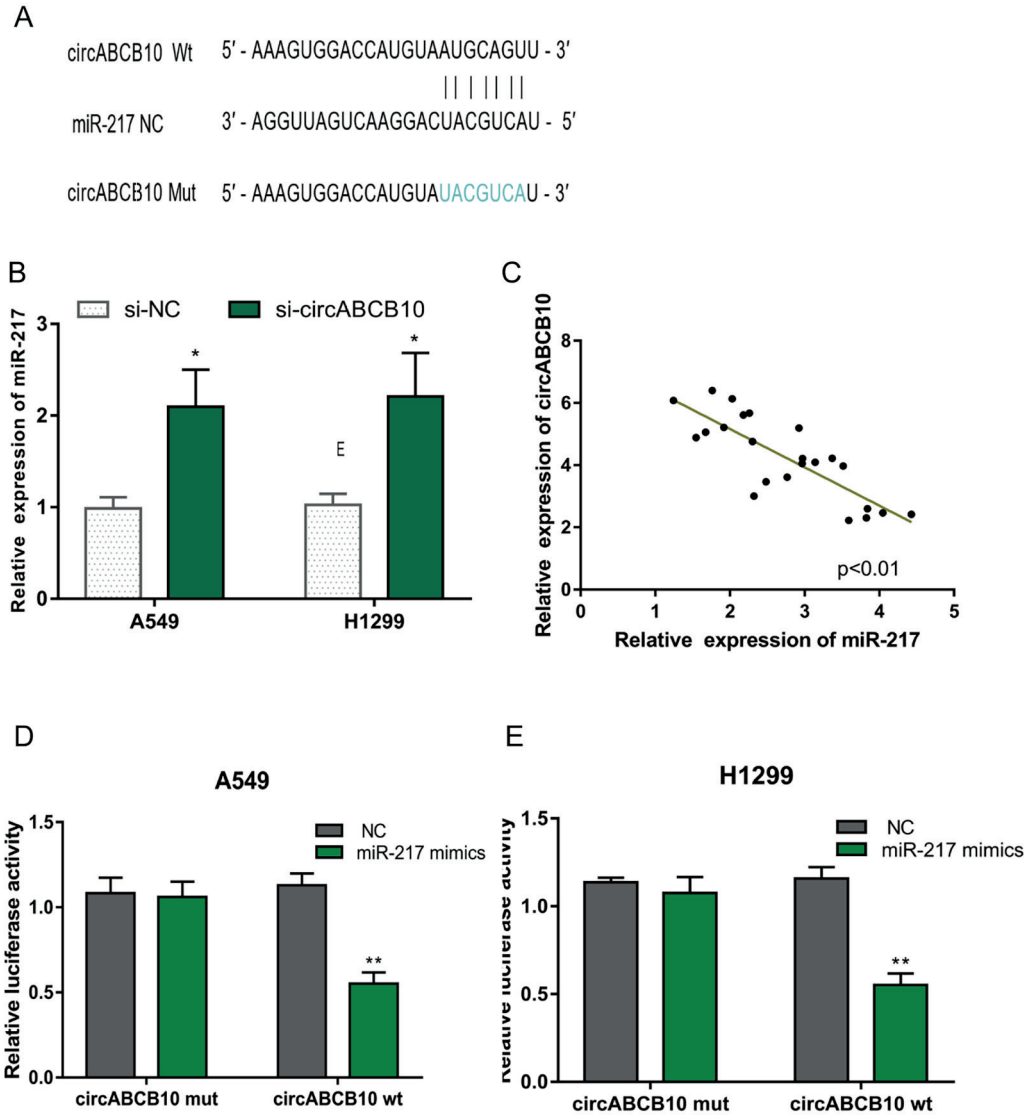

Figure 4. A, Bioinformatics technology predicts that the 3'UTR region of circABCB10 has a binding site with miR-217; **B,** The results of gene expression interference experiments on lung cancer cells show that circABCB10 is negatively correlated with miR-217; **C,** Pearson algorithm correlation analysis reveals that circABCB10 and miR-217 had a negative correlation in 23 cases of lung cancer; **D-E,** Dual-Luciferase reporter gene experiment show that circABCB10 and miR-217 have a binding relationship in lung cancer cells. * $p<0.05$, ** $p<0.01$.

circular RNA may serve as a key oncogene in the progression of LCa.

To explore the molecular mechanism of circABCB10's role in LCa, we used the circRNA target prediction website to predict possible molecular targets for circABCB10 and identified microRNA-217 as a potential downstream target for circABCB10. MicroRNA-217 can be engaged in the modulation of tumor development. In particular, microRNA-217 can inhibit the EMT process in gastric cancer cells by negatively regulating PTPN14[23]; it can also suppress the migration capacity and proliferation of HeLa cells *via* regulating the MAPK signaling pathway[24]. In addition, microRNA-217 has been confirmed to act on Sirt1-mediated progression of osteosarcoma[25]. In LCa, microRNA-217 has been shown to be an important tumor suppressor, including its involvement in the intracellular EMT transformation process and the sensitivity of tumor

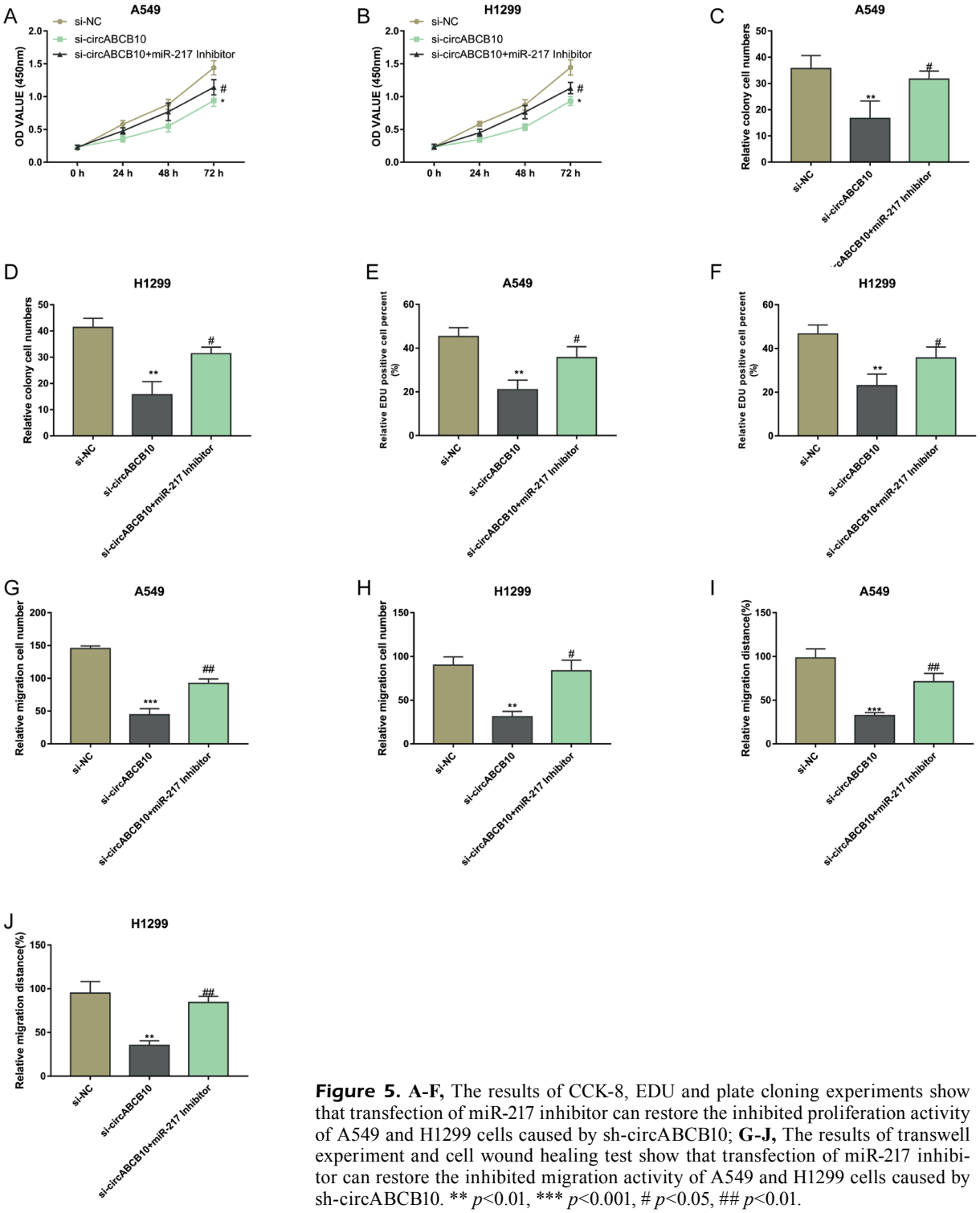

Figure 5. A-F, The results of CCK-8, EDU and plate cloning experiments show that transfection of miR-217 inhibitor can restore the inhibited proliferation activity of A549 and H1299 cells caused by sh-circABCB10; **G-J,** The results of transwell experiment and cell wound healing test show that transfection of miR-217 inhibitor can restore the inhibited migration activity of A549 and H1299 cells caused by sh-circABCB10. ** $p<0.01$, *** $p<0.001$, # $p<0.05$, ## $p<0.01$.

cells to chemotherapy[26,27]. It was also found that microRNA-217 can mediate the regulatory role of non-coding RNA in LCa, such as participating in the LINC01614/microRNA-217 / FOXP1 signal axis, and acting as a key central regulatory factor[28]. The present study revealed a negative correlation between circABCB10 and microRNA-217, and further showed that circABCB10

can bind to microRNA-217 in LCa cells. Consistently, our functional reversal experiment *in vitro* showed that microRNA-217 was closely involved in the effect of circABCB10 on the proliferative ability and migration capacity of LCa cells, suggesting that circABCB10 may play a carcinogenic role by down-regulating microRNA-217 in LCa cells. The circABCB10/ microRNA-217 signaling pathway may become a new target for the diagnosis and treatment of LCa. Our study further reveals the role and potential mechanism of circABCB10 in LCa and provides new options for accurate molecular targeted therapy of LCa.

Conclusions

In summary, circABCB10, abnormally highly expressed in both LCa tissues and cell lines, can lead to tumor malignancy in LCa. microRNA-217 is a key downstream gene that mediates the functional regulation of circABCB10 on LCa progression. We proposed, for the first time, that circABCB10 may have an important biological role in lung cancer and explored its possible molecular mechanisms. We provide a theoretical basis for the clinical diagnosis and treatment of lung cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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