European Review for Medical and Pharmacological Sciences 2020; 24: 12208-12215

# Circ-ABCB10 promotes growth and metastasis of nasopharyngeal carcinoma by upregulating ROCK1

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**Abstract. – OBJECTIVE: Nasopharyngeal carcinoma (NPC) is one of the most ordinary head and neck tumors. This study aims to uncover the role of circ-ABCB10 functions in the progression of NPC.**

**PATIENTS AND METHODS: The circ-ABCB10 expression was detected in paired NPC patients' tissue samples and cell lines. The role of circ-ABCB10 in NPC proliferation was identified through proliferation assay, Ethynyl deoxyuridine (EdU) assay and colony formation assay. Next, the role of circ-ABCB10 in NPC metastasis was measured through wound healing assay and transwell assay. Finally, the underlying mechanism was further uncovered through Western blot assay and real-time quantitative polymerase chain reaction (RT-qPCR).**

**RESULTS: It was found that circ-ABCB10 expression was significantly higher in NPC tissues than that in adjacent samples. In addition, cell proliferation, migration and invasion of NPC were promoted through overexpression of circ-ABCB10 *in vitro*. Results of further experiments revealed that ROCK1 was upregulated via overexpression of circ-ABCB10 in NPC.**

**CONCLUSIONS: This study indicated that circ-ABCB10 promoted NPC cell proliferation and metastasis via upregulating ROCK1 *in vitro*.**

*Key Words:*
Circ-ABCB10, Nasopharyngeal carcinoma, ROCK1.

## Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors of head and neck. The incidence of NPC is high especially in Southeast Asia and South China[1]. NPC is characterized by familial aggregation and regional concentration, which suggests that genetic factors play an important role in the occurrence and development of NPC[2]. Moreover, EB virus has been reported to be closely related to the pathogenesis of NPC[3]. NPC at early stage has a good curative effect on radiotherapy[4]. However, more than 75% of NPC patients with cervical lymph node metastasis have poor prognosis. Local recurrence and distant metastasis are the main causes of death of patients with NPC. The 5-year survival rate of patients with NPC is still very low[5,6]. Therefore, searching for molecular targets for early diagnosis and treatment of NPC is a very important part in clinical research.

A circular RNA (circRNA) is a kind of single-stranded endogenous closed cyclic RNA with no 3'-terminal poly (A) and 5'-terminal cap structures. It has been found that more than 10% of the genes could produce circRNAs by reverse splicing. CircRNAs of some genes accumulate in cells, and the expression of circRNAs far exceeds that of corresponding linear RNAs[7]. Unlike linear RNAs, circRNAs are covalently closed ring molecules and cannot be degraded by nucleic acid exonucleases. In addition, circRNAs are highly conserved in evolution among different specimens[8]. With the development of researches, circRNAs have been found to be closely associated with the occurrence, development and prognosis of many diseases. Studies on different tumors have shown that circRNAs have both positive and negative effects on the occurrence and development of tumors. In particular, circ-ITCH inhibits the proliferation of esophageal cancer cell lines by inhibiting Wnt signaling pathway[9]. Circ-Amotl1 promotes tumorigenesis by inducing c-Myc into the nucleus[10]. By serving as a sponge of miR-7, CDR1as enhances the invasiveness of glioma and breast cancer *via* regulating epidermal growth factor receptor (EGFR) and Pak1 (P21 activated kinase 1)[11,12].

Circ-ABCB10 is a newly discovered circRNA in human diseases. Although the association be-



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tween circ-ABCB10 and tumorigenesis has been reported in some malignant tumors, the function of circ-ABCB10 in NPC remains unstudied. In this research, it was discovered that circ-ABCB10 might act as an oncogene in NPC and was associated with ROCK1.

## Patients and Methods

### Tissue Specimens

A total of 45 paired tumor tissues and adjacent non-tumor tissues were sequentially gathered from NPC patients who underwent surgery in Lianyungang First People's Hospital. Participants in this study provided written informed consents. This investigation was approved by the Ethics Committee of Lianyungang First People's Hospital. The tumors were classified according to World Health Organization classification.

### Cell Culture

Three NPC cancer cell lines (CNE2, 5-8F and 6-18B), and immortalized normal nasopharyngeal epithelial cell line (NP69) were purchased from the Chinese Academy of Science (Shanghai, China). Cells were maintained in 10% fetal bovine serum (FBS, Invitrogen, Carlsbad, CA, USA), Roswell Park Memorial Institute-1640 (RPMI-1640, Invitrogen, Carlsbad, CA, USA), as well as penicillin/streptomycin (Sigma-Aldrich, St. Louis, MO, USA). Besides, cells were cultured in an incubator containing 5% $CO_2$ at 37°C.

### Cell Transfection

Lentivirus directly against circ-ABCB10 was provided by GenePharma (Shanghai, China). Empty vector was also synthesized. Then, circ-ABCB10 lentivirus or empty vector was transfected into 6-18B NPC cells through Lipofectamine 3000 reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol.

### RNA Extraction and Real Time Quantitative Polymerase Chain Reaction (RT-qPCR)

Total RNAs were extracted from cells or tissues using TRIzol reagent (TaKaRa Bio, Inc., Otsu, Shiga, Japan) and then reversely transcribed to complementary deoxyribose nucleic acids (cDNAs) through reverse Transcription Kit (TaKaRa, Otsu, Shiga, Japan). The primer sequences used for RT-qPCR were as follows: circ-ABCB10 primers forward: 5′-CTAAGGAGTCACAGGAAGACATC-3′, reverse: 5′-GTAGAATCTCTCAGACTCAAGGTTG-3′; glyceraldehyde 3-phosphate dehydrogenase (GAPDH) primers forward: 5′-CCAAAATCAGATGGGGCAATGCTGG-3′ and reverse 5′-TGATGGCATGGACTGTGGTCATTCA-3′. PCR was performed three times in the following sequence: pre-denaturation at 95°C for 1 min, followed by 40 cycles at 95°C for 15 s, 60°C for 30 s, and 72°C for 30 s. Finally, the $2^{-\Delta\Delta Ct}$ method was utilized for calculating relative expression.

### Cell Counting Kit-8 (CCK-8) Assay

Following the protocol of CCK-8 assay (Dojindo Laboratories, Kumamoto, Japan), cell growth ability of transfected cells in 96-well plates was assessed at 24, 48, and 72 hours. Spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) was utilized to measure the absorbance at 450 nm.

### Colony Formation Assay

NPC cells were placed in a 6-well plate for 10 days. Then colonies were treated with 10% formaldehyde for 30 min and stained for 5 min with 0.5% crystal violet. The Image-Pro Plus 6.0 (Media Cybernetics, Silver Springs, MD, USA) was used for data analysis.

### Ethynyl Deoxyuridine (EdU) Incorporation Assay

According to the manufacturer's manual, an EdU Kit (Roche, Mannheim, Germany) was utilized to monitor the cell proliferation of transfected cells. Zeiss Axiophot Photomicroscope (Carl Zeiss, Oberkochen, Germany) was performed to take the representative images.

### Wound Healing Assay

Cells, transferred into 6-well plates, were cultured in RPMI-1640 medium overnight. After scratched with a plastic tip, cells were cultured in serum-free RPMI-1640. At last, wound closure was viewed at 48 h. Each assay was independently repeated for three times.

### Transwell Assay

Transwell chambers with 8 μm pores were provided by Corning (Corning, NY, USA). Cells were then seeded into the upper chambers of a 24-well plate. 20% FBS-RPMI-1640 was added to the lower chamber of the culture inserts. After cultured for 24 h, these inserts were fixed with methanol for 30 min and stained by hematoxylin for 20 min.

Finally, the number of migrated cells was counted by a light microscope (Olympus, Tokyo, Japan).

### Matrigel Assay

Transwell chambers with 8 μm pores were provided by Corning (Corning, NY, USA). The membrane was precoated with 50 μL Matrigel (BD Biosciences, Heidelberg, Germany). Cells were then seeded into the upper chambers of a 24-well plate. 20% FBS-RPMI-1640 was added to the lower chamber of the culture inserts. After cultured for 24 h, these inserts were fixed with methanol for 30 min and stained by hematoxylin for 20 min. Ultimately, the number of migrated cells was counted by a light microscope (Olympus, Tokyo, Japan).

### Western Blot Analysis

Reagent radioimmunoprecipitation assay buffer (RIPA; Beyotime, Shanghai, China) was utilized to extract proteins from cells. Bicinchoninic acid (BCA) protein assay kit (TaKaRa, Otsu, Shiga, Japan) was chosen for quantifying protein concentrations. Next, the target proteins were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and incubated with antibodies after placed to the polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Cell Signaling Technology (CST, Danvers, MA, USA) provided rabbit anti-GAPDH and rabbit anti-ROCK1, as well as goat anti-rabbit secondary antibody. Image J software (NIH, Bethesda, MD, USA) was applied for assessment of protein expression.

### Statistical Analysis

All statistical analyses were performed by Statistical Product and Service Solutions (SPSS) 21.0 (IBM Corp., Armonk, NY, USA). Independent-sample *t*-test was used to compare the difference between two groups. Moreover, $p<0.05$ was considered to indicate a statistically significant difference.

## Results

### Expression Level of Circ-ABCB10 In Tissues and Cells of NSCLC

RT-qPCR was performed in 45 paired NPC patients' tissue samples and NPC cell lines. As shown in Figure 1A, upregulated circ-ABCB10 was observed in tumor tissue samples compared with that in adjacent tissues. The upregulated circ-ABCB10 was associated with tumor size and lymphatic metastasis (Table I). Compared with that in NP69 cells, the circ-ABCB10 expression level was significantly higher in NPC cells (Figure 1B).

### Overexpression of Circ-ABCB10 Promoted Cell Proliferation In 5-8F NPC Cells

To determine whether circ-ABCB10 could really play a vital role in NPC, circ-ABCB10 ex-

**Table I.** Correlation between Circ-ABCB10 expression and clinicopathological characteristics in NPC patients.

| Characteristics | Patients | Expression of Circ-ABCB10 | | *p*-value |
|---|---|---|---|---|
| | | High expression | Low expression | |
| Total | 45 | 21 | 24 | |
| Age (years) | | | | 0.841 |
| ≤ 50 | 25 | 12 | 13 | |
| > 50 | 20 | 9 | 11 | |
| Gender | | | | 0.714 |
| Male | 27 | 12 | 15 | |
| Female | 18 | 9 | 9 | |
| TNM stage | | | | 0.423 |
| I-II | 20 | 8 | 12 | |
| III-IV | 25 | 13 | 12 | |
| Tumor size | | | | 0.011 |
| < 3 cm | 30 | 10 | 20 | |
| > 3 cm | 15 | 11 | 4 | |
| Lymphatic metastasis | | | | 0.005 |
| No | 27 | 8 | 19 | |
| Yes | 18 | 13 | 5 | |

$p$ <0 .05 is considered as statistically significant.

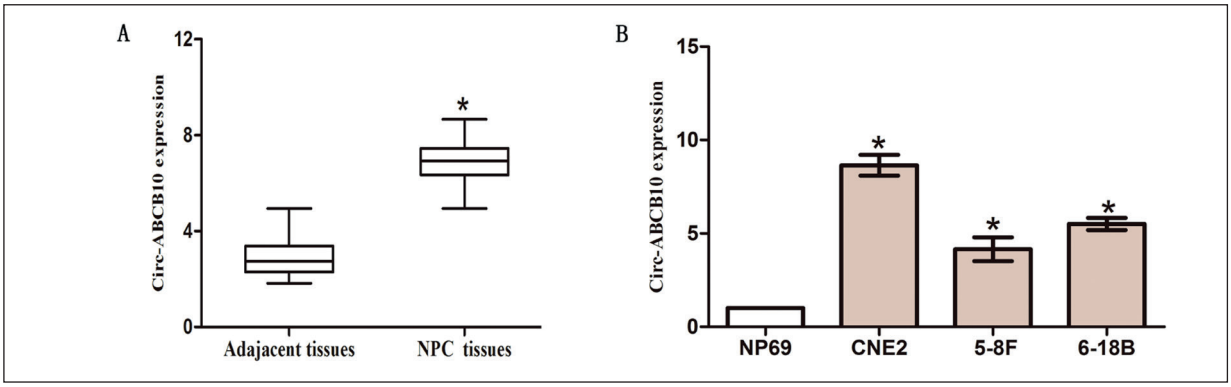


**Figure 1.** Expression levels of circ-ABCB10 were increased in NPC tissues and cell lines. **A,** Circ-ABCB10 expression was significantly increased in the NPC tissues compared with that in adjacent tissues. **B,** Expression levels of circ-ABCB10 relative to GAPDH were determined in the human NPC cell lines and immortalized normal nasopharyngeal epithelial cell line (NP69) by RT-qPCR. Data were presented as the mean ± standard error of the mean. *$p$<0.05.

pression level was upregulated in 6-18B cells using lentivirus. As shown in Figure 2A, circ-ABCB10 expression was remarkably upregulated in RNA level after transfection with lentivirus. Then, cell proliferation assay, colony formation assay and EdU assay were carried out in 6-18B cells. As shown in Figure 2B, an evident promotion of cell proliferation *via* overexpression of circ-ABCB10 (transfection with lentivirus) compared with the EV (transfection with empty vector) was viewed in 5-8F cells ($p$<0.05). To further confirm the outcome of CCK8 assay, EdU assays were performed in 5-8F cells. As shown in Figure 2C, EdU positive cells were

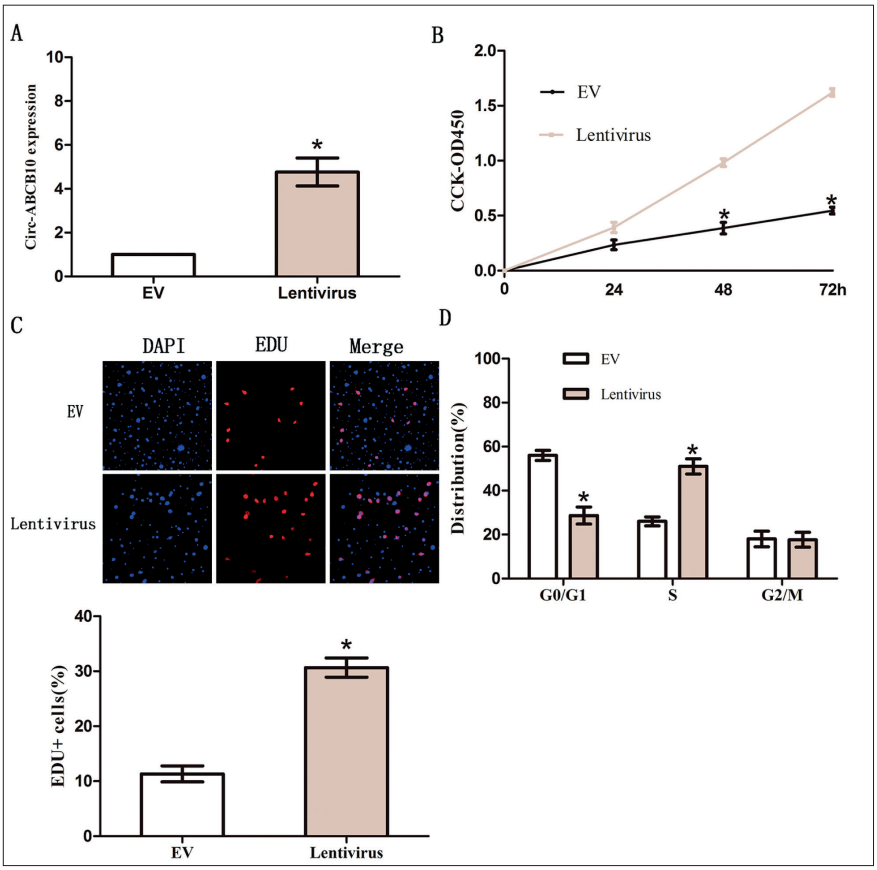


**Figure 2.** Overexpression of circ-ABCB10 promoted 5-8F NPC cell proliferation. **A,** Circ-ABCB10 expression in NPC cells transfected with empty vector (EV) or circ-ABCB10 lentivirus (Lentivirus) was detected by RT-qPCR. GAPDH was used as an internal control. **B,** CCK-8 assay showed that overexpression of circ-ABCB10 significantly promoted cell proliferation in NPC cells. **C,** EdU assay showed that the EdU positive cells were promoted in circ-ABCB10 lentivirus (Lentivirus) group compared with those in EV group in NPC cells. (magnification: 40×) **D,** Cell cycle assay revealed that the percentage of G0/G1 cells was decreased and the percentage of S cells was increased after overexpression of circ-ABCB10 in 5-8F cells. The results represented the average of three independent experiments (mean ± standard error of the mean). *$p$<0.05, as compared with the control cells.

also reduced by circ-ABCB10 overexpression ($p<0.05$), which was consistent with the results of CCK-8 assays. To detect the effect of circ-ABCB10 on NPC cell cycle, cell cycle assay was performed. The outcome of cell cycle assay also revealed that the percentage of G0/G1 cells was decreased and the percentage of S cells was increased after overexpression of circ-ABCB10 in 5-8F cells (Figure 2D). These together suggested circ-ABCB10 as a new oncogene in proliferation and cell cycle of NPC.

### Overexpression of Circ-ABCB10 Promoted Cell Migration and Invasion In 5-8F NPC Cells

To explore the function of circ-ABCB10 in the migrated and invaded abilities of NPC cells, wound healing assay and transwell assay were performed. Scratch wound assay indicated that a significant increase was observed in the wound closure of 5-8F cells transfected with circ-ABCB10 lentivirus (Figure 3A). Transwell assay detected a significant increase in the number of migrated 5-8F cells transfected with circ-ABCB10 lentivirus (Figure 3B). Besides, transwell assay also revealed a significant increase in the number of invaded 5-8F cells transfected with circ-ABCB10 lentivirus (Figure 3C). These together suggested circ-ABCB10 as a new oncogene in metastasis of NPC.

### The Interaction Between ROCK1 and Circ-ABCB10 In NPC

Starbase v2.0 (http://starbase.sysu.edu.cn/starbase2/rbpCircRNA.php) was used to find the target proteins of circ-ABCB10. ROCK1 was selected from these proteins which were interacted with circ-ABCB10. As shown in Fig-

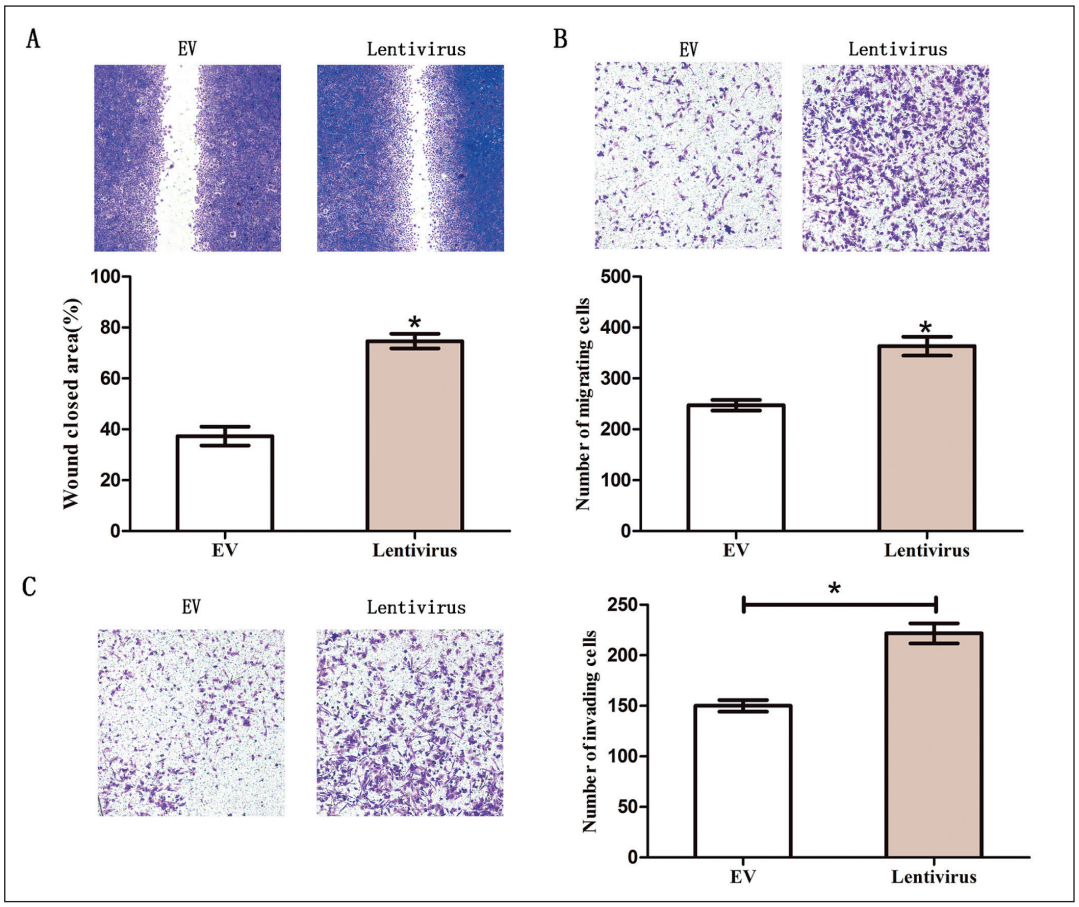


**Figure 3.** Overexpression of circ-ABCB10 promoted 5-8F NPC cell migration and invasion. **A,** Wound healing assay showed that overexpression of circ-ABCB10 significantly increased wound closure in NPC cells (magnification: 10×). **B,** Transwell assay showed that overexpression of circ-ABCB10 significantly promoted cell migration in NPC cells (magnification: 40×). **C,** Transwell assay showed that overexpression of circ-ABCB10 significantly promoted cell invasion in NPC cells (magnification: 40×). The results represented the average of three independent experiments (mean ± standard error of the mean). *$p<0.05$, as compared with the control cells.

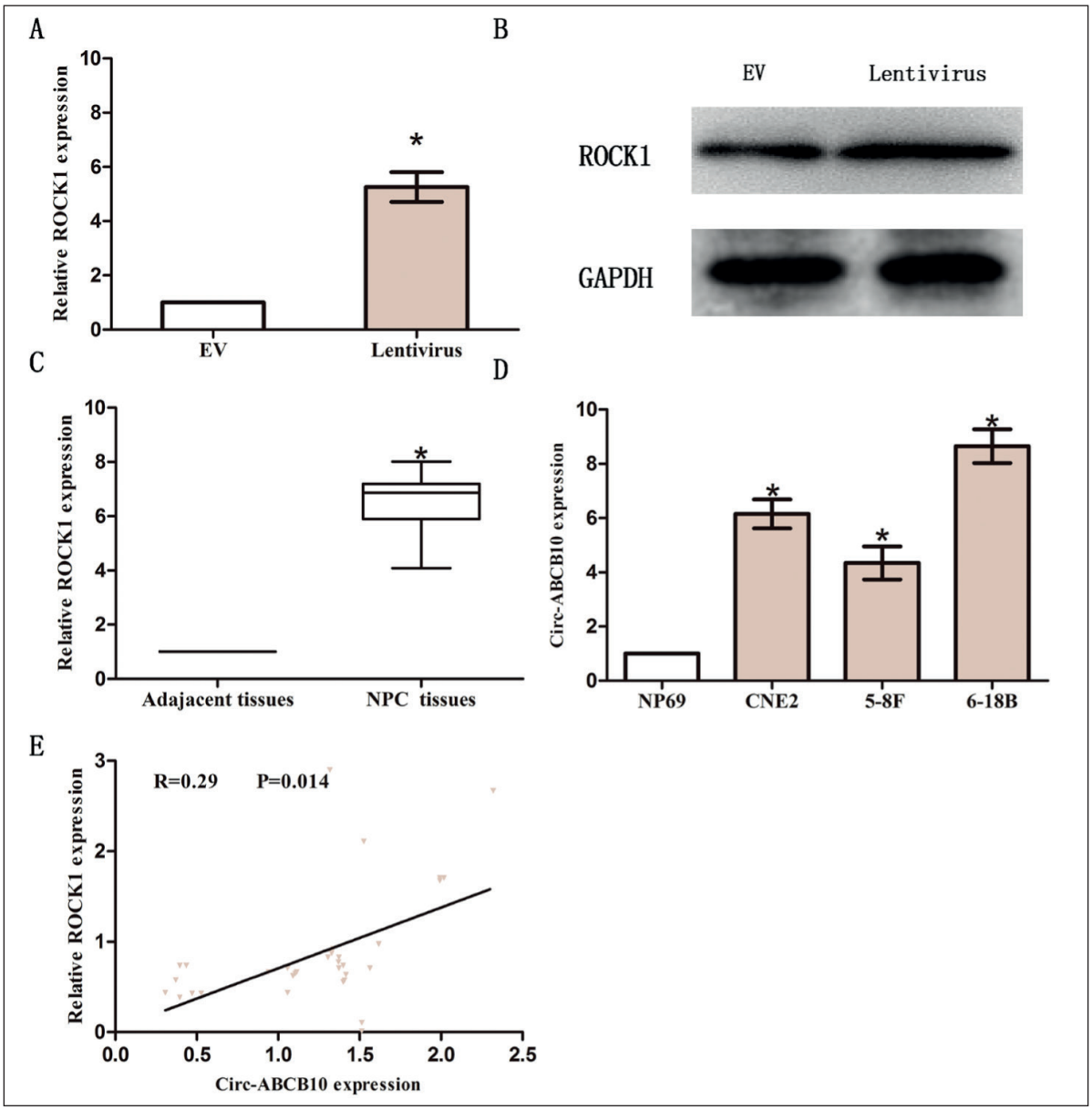


**Figure 4.** The association between circ-ABCB10 and ROCK1 in NPC. **A,** RT-qPCR results showed that the ROCK1 expression was increased in circ-ABCB10 lentivirus (Lentivirus) group compared with that in empty vector (EV) group. **B,** Western blot assay results detected that the ROCK1 expression was increased in circ-ABCB10 lentivirus (Lentivirus) group compared with that in empty vector (EV) group. **C,** Upregulated ROCK1 was observed in tumor tissue samples compared with that in adjacent tissues. **D,** Compared with that in NP69 cells, ROCK1 level was significantly higher in NPC cells. **E,** The linear correlation between the expression level of ROCK1 and circ-ABCB10 in NPC tissues. The results represented the average of three independent experiments. Data were presented as the mean ± standard error of the mean. *$p<0.05$.

ure 4A, RT-qPCR assay showed a significant upregulation of ROCK1 after overexpression of circ-ABCB10. Western blot assay revealed that the expression of ROCK1 was upregulated after overexpression of circ-ABCB10 (Figure 4B). As shown in Figure 4C, upregulated ROCK1 was observed in tumor tissue samples compared with that in adjacent tissues. Compared with that in NP69 cells, ROCK1 expression level was significantly higher in NPC cells (Figure 4D). Meanwhile, the results of linear correlation analysis showed that the expression of ROCK1 was positively correlated with circ-ABCB10 expression in NPC tissues (Figure 4E).

## Discussion

In recent years, circRNAs have attracted increasing attention from the researchers. Several circRNAs have been discovered, and the biological function has been gradually recognized. CircRNA is a precursor RNA (pre-RNA), which is formed by reverse splicing and covalent bonding. Because of its special closed ring structure, circRNAs cannot be easily degraded by nucleic acid exonuclease. As a result, circRNAs are more stable than microRNAs or lncRNAs, indicating that they may become a potential biomarker for disease diagnosis and prognosis[13]. In general, the expression level of circRNAs is low *in vivo*. However, with the deepening of research, it has been found that circRNAs are abnormally expressed in specific cells or tissues to regulate transcription, affect post-transcriptional regulation and shear through binding to microRNAs[14]. Moreover, the research has reported that circRNAs may play an important role in the diagnosis and prognosis of NPC. For example, circRNA_000285 is overexpressed in NPC cases with tumor size larger than 3 cm, lower differentiation and distant metastasis[15]. CircHIPK3 functions as an oncogene in NPC and promotes cell proliferation and cell invasion *via* depressing miR-4288-induced ELF3 inhibition[16]. Silencing of circ_0008450 inhibits cell proliferation, metastatic properties and promotes apoptotic cell in NPC by restraining miR-577-mediated repression of CXCL9[17].

Circ-ABCB10 is a novel circRNA, which is also known as hsa_circ_0008717. Circ-ABCB10 is located at chr1:229665945-229678118 in gene symbol ABCB10 with 724 nts in length. With the rapid development of RNA sequencing technology and more and more studies being carried out, the novel circRNA has been revealed to play an important role in the tumorigenesis of several cancers. Circ-ABCB10 is upregulated in epithelial ovarian cancer. circ-ABCB10 enhances cell proliferation and reduces cell apoptosis in epithelial ovarian cancer through negatively modulating the expression of miR-203 miR-1252 and miR-1271[18]. In breast cancer, through sponging miR-1271, circ-ABCB10 facilitates cell proliferation and tumorigenesis[19]. In addition, circ-ABCB10 is overexpressed in clear cell renal cell carcinoma tissues, and the high expression of circ-ABCB10 is closely related to advanced pathological grade and the tumor node metastasis stage in the patients[20]. In the present study, circ-ABCB10 was found to be upregulated in both NPC tissues and cells. The upregulated circ-ABCB10 was associated with tumor size and lymphatic metastasis. Furthermore, after circ-ABCB10 was overexpressed, the abilities of NPC cell growth, migration and invasion were promoted. These results indicated that circ-ABCB10 functioned as an oncogene in NPC.

Rho-associated coiled coil-containing protein kinase (ROCK) is a serine/threonine protein kinase and also a downstream effector protein of RhoA. It has been reported that ROCK has two isomers, ROCK1 and ROCK2. ROCK1 plays an important role in the regulation of cell movement and cell migration through modulating cytoskeleton recombination and cell adhesion. Rho/ROCK signaling pathway is one of the important mechanisms of cell invasion[21]. Scholars have shown that ROCK1 plays a crucial role in signaling pathway of many tumors. So, by sponging miR-124, circular RNA HIPK3 enhances the progression of gallbladder cancer *via* ROCK1 and CDK6 pathway[22]. Mst1 regulates cell apoptosis in non-small cell lung cancer through ROCK1/Factin pathways induced mitochondrial damage[23]. Elevated expression of ROCK1 has been detected in NPC, which is also significantly associated with advanced N stage[24]. Moreover, ROCK1 expression could be upregulated through overexpression of circ-ABCB10. The expression of ROCK1 is upregulated in NPC cells and tissues, which was positively correlated with circ-ABCB10 expression in NPC tissues. All the results in this study indicated that ROCK1 was upregulated by overexpression of circ-ABCB10 in NPC.

## Conclusions

To sum up, circ-ABCB10 could promote NPC cell proliferation and metastasis by upregulating ROCK1. These findings implied that circ-ABCB10 could serve as a promising mark for NPC.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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