European Review for Medical and Pharmacological Sciences 2019; 23 (3 Suppl): 256-263

Circ_0017247 accelerates epithelial-mesenchymal transition in non-small cell lung cancer

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Abstract. – OBJECTIVE: Recently, the vital role of circular RNAs is discovered in many diseases, including tumor progression. Non-small cell lung cancer (NSCLC) is one of the most ordinary malignant tumors. The purpose of our study is to detect the potential function of circ_0017247 in NSCLC to offer new biomarkers and targets.

PATIENTS AND METHODS: The level of circ_0017247 in NSCLC tissues and cell lines was monitored by Rea Time-quantitative Polymerase Chain Reaction (RT-qPCR). Pearson's Chi-square test was used to determine the association between circ_0017247 expression and several clinicopathological factors. Then, circ_0017247 was knocked down in NSCLC cells to uncover its function in metastasis of NSCLC. Cell migrated and invaded ability was measured through transwell assay, Matrigel assay, and wound healing assay. The Western blot assay was performed to analyze the effect of circ_0017247 on the epithelial-mesenchymal transition (EMT) process.

RESULTS: In the research, the expression level of circ_0017247 was significantly increased in NSCLC tissues compared with that in the adjacent samples. Circ_0017247 expression was associated with lymphatic metastasis. The expression of circ_0017247 was also increased in NSCLC cell lines. Downregulation of circ_0017247 led to the inhibition of cell migration and invasion in NSCLC. In addition, results of further [illegible] revealed that the EMT-related proteins were regulated via the knockdown of circ_0017247 in NSCLC.

CONCLUSIONS: Circ_0017247 could enhance cell migration and invasion in NSCLC by inducing EMT process.

Key Words:
Circular RNA, Circ_0017247, Non-small cell lung cancer, Epithelial-mesenchymal transition.

Introduction

Lung cancer remains a worldwide threat. In 2018, 234,000 patients were diagnosed with lung cancer, and 154,000 patients died because of lung cancer in America[1]. As the major type of lung cancer, non-small cell lung cancer (NSCLC) contributes to 85% of all lung cancer cases. Moreover, the morbidity and mortality of NSCLC remain a huge problem for the following decades[2]. Despite tremendous efforts have been made in tumorigenesis and therapeutic treatment of NSCLC, the prognosis remains dismal, with the 5-year survival rate below [illegible][3]. Therefore, it is very urgent to reveal the underlying molecular mechanism of NSCLC and find out new therapeutic targets for the patients.

Circular RNA (circRNA) was first discovered in 1976 with complete closed-loop structure. Recently, with the development of high-throughput sequencing technology, circRNAs have been [illegible] stars which play an important role in various diseases, including diverse cancers. For example, by regulating the expression of miR-138, hsa_circ_0020397 promotes cell viability and invasion in colorectal cancer by targeting TERT and PD-L1[4]. By regulating miR-1324/FZD5/Wnt/β-catenin signaling, circ_0067934 facilitates tumor growth and cell migration in hepatocellular carcinoma[5]. Overexpression of hsa_circ_0001649 inhibits cell proliferation, cell invasion, and cell migration in cholangiocarcinoma[6]. By activating expression of TPX2 *via* restraining miR-8075, hsa_circRNA_101996 promotes cell proliferation and invasion in cervical cancer[7]. A recent study[8] discovers that circ_0017247 is screened as a new oncogene in malignant tumors. However, the function of circular RNA in NSCLC and the potential molecular mechanism have not been studied yet. To uncover the role of circ_0017247 in NSCLC, its expression was detected in NSCLC tissues and the related mechanism was analyzed.

In our work, circ_0017247 was remarkably upregulated in NSCLC tissues and cell lines. Moreover, circ_0017247 promoted migration and invasion of NSCLC *in vitro*. Our further experi-

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ments also showed that circ_0017247 induced the epithelial-mesenchymal transition (EMT) process of NSCLC.

Patients and Methods

Tissue Samples

A total of 53 NSCLC tissues and para-cancer tissues were obtained at the 960th PLA Hospital. Clinical data of the patients were collected. The clinicopathological characters were analyzed by two pathologists. After surgical resection, all the tissue samples were snap-frozen in liquid nitrogen immediately. This research complies with the Ethics Committee of the 960th PLA Hospital. Written informed consents were gathered from all the patients enrolled.

Cell Culture and Transfection

Human NSCLC cell lines (SPCA1, H1299, PC-9, and H358) and a normal human bronchial epithelial cell line (16HBE) were purchased from the Shanghai Cell Biochemical Institute (Shan[illegible] China). The culture medium consisted o[illegible] well Park Memorial Institute-1640 (RPM[illegible]0; HyClone, South Logan, UT, USA), 10% [illegible] bovine serum (FBS; Invitrogen, Carlsbad, C[illegible] USA), and penicillin/streptomycin. Besides, cell[illegible] were cultured in an incubator cont[illegible]5% CO_2 at 37°C.

After NSCLC cells were [illegible]red [illegible] on 6-well plates, they wer[illegible]nsfe[illegible] cDNA oligonucleotides spe[illegible]argeting circ_0017247 (shRNA) an[illegible]ntrol [illegible]rma; Shanghai, China) using [illegible]ofectamine [illegible]n-vitrogen, Carlsbad, C[illegible]A). The transf[illegible]tion efficiency was monit[illegible] Time-quantitative Polymerase Ch[illegible] Reac[illegible]qPCR).

RNA Extracti[illegible] and RT-qPCR

TRIzol RN[illegible] solati[illegible] kit (Invitrogen, Carlsbad, CA, US[illegible] was [illegible]ed to separate the total mRNA fr[illegible]nd c[illegible] The synthesis of cDNAs wa[illegible]ted [illegible]ough the reverse Transcri[illegible]n Kit ([illegible]iotechnology Co., Ltd., [illegible]China), [illegible]otal RNA was revers[illegible]nsc[illegible]ed. The primer sequences used fo[illegible]-qPC[illegible]ows: circ_0017247, forw[illegible]CTGC[illegible]GAAAGTGTGTCCC-5'; circ_[illegible] reverse: 3'-TCCTATGAATGAG-CCATC[illegible]; glyceraldehyde 3-phosphate dehydrogenas[illegible]GAPDH) primers forward: 5′-CAATGACCCCTTCATTGACC-3′ and reverse 5′-TTGATTTTGGAGG[illegible] The conditions were as follow[illegible]e-denatu[illegible] at 95°C for 1 min, followed [illegible]0 cycles at 9[illegible] for 15 s, 60°C for 30 s, and [illegible] 30 s.

Wound Healing [illegible]ay

After transfecti[illegible]NSCLC cells [illegible] seeded in 6-well plates [illegible] inc[illegible]ed in RPMI-1640 medium overni[illegible] The [illegible]ells w[illegible] scratched with a plastic tip[illegible]red in [illegible]um-free RPMI-1640. E[illegible] assay [illegible]d in triplicate independe[illegible] The rela[illegible]ce was viewed under a [illegible]microscope (O[illegible]mpus, Tokyo, Japan) at[illegible]

Tra[illegible]well Assay

[illegible]r transfection, [illegible]×10^5 cells in 200 µL [illegible]m-free RPMI-1640 were replanted in the [illegible] chamber (C[illegible]ning, Corning, NY, USA). [illegible]M-1640 and [illegible]S were added to the lower [illegible]ber. Nex[illegible]ey were cultured overnight in a[illegible]plemented with 5% CO_2 at 37°C. The [illegible]ace of chambers was treated with methanol for 30 min after wiped by a cotton [illegible] Then, they were stained in crystal violet for [illegible]ive fields were randomly chosen under [illegible]eica DMI4000B microscope (Leica Microsys[illegible]ms, Heidelberg, Germany).

[illegible]atrigel Assay

After transfection, 1×10^5 cells in 200 µL serum-free RPIM-1640 were replanted in the top chamber (Corning, Corning, NY, USA) with 50 µg Matrigel (BD, Bedford, MA, USA). RPMI-1640 and FBS were added to the lower chamber. Then, they were cultured overnight in an incubator supplemented with 5% CO_2 at 37°C. The top surface of chambers was treated by methanol for 30 min after wiped by a cotton swab. Subsequently, they were stained in crystal violet for 20 min. Five fields were randomly chosen under a Leica DMI4000B microscope (Leica Microsystems, Heidelberg, Germany).

Western Blot Analysis

Reagent radioimmunoprecipitation assay (RIPA; Beyotime, Shanghai, China) was utilized to extract the protein from cells. Bicinchoninic acid (BCA) protein assay kit (TaKaRa, Dalian, China) was chosen to quantify protein concentrations. The target proteins were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Then, they were incubated with antibodies after being replaced

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to the polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Cell Signaling Technology (CST, Danvers, MA, USA) provided us rabbit anti-GAPDH and rabbit anti-E-cadherin, rabbit anti-N-cadherin, rabbit anti-Vimentin, as well as goat anti-rabbit secondary antibody. Image J software (NIH, Bethesda, MD, USA) was applied for the assessment of protein expression.

Statistical Analysis

Statistical analysis was conducted by Statistical Product and Service Solutions (SPSS) 17.0 (SPSS, Chicago, IL, USA). Graph PAD 4.0 (GraphPad Software, Inc., La Jolla, CA, USA) helped to present these consequences. Pearson's Chi-square test and independent-sample *t*-test were used when appropriate. Quantitative data was presented as mean ± SD (standard deviation). Moreover, $p<0.05$ was a statistically significant difference.

Results

The Association Between Circ_0017[illegible] Expression and Pathological Characte[illegible] of NSCLC Patients

NSCLC patients were divid[illegible] to two groups, low and high circ_00[illegible] e NSCLC patients in high circ[illegible]24[illegible] sion group present with ly[illegible] atic [illegible] ($p<0.05$), while no differenc[illegible] e two groups were seen in age, [illegible] er, T[illegible] ge, and tumor size (Table I).

Circ_0017247 Express[illegible] el Wa[illegible] Higher in NSCLC Tissues [illegible]

Circ_0017247 e[illegible] ession was [illegible] ed *via* RT-qPCR in 53 [illegible] CLC [illegible] ients' ti[illegible] ue samples and matc[illegible] adj[illegible] t sam[illegible] les. Results showed that [illegible] 7 wa[illegible] ignificantly higher in tu[illegible] or ti[illegible] ples [illegible] n in adjacent tissues (Fi[illegible] e 1A). [illegible] 247 expression in huma[illegible] SCLC cell li[illegible] and 16HBE was also d[illegible] The circ_0017247 expression level [illegible] hi[illegible] NSCLC cells than that in 16H[illegible] E (Figure [illegible] esults suggested that ci[illegible] 017247 might [illegible] ction in the develop[illegible] t of NSCLC. Then, we chose SPCA1 and [illegible] 58 cells for t[illegible] e knockdown of circ_0017247 [illegible] transfectio[illegible] fficiency was detected by [illegible] PCR (Fi[illegible] 1C).

Circ_0017247 Knockdown Inhibited Cell [illegible] igration in NSCLC Cells

[illegible] ore how circ_0017247 affected cell mi[illegible] tion of NSCLC cells, wound healing assay and [illegible] answell assay were performed. As shown in Figure 2A, the migrated length of NSCLC cells was [illegible] educed after circ_0017247 was knocked down. [illegible] s shown in Figure 2B, the number of migrated cells remarkably decreased after circ_0017247 was knocked down in NSCLC cells.

Table I. Correlation between [illegible] 0017[illegible] on and clinicopathological characteristics in NSCLC patients.

Characteristics	[illegible]	Expression of circ_0017247		*p*-value
		Low expression	High expression	
Total	53	25	28	
Age (years)				0.238
≤ 50	21	12	9	
> 50	32	13	19	
Gender				0.707
Male	[illegible]	12	12	
Female	[illegible]	13	16	
TNM stage				0.833
I-II[illegible]	31	15	16	
I[illegible]	22	10	12	
T[illegible] size				0.708
[illegible] cm	29	13	16	
[illegible]	24	12	12	
Ly[illegible] etastasis				0.03
No	26	16	10	
Yes	27	9	18	

$p<0.05$ is conside[illegible] d as statistically significant.

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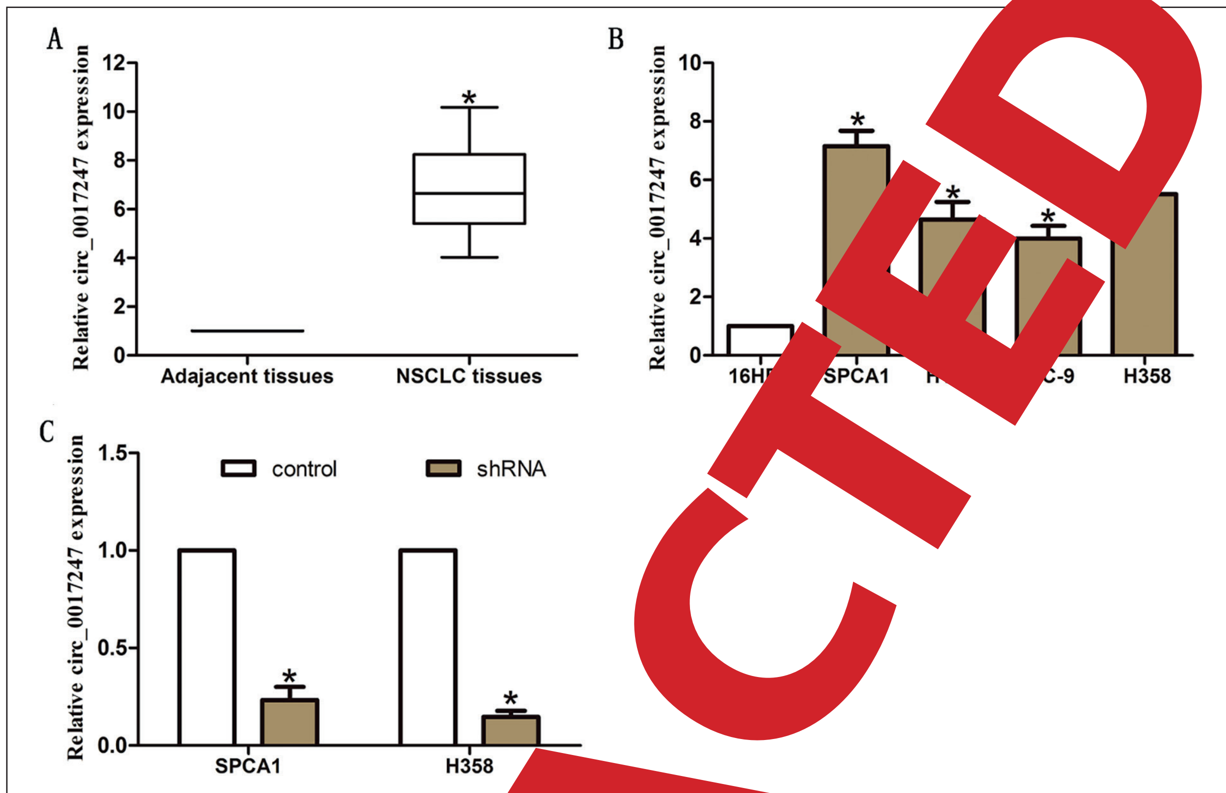

Figure 1. Expression levels of circ_0017247 were i[illegible]ed in N[illegible]s and cell lines. ***A,*** Circ_0017247 expression was significantly increased in the NSCLC tissues compare[illegible] adj[illegible] tissues. ***B,*** Expression levels of circ_0017247 relative to GAPDH were determined in the human NSCLC cell li[illegible]BE by RT-qPCR. ***C,*** Circ_0017247 expression in NSCLC cells transfected with circ_0017247 shRNA and control w[illegible]cted by RT-qPCR. GAPDH was used as an internal control. Data are presented as the mean ± standard e[illegible] of the mean[illegible]05.

Circ_0017247 Knockdow[illegible]d Cell Invasion in NSCLC Ce[illegible]

To explore how cir[illegible]17247 aff[illegible]ll migration of NSCL[illegible]ls, Matrigel [illegible]say was performed. As [illegible] Figure 3, after circ_0017247 was k[illegible]cked [illegible] number of invaded cells wa[illegible] remarkably de[illegible]d.

Circ_0017[illegible] Kno[illegible]own Inhibited EMT Pro[illegible]LC

Previous st[illegible]e r[illegible]ted the key role of the E[illegible] proces[illegible] metastasis. In our work[illegible]ct of ci[illegible]17247 on the EMT pro[illegible] wa[illegible]rther analyzed, and EMT-related pr[illegible]s in[illegible]herin, N-cadherin, and [illegible]evious [illegible]esearches identified that E-ca[illegible]as downregulated, while N-cadherin a[illegible]tin were upregulated when the EMT pr[illegible] was induced. RT-qPCR assay showed that the expression of E-cadherin in SPCA1 cells was higher in circ_0017247 shRNA group than that in control group, while the expression of N-cadherin and Vimentin in SPCA1 cells was lower in circ_0017247 shRNA group than in control group (Figure 4A). Western blot assay showed that the protein level of E-cadherin in SPCA1 cells was upregulated in circ_0017247 shRNA group compared with control group, while the expression of N-cadherin and Vimentin in SPCA1 cells was downregulated in circ_0017247 shRNA group compared with control group (Figure 4B). RT-qPCR assay showed that the expression of E-cadherin in H358 cells was higher in circ_0017247 shRNA group than in control group, while the expression of N-cadherin and Vimentin in H358 cells was lower in circ_0017247 shRNA group than in control group (Figure 4C). Western blot assay showed that the protein level of E-cadherin in H358 cells was upregulated in circ_0017247 shRNA group compared with that in control

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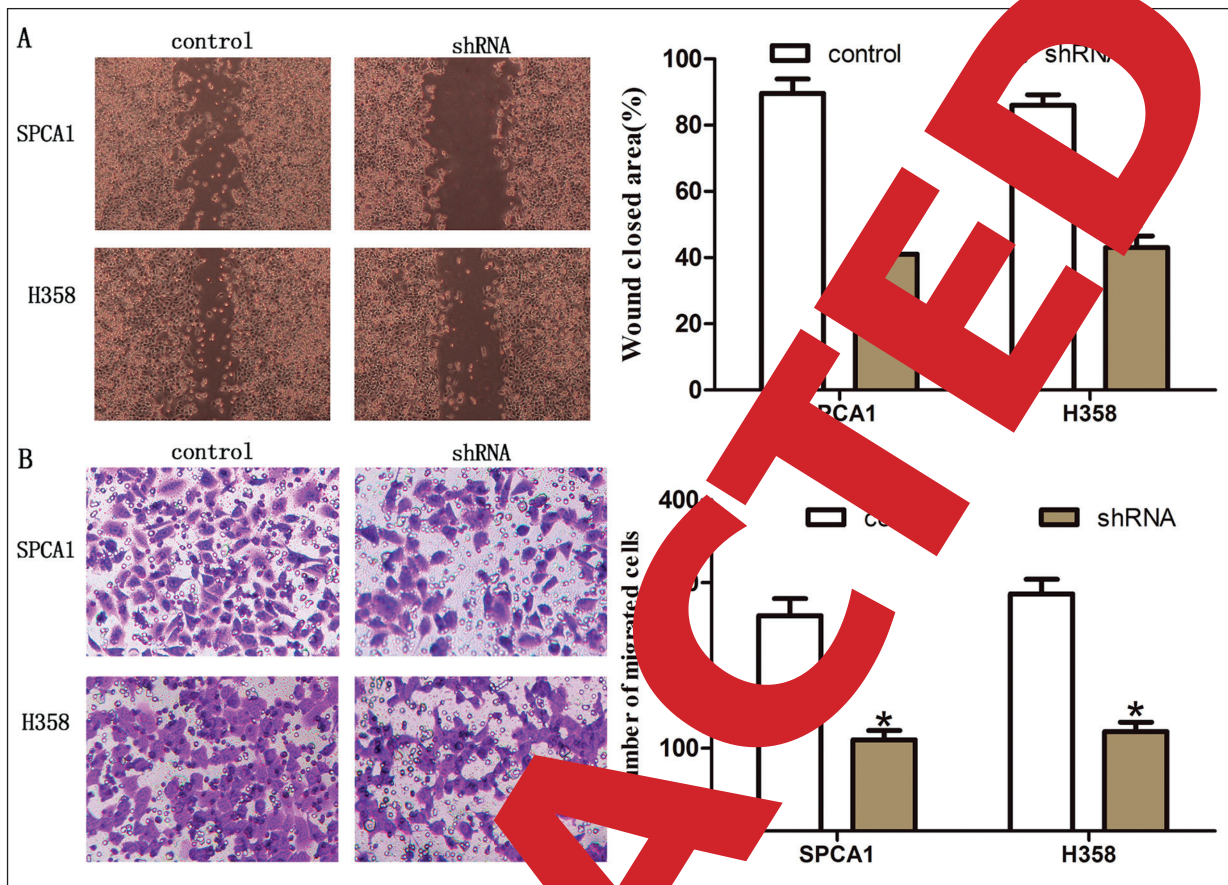

Figure 2. Knockdown of circ_0017247 inhibited NSCLC [illegible] igration. ***A*,** Wound healing assay showed that the migrated length of cells in circ_0017247 group wa[illegible]ly decreas[illegible]pared with control group in NSCLC cells (magnification: 40×). ***B*,** Transwell assay showed that [illegible] of circ_00[illegible]7 significantly repressed cell migration in NSCLC cells (magnification: 40×). The results repr[illegible] the a[illegible] of three independent experiments (mean ± standard error of the mean). *p<0.05, as compared with the cont[illegible]lls.

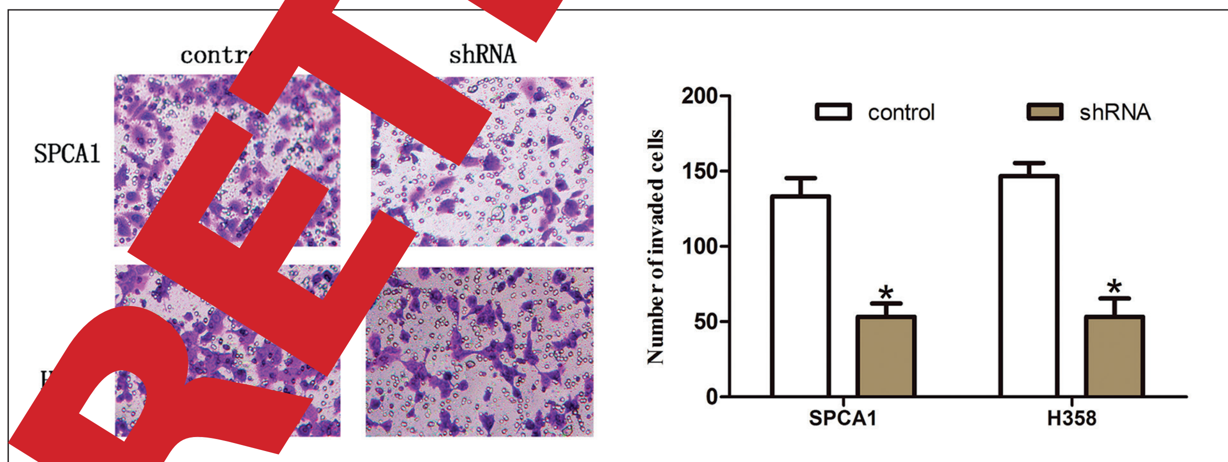

Figure 3. [illegible]wn of circ_0017247 inhibited NSCLC cell invasion. Transwell assay showed that knockdown of circ_0017247 si[illegible]ntly repressed cell invasion in NSCLC cells (magnification: 40×). The results represent the average of three independent [illegible]periments (mean ± standard error of the mean). *p<0.05, as compared with the control cells.

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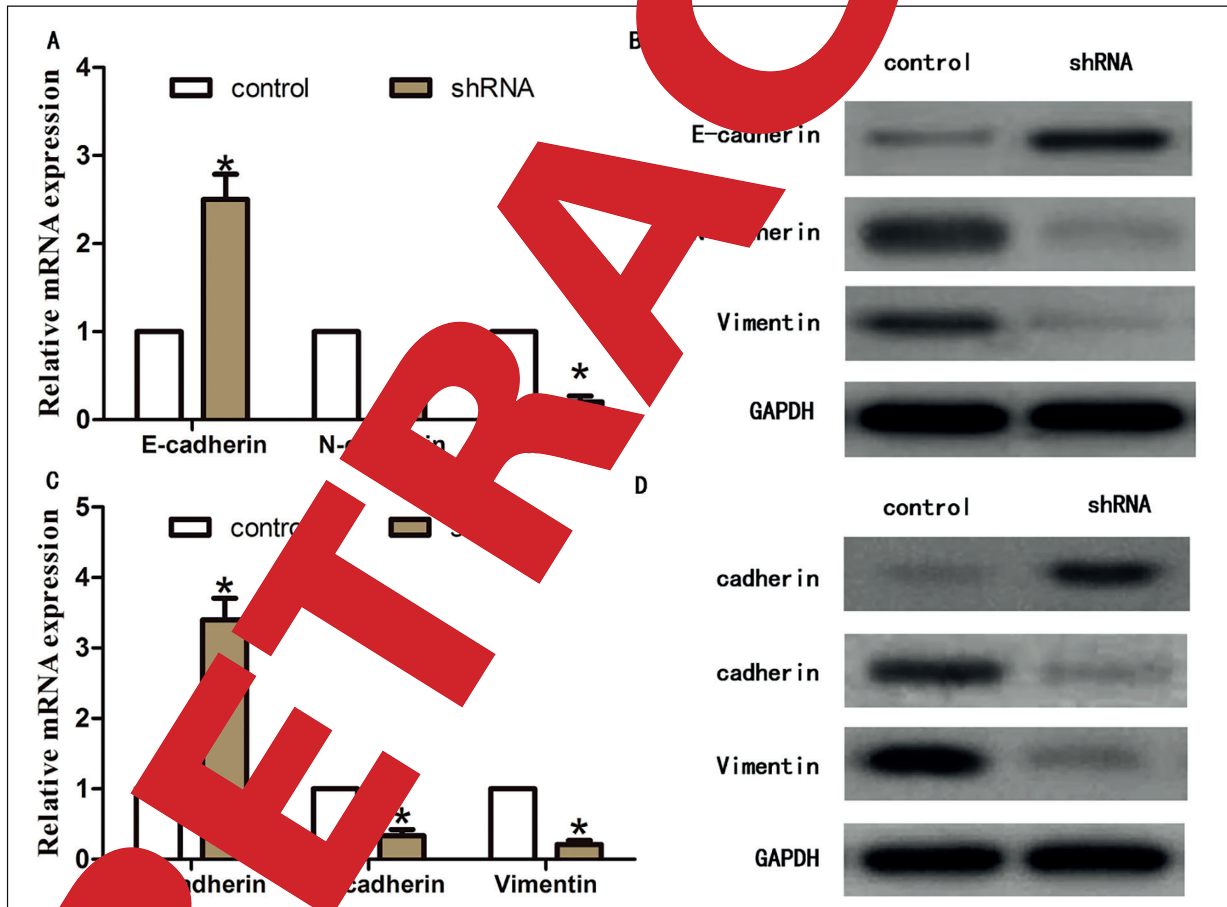
group, while the expression of N-cadherin and Vimentin in H358 cells was downregulated in circ_0017247 shRNA group compared with that in control group (Figure 4D).

Discussion

Circ_0017247 was initially discovered in osteosarcoma and promoted cell proliferation of osteosarcoma[9]. Increasing evidence identified the vital role of circular RNAs in NSCLC. As a miR-1252 sponge, hsa_circ_0043256 inhibits cell proliferation and induces cell apoptosis in NSCLC[10]. Mediated by miR-503/LARP1 signaling, the silencing of circ-BANP suppresses both cell proliferation and migration in lung cancer[11]. Has_circ_0001946 enhance[illegible]s in lung adenocarcinoma by [illegible] activatio[illegible] the Wnt/β-catenin signaling [illegible]hway[12]. Up[illegible]la-tion of hsa_circ_10039[illegible]dly inhib[illegible]ell proliferation and reduces [illegible]grati[illegible] and invasion in lung ca[illegible]r by ta[illegible]F21[13]. In this report, ci[illegible]017247 was [illegible]gulated in NSCLC sam[illegible] and [illegible]l lines. Notably, high circ_0017[illegible] exp[illegible]on w[illegible] associated with lymphatic [illegible] which [illegible]ggested that circ_001724[illegible] migh[illegible] metastasis of NSCLC.

To fu[illegible] determine wh[illegible]er circ_0017247 partici[illegible] regulation of NSCLC metastas[illegible] circ_[illegible]7 was knocked down in NS[illegible]C cells. W[illegible]aling assay and trans[illegible] assay were co[illegible]ucted in these treated



Fi[illegible] 4. Ci[illegible]kdown inhibited EMT process of NSCLC. ***A,*** RT-qPCR assay was used to detect the mRNA e[illegible] o[illegible]-cadherin, and Vimentin of SPCA1 cells in circ_0017247 shRNA group and control group. ***B,*** Wes[illegible]y was used to detect the protein level of E-cadherin, N-cadherin, and Vimentin of SPCA1 cells in circ_0017247 shRNA g[illegible]ontrol group. ***C,*** RT-qPCR assay was used to detect the mRNA expression of E-cadherin, N-cadherin, and Vimenti[illegible]cells in circ_0017247 shRNA group and control group. ***D,*** Western blot assay was used to detect the protein level of E[illegible]herin, N-cadherin, and Vimentin of H358 cells in circ_0017247 shRNA group and control group. Data are presented as the mean ± standard error of the mean. *$p<0.05$.

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cells. Results showed that circ_0017247 knockdown repressed cell migrated ability of NSCLC cells. Moreover, Matrigel assay was also conducted. Results showed that circ_0017247 knockdown repressed cell invaded ability of NSCLC cells. The above data indicated that circ_0017247 promoted cell migration and invasion of NSCLC.

EMT is a multistep process which enables cell invasiveness and motility. EMT is characterized by the progressive loss of cell-to-cell contacts resulting in filopodia formation and mesenchymal gene expression in the invasion of cancers. For example, URG11 promotes cell proliferation and EMT in benign prostatic hyperplasia cells through the RhoA/ROCK1 pathway[14]. EMT is associated with poor tumor differentiation in pancreatic ductal adenocarcinoma and it can be increased by gemcitabine[15].

Recently, some researchers found that the EMT process could be regulated by noncoding RNAs, including microRNAs, long noncoding RNAs, and circular RNAs. Through the activation of ZEB1 and the interaction with miR-139-5p, lncRNA HCP5 enhances the epithelial-mes[illegible]mal transition in colorectal cancer[16]. Cir[illegible] inhibits cell migration and EMT in bladde[illegible]cer by sponging miR-221[17]. In the present [illegible]per, the potential interaction between the EM[illegible] process and circ_0017247 was first [illegible]stigated. E-cadherin, N-cadherin, and Vi[illegible]e vital proteins in the EMT process, [illegible] dete[illegible] the expression of those proteins i[illegible]SCLC [illegible] found that they could be reg[illegible] knockdown of circ_0017247. All these [illegible]dicated that circ_0017247 could [illegible]ce the E[illegible]ss of NSCLC.

Conclusions

We showed [illegible] circ_0017247 was remarkably upregulated [illegible]SCL[illegible]ssues and was associated with th[illegible]etast[illegible] of NSCLC patients. Circ_0[illegible]cilitat[illegible]ell migration and invasion of NSC[illegible]ing the EMT process. [illegible]ndings [illegible]t that circ_0017247 may [illegible] prospective therapeutic target for N[illegible]C.

Conflict of [illegible]st

The Authors declar[illegible] that they have no conflict of interests.

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