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Hsa_circ_0041103 induces proliferation, migration and invasion in bladder cancer *via* the miR-107/FOXK1 axis

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Abstract. – OBJECTIVE: CircRNAs have been proven to be vital during the process of malignant tumors. Their functions in bladder cancer (BCa) process remain largely unclear. This study aims to elucidate the role of circ0041103 in affecting the malignant phenotypes of BCa, and the possible molecular mechanism.

PATIENTS AND METHODS: Circ0041103 expression levels in BCa tissues and cell lines were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The clinical significance of circ0041103 in influencing tumor size, tumor staging and lymphatic metastasis of BCa was analyzed. Regulatory effects of circ0041103 on proliferative and metastatic capacities of T24 and UM-UC-3 cells were examined through functional experiments. The binding target of circ0041103 and its downstream protein were predicted by online bioinformatic tools, which were further confirmed by Dual-Luciferase reporter assay and Pearson correlation test. The role of circ0041103/miR-107/ FOXK1 axis in regulating BCa process was explored by rescue experiments.

RESULTS: Circ0041103 was abnormally upregulated in BCa tissues and cell lines. Its level was higher in BCa tissues with a larger tumor size, or worse tumor staging, or BCa cases with lymphatic metastasis. Knockdown of circ0041103 inhibited proliferative and metastatic capacities of T24 and UM-UC-3 cells. MiR-107 was the binding target of circ0041103, and FOXK1 was the downstream gene of miR-107. Overexpression of circ0041103 could reverse the inhibited proliferative and metastatic capacities of T24 and UM-UC-3 cells overexpressing miR-107.

CONCLUSIONS: Circ0041103 is upregulated in BCa and predicts a poor prognosis in BCa. It stimulates BCa cells to proliferate and migrate *via* the miR-107/FOXK1 axis.

Key Words:
Bladder cancer, Circ0041103, MiR-107, FOXK1.

Introduction

Bladder cancer (BCa) is a common malignant tumor in the urinary system, which is the ninth-ranking malignancy globally[1]. In each year, about 400,000 people are diagnosed as BCa in the world, and it leads to 150,000 deaths[2]. Surgery, chemotherapy and radiotherapy are the traditional strategies for BCa. At present, the clinical recurrence and invasive rates of BCa still remain high, resulting in an unoptimistic 5-year survival[3]. It is urgent to clarify the molecular mechanism of the malignant process of BCa, thus providing novel targets for diagnosis and treatment.

Forty years ago, circRNAs were discovered for the first time in eukaryotic cells under an electron microscope[4]. CircRNAs are a novel type of noncoding RNAs, which are featured by the covalent closed loop in the structure without 5' and 3' ends[5]. Due to the unique structure, circRNAs are highly resistant to exonucleases. This feature makes circRNAs better than linear RNA in the application of biological markers[6]. Very recently, many studies have shown the vital functions of circRNAs in human cancers. Of note, circMTO1 blocks glioblastoma cells to proliferate through the miR-92/WWOX signaling[7]. Circ_0102049 triggers the proliferative ability of osteoblastoma cells by the sponge effect on miR-1304-5p and thus upregulates MDM2[8]. Hsa_circ_0012673 promotes lung adenocarcinoma to proliferate by sponging miR-22[9].

MicroRNAs (miRNAs) are 22-nucleotides noncoding RNAs that exerts post-transcriptional regulation by inducing mRNA degradation and inhibiting mRNA translation[10,11]. MiRNAs serve as either oncogenic or anti-cancer role in tumor process. Abnormally expressed miRNAs are able

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to affect tumor occurrence and deterioration[12]. In addition, miRNAs are extensively involved in biological activities[13]. MiR-107 participates in human cancers. MiR-107 regulates the growth and metastasis of gastric cancer by downregulating FAT4 and activating the PI3K/AKT signaling[14]. MiR-107 inhibits apoptosis of colorectal cancer cells by targeting Par4[15]. By activating the ATR/Chk1 signaling, miR-107 weakens the invasiveness of cervical cancer by targeting MCL1[16].

Circ0041103 is abnormally upregulated in BCa[17]. This study designed a series of *in vitro* experiments to elucidate the biological functions of circ0041103 in affecting the process of BCa.

Patients and Methods

Sample Collection of BCa

Fifty cases of BCa treated by surgery were recruited. None of them had preoperative chemotherapy or radiotherapy. Tissue samples were frozen in liquid nitrogen and stored at -80°C. Tumor staging of BCa was defined according to the criteria proposed by Union for International Cancer Control (UICC). This investigation was approved by the research Ethics Committee of Huaibei People's Hospital and complied with the Helsinki Declaration. Informed consent was obtained from patients prior to sample collection.

Cell Culture and Transfection

Human bladder epithelial cell line (SV-HUC-1) and BCa cell lines (T24, UM-UC-3, RT4, 5637) were provided by American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were cultivated in Roswell Park Memorial Institute-1640 (RPMI-1640; HyClone, South Logan, UT, USA) with 10% fetal bovine serum (FBS; HyClone, South Logan, UT, USA) in a humidified environment with 5% CO_2 at 37°C.

One day prior to transfection, cells were seeded in a 6-well plate and cultivated to higher than 60% of density. Cell transfection was routinely conducted using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA).

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

RNA was reversely transcribed to complementary deoxyribose nucleic acid (cDNA) and subjected to qRT-PCR using the SYBR Premix Ex Taq II (TaKaRa, Dalian, China) on the Applied Biosystems 7500 system (Applied Biosystems, Foster City, CA, USA). Relative level was calculated using $2^{-\Delta\Delta CT}$ method. Primer sequences were as follows: hsa_circ_0041103: F: 5′-GGCCTCTCTCCTGATACAGC-3′; R: 5′-CTCGGGTCTGCGGTAATCC-3′; miR-107: F 5′-GCCGAATTCAAAGCGAGATTCCATCAGCA-3′; R 5′-GCCGGATCCTGTCAACCCAGAACTCAAAGG-3′; FOXK1: F 5′-ACACGTCTGGAGGAGACAGC-3′; R 5′-GAGAGGTTGTGCCGGATAGA-3′; GAPDH: F 5′-ATGGGGAAGGTGAAGGTCG-3′; R 5′-GGGGTCATTGATGGCAACAATA-3′; U6: F 5′-CTCGCTTCGGCAGCACA-3′; R 5′-ACGCTTCACGAATTTGCGT-3′.

Cell Counting Kit-8 (CCK-8) Assay

Cells were inoculated in a 96-well plate with 5×10^3 cells per well. At the appointed time points, absorbance value at 450 nm of each sample was recorded using the CCK-8 kit (RIBOBIO, Guangzhou, China) for plotting the viability curves.

5-Ethynyl-2′-Deoxyuridine (EdU) Assay

Cells were pre-inoculated in a 24-well plate with 5×10^3 cells/well. They were incubated in 4% methanol for 30 min, followed by 10-min permeabilization in 0.5% TritonX-100, and 30-min reaction in 400 μL of 1×ApollorR. Afterwards, the cells were dyed in 4',6-diamidino-2-phenylindole (DAPI) for other 30 min. EdU-stained cells were calculated under a fluorescence microscope (CKX41-F32FL, Olympus, Tokyo, Japan) for calculating the percentage of positive EdU-stained cells.

Transwell

Transwell chambers (Millipore, Billerica, MA, USA) were inserted in each well of a 24-well plate, where 5×10^4 cells were applied in the upper layer of the chamber, and 600 μL of medium containing 10% FBS was applied in the bottom. After 48-h incubation, cells in the bottom were reacted with 15-min methanol, 20-min crystal violet and captured using a microscope. Migratory cells were counted in 5 randomly selected fields per sample. Invasion assay was conducted using transwell chamber precoated with 100 μg Matrigel.

Dual-Luciferase Reporter Assay

Binding sites between two genes were predicted using online databases. Cells were seeded in the 24-well plate one day prior to co-transfection. They were co-transfected with Luciferase vectors and miR-107 mimics or negative control for 48 h. Luciferase activity was measured using the Du-

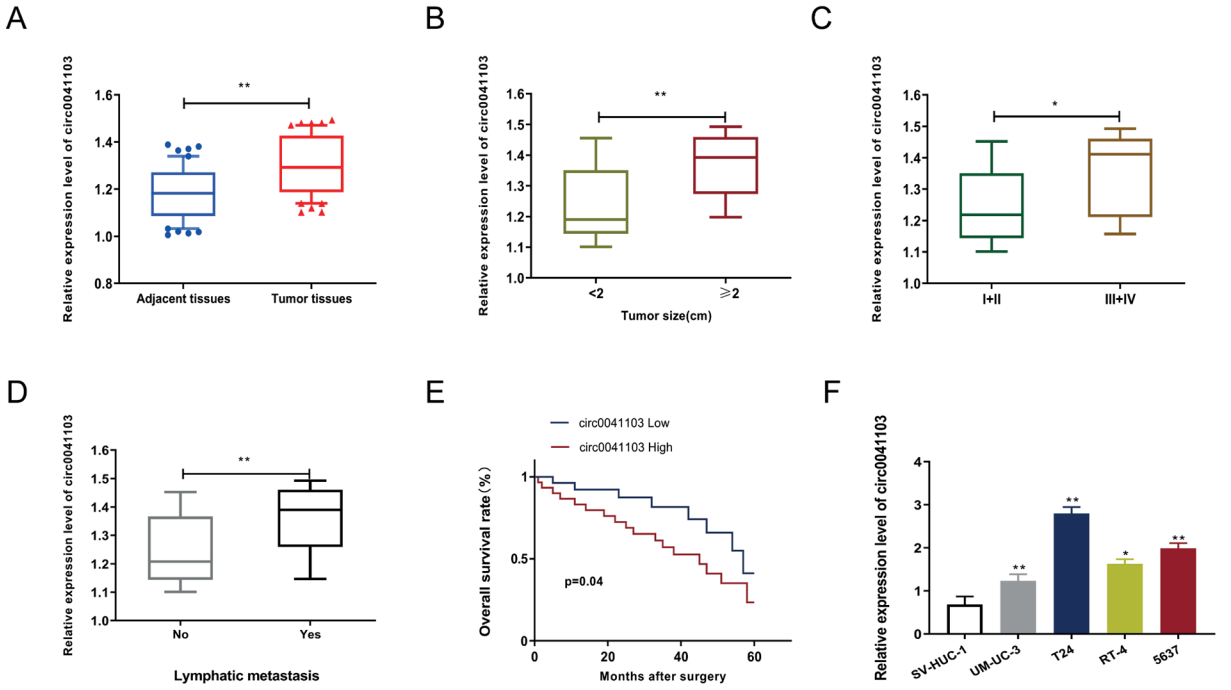

Figure 1. Differential level of circ0041103 in BCa and its clinical significance. **A,** Circ0041103 levels in BCa and adjacent tissues. **B,** Circ0041103 levels in BCa tissues classified by tumor size. **C,** Circ0041103 levels in BCa tissues classified by tumor staging. **D,** Circ0041103 levels in BCa tissues classified by the state of lymphatic metastasis. **E,** Overall survival in BCa patients based on circ0041103 levels. **F,** Circ0041103 levels in BCa cell lines; **p*<0.05; ***p*<0.01.

al-Luciferase reporter assay system (Promega, Madison, WI, USA).

Statistical Analysis

Data processing was conducted using Statistical Product and Service Solutions (SPSS) 19.0 (SPSS Inc., Chicago, IL, USA). Two-paired independent *t*-test was performed for comparing the differences between groups. Kaplan-Meier method was introduced for survival analysis. A significant difference was set at $p < 0.05$.

Results

Differential Level of Circ0041103 in BCa and Its Clinical Significance

Differential level of circ0041103 in BCa and adjacent normal tissues was first detected by qRT-PCR. It is shown that circ0041103 was highly expressed in BCa tissues than controls (Figure 1A). Specifically, circ0041103 level was higher in BCa tissues larger than 2 cm in size than those smaller ones (Figure 1B). Classified by tumor staging, higher expression level of circ0041103 was detected in stage III+IV BCa cases in comparison to stage I+II ones (Figure 1C). BCa patients with lymphatic metastasis had a higher abundance of circ0041103 than non-metastatic patients (Figure 1D). Furthermore, Kaplan-Meier survival analysis demonstrated that high level of circ0041103 was an unfavorable factor to the overall survival of BCa (Figure 1E). *In vitro* level of circ0041103 in BCa cell lines was also detected by qRT-PCR. It was highly expressed in BCa cell lines than that of the bladder epithelial cell line (Figure 1F).

Knockdown of Circ0041103 Weakened Proliferative and Metastatic Capacities of BCa

Two lines of circ0041103 siRNAs were synthesized. Transfection of either si-circ0041103#1 or si-circ0041103#2 could effectively downregulate circ0041103 in T24 and UM-UC-3 cells (Figure 2A). QRT-PCR data showed that si-circ0041103#2 had the better transfection efficacy than the other one, which was utilized in the following experiments. CCK-8 assay uncovered that the knockdown of circ0041103 declined viability in BCa cells (Figure 2B). Consistently, reduced

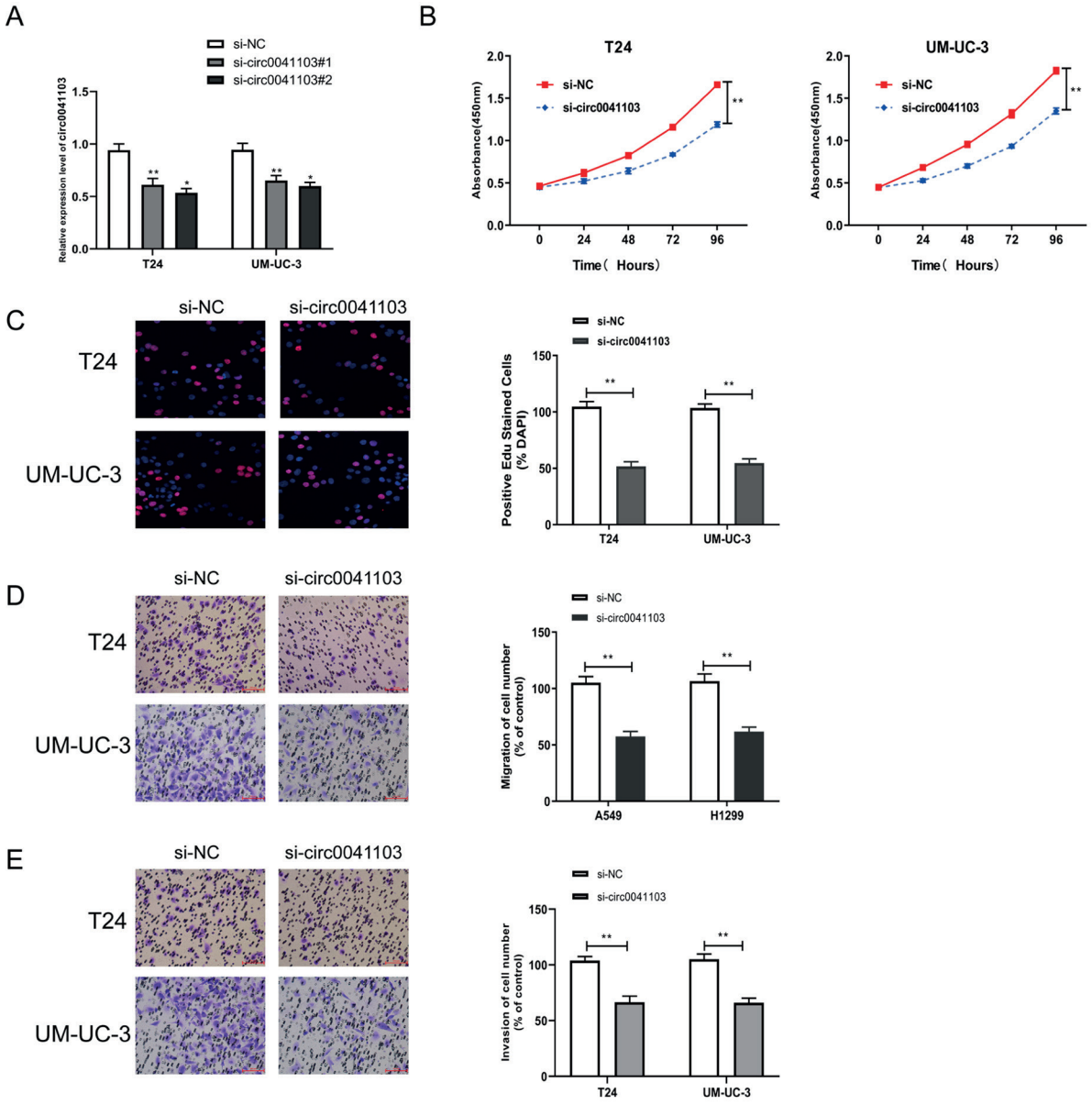

Figure 2. Knockdown of circ0041103 weakened proliferative and metastatic capacities of BCa. **A,** Transfection efficacy of circ0041103 siRNAs in T24 and UM-UC-3 cells. **B,** Cell viability in T24 and UM-UC-3 cells with circ0041103 knockdown. **C,** EdU-stained cells in T24 and UM-UC-3 cells with circ0041103 knockdown (magnification 200×). **D,** Migration in T24 and UM-UC-3 cells with circ0041103 knockdown (magnification 200×). **E,** Invasion in T24 and UM-UC-3 cells with circ0041103 knockdown (magnification 200×); *p<0.05; **p<0.01.

percentage of EdU-stained cells by knockdown of circ0041103 in T24 and UM-UC-3 cells also indicated that circ0041103 could stimulate proliferative capacity of BCa (Figure 2C). Subsequently, migratory and invasive capacities of BCa affected by circ0041103 were examined *via* transwell assay. Knockdown of circ0041103 markedly attenuated metastatic capacity of T24 and UM-UC-3 cells (Figure 2D, E).

Circ0041103 Exerted miRNA Sponge on MiR-107

Potential candidates of circ0041103 targets were predicted using TargetScan (http://www.targetscan.org/vert_71/) and StarBase (http://starbase.sysu.edu.cn/index.php). After cross-match analysis, miR-107 was chosen to be the most potential target (Figure 3A). Furthermore, regulatory effect of circ0041103 on relative levels of

pri-miR-107, pre-miR-107 and mature miR-107 in BCa cells were detected. Circ0041103 was only able to regulate the level of mature miR-107, suggesting that circ0041103 exerted its biological function through post-transcriptional regulation (Figure 3B). The binding site in the 3'UTR of miR-107 and circ0041103 was predicted by bioinformatic tools (Figure 3C). Afterwards, Dual-Luciferase reporter assay showed that miR-107 was capable of mediating Luciferase activity in the wild-type circ0041103 vector, rather than the mutant-type one (Figure 3D). Thus, we have proven that circ0041103 exerted the sponge effect on miR-107. Compared to adjacent normal tissues, miR-107 was downregulated in BCa tissues (Figure 3E). It was negatively regulated by circ0041103 in BCa samples (Figure 3F, 3G).

Regulatory Effects of MiR-107 on BCa Cell Phenotypes Were Abolished by Circ0041103

We designed a series of rescue experiments to clarify the role of circ0041103 and miR-107 in BCa process. Transfection efficacy of miR-107 mimics and circ0041103 OE was detected in T24 and UM-UC-3 cells (Figure 4A). Overexpression of miR-107 in BCa cells remarkably reduced viability and percentage of EdU-stained cells, and interestingly, the attenuated proliferative capacity was reversed by co-overexpression of circ0041103

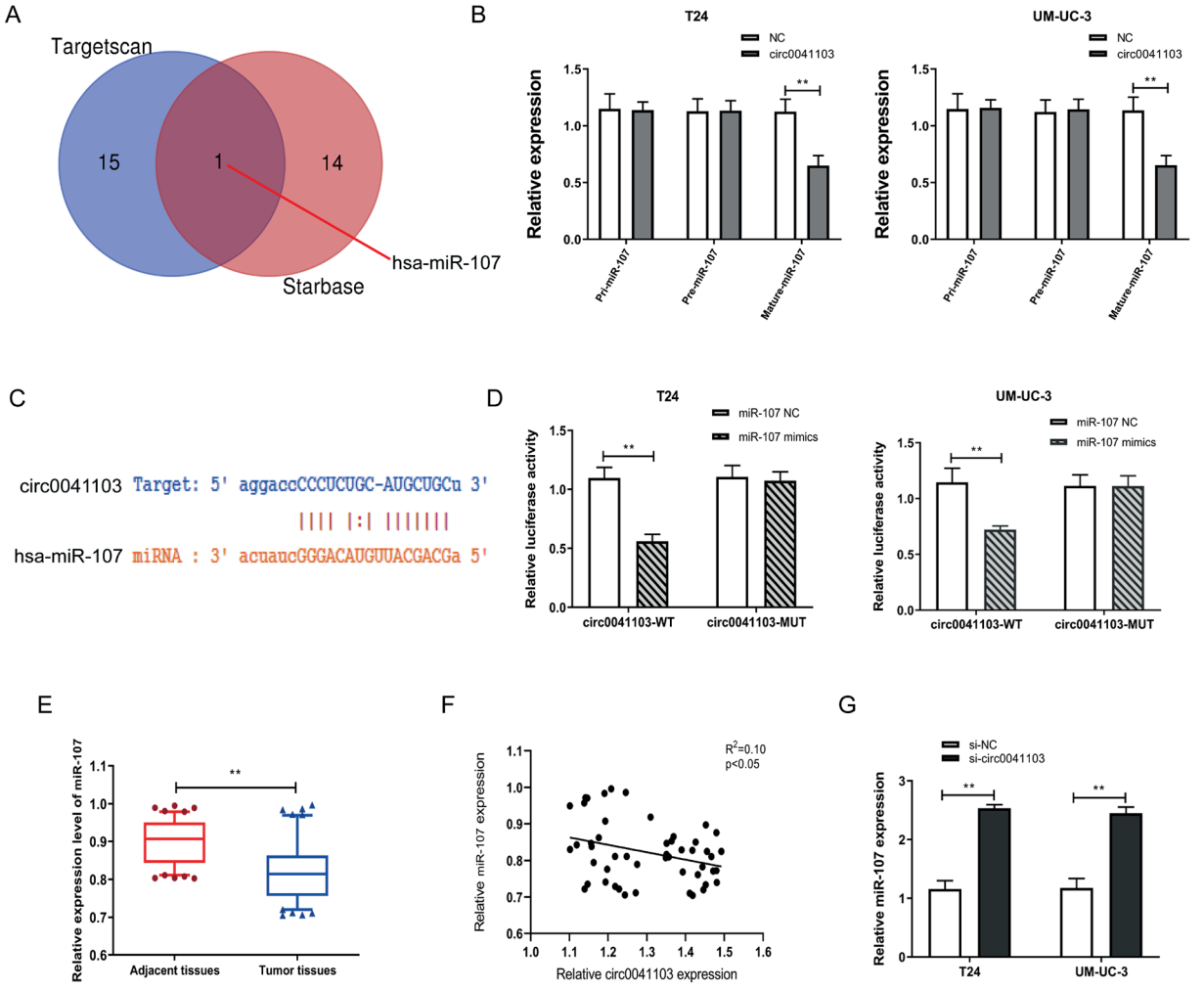

Figure 3. Circ0041103 exerted miRNA sponge on miR-107. **A,** Prediction of potential RNAs binding circ0041103. **B,** Relative levels of pri-miR-107, pre-miR-107 and mature miR-107 in T24 and UM-UC-3 cells regulated by circ0041103. **C,** Binding sites in the 3'UTR of circ0041103 and miR-107. **D,** Luciferase activity in circ0041103 vectors regulated by miR-107. **E,** MiR-107 levels in BCa and adjacent tissues. **F,** A negative correlation between circ0041103 and miR-107. **G,** MiR-107 level in T24 and UM-UC-3 cells with circ0041103 knockdown; *p<0.05; **p<0.01.

(Figure 4B, 4C). Similarly, the suppressed metastasis in BCa cells overexpressing miR-107 was abolished by overexpressed circ0041103 (Figure 4D, E).

FOXK1 Was the Direct Target of MiR-107

Through prediction using DIANA and StarBase, and cross-match analysis, FOXK1 was selected as the direct target of miR-107 (Figure 5A). Their binding relation was further verified by Dual-Luciferase reporter assay (Figure 5B, 5C). Compared with adjacent tissues, FOXK1 was upregulated in BCa tissues (Figure 5D). Pearson correlation test revealed that FOXK1 was negatively correlated to miR-107, and positively correlated to circ0041103 in BCa tissues (Figure 5E).

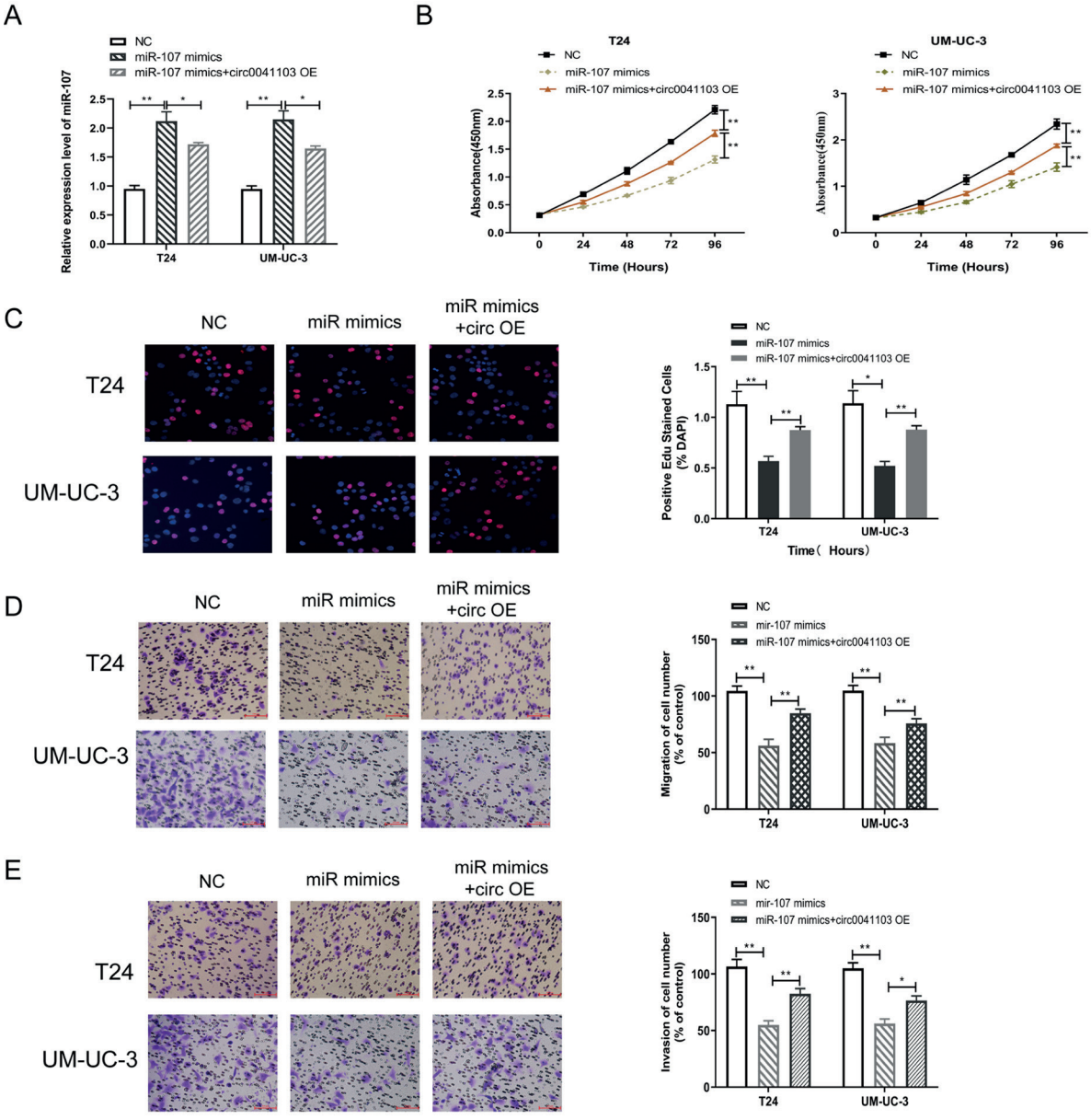

Figure 4. Regulatory effects of miR-107 on BCa cell phenotypes were abolished by circ0041103. **A,** Transfection efficacy of miR-107 mimics and circ0041103 OE in T24 and UM-UC-3 cells. **B,** Viability in T24 and UM-UC-3 cells co-regulated by miR-107 and circ0041103. **C,** EdU-stained cells in T24 and UM-UC-3 cells co-regulated by miR-107 and circ0041103 (magnification 200×). **D,** Migration in T24 and UM-UC-3 cells co-regulated by miR-107 and circ0041103 (magnification 200×). **E,** Invasion in T24 and UM-UC-3 cells co-regulated by miR-107 and circ0041103 (magnification 200×); *p<0.05; **p<0.01.

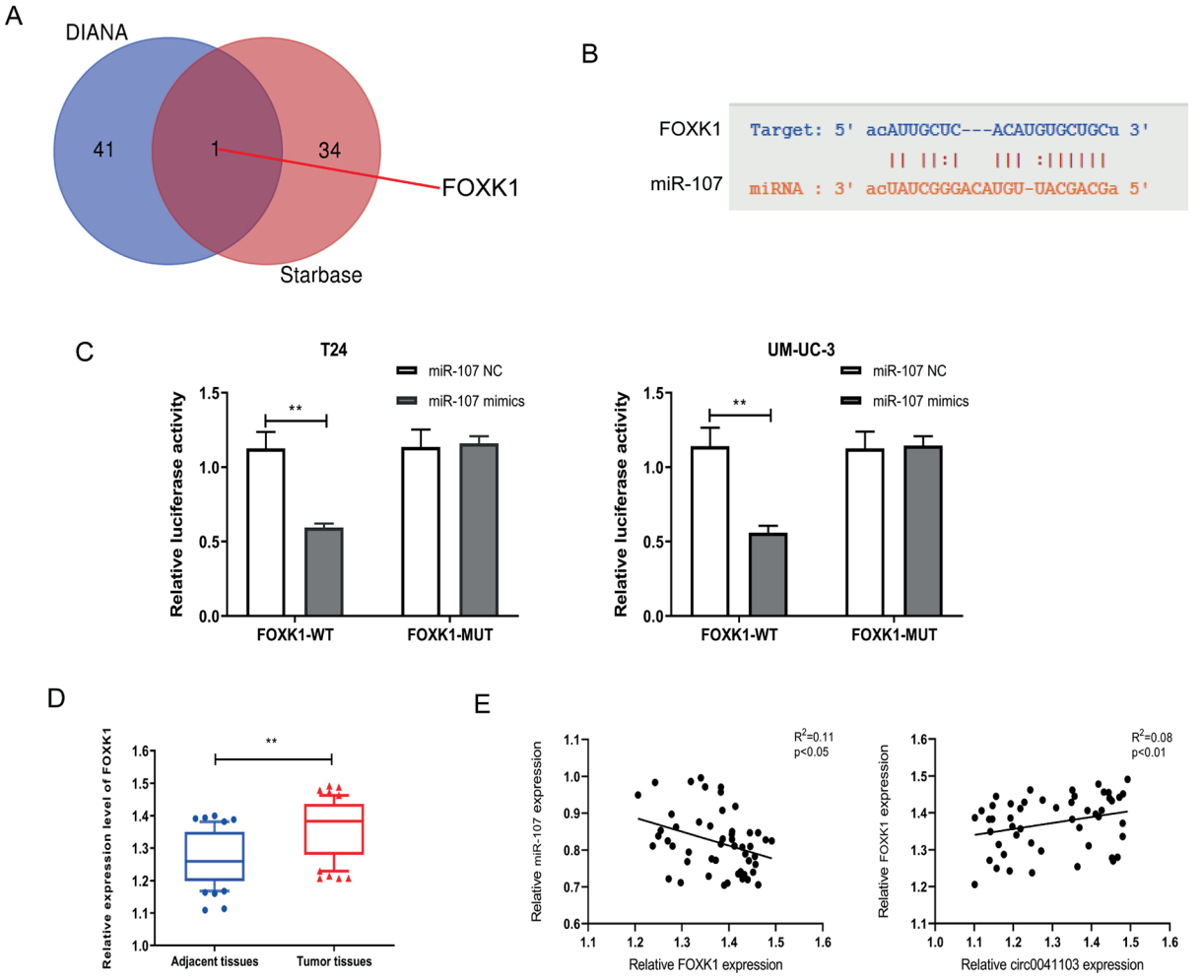

Figure 5. FOXK1 was the direct target of miR-107. **A,** Prediction of potential targets binding miR-107. **B,** Binding sites in the 3'UTR of miR-107 and FOXK1. **C,** Luciferase activity in FOXK1 vectors regulated by miR-107. **D,** FOXK1 levels in BCa and adjacent tissues. **E,** A negative correlation between miR-107 and FOXK1 and a positive correlation between circ0041103 and FOXK1; **p*<0.05; ***p*<0.01.

Discussion

The diagnosis of BCa mainly relies on cystoscope and urine cytology[18]. However, these diagnostic methods have limited clinical applications. A large number of patients cannot be diagnosed in time. Seriously, the median survival of BCa is 15 months and the 5-year survival is as low as 15%[19]. Currently, great efforts have been made on blocking malignant phenotypes of BCa[20]. Here, circ0041103 was detected to be upregulated in BCa tissues, especially BCa cases with large tumor size, advanced staging or lymphatic metastasis. In addition, Kaplan-Meier survival curves revealed that BCa patients expressing high level of circ0041103 had poor prognosis. It is indicated that circ0041103 was a prognostic factor for BCa.

It is previously reported that circRNAs have a close relation to disease state and prognosis[21]. They are involved in tumor process by sponging miRNAs, and thus affect miRNA activities and functions, circRNAs can be used as ceRNA to compete with mRNA to bind miRNA to regulate tumor progression. The complicated circRNA-miRNA axis is responsible for targeting cell cycle progression, signaling transduction, epigenetic modification, etc.[22]. We generated circ0041103 knockdown models by transfection of circ0041103 siRNAs in T24 and UM-UC-3 cells. Knockdown of circ0041103 markedly weakened proliferative and metastatic capacities of T24 and UM-UC-3 cells. Subsequently, miR-107 was predicted to share a binding site in the 3'UTR with that of circ0041103 using TargetS-

can and Starbase, and their binding relation was further proven by Dual-Luciferase reporter assay. Rescue experiments showed that the overexpression of circ0041103 could reverse the inhibited proliferative and metastatic capacities of T24 and UM-UC-3 cells overexpressing miR-107.

MiRNAs are able to negatively regulate protein expressions by recognizing and binding mRNA 3'UTR[23]. Through analyses using DIANA and StarBase, FOXK1 was identified to be the direct target of miR-107. Transcription factors of the FOX family are highly conserved with the structural features of forkhead box or biplane helix[24]. They are able to regulate transcriptional activities of target genes by binding DNAs, thus participating in the regulation of signaling transduction, cell cycle progression and metabolism[25]. FOXK1 is a member of the FOX family, and has been shown to play a key role in cell proliferation, cell growth, and metabolism[26]. Cui et al[27] pointed out that the knockdown of FOXK1 suppresses the viability of hepatocellular carcinoma cells *via* inhibiting the glycolysis. By activating the transcription factor Snail, FOXK1 accelerates glioblastoma cells to proliferate and migrate[28]. FOXK1 induces EMT and thereafter enhances the invasiveness of colorectal carcinoma[29]. Pearson correlation test revealed that in our experiments, FOXK1 was negatively correlated to miR-107, and positively correlated to circ0041103 in BCa tissues. Based on the above findings, circ0041103/miR-107/FOXK1 axis was identified to aggravate the process of BCa. Our findings provide useful biomarkers for clinical diagnosis and treatment of BCa. In this study, we found that circ0041103 can be used as ceRNA of FOXK1 to regulate the role of miR-107 in BCa. In BCa, circ0041103 can regulate the expression of FOXK1 by sponging miR-107. This may be a new target for the diagnosis and treatment of BCa.

Conclusions

Circ0041103 is upregulated in BCa, and predicts a poor prognosis in BCa. It stimulates BCa cells to proliferate and migrate *via* the miR-107/FOXK1 axis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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