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Circular RNA_LARP4 inhibits cell proliferation and invasion of nasopharyngeal carcinoma by repressing ROCK1

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Abstract. – OBJECTIVE: **Nasopharyngeal carcinoma (NPC) is one of the most ordinary malignant tumors. Recent studies have revealed that circular RNAs play an important role in the progression of tumorigenesis. This study aims to identify how circular RNA_LARP4 functio[illegible] the progression of NPC.**

PATIENTS AND METHODS: We per[illegible]ed Real Time quantitative-Polymerase Chai[illegible]e-action (RT-qPCR) in 58 paired NPC pati[illegible] tissue samples and cell lines to detect circ[illegible] RNA_LARP4 expression. The f[illegible] of circ[illegible]lar RNA_LARP4 in the NP[illegible]ion wa[illegible] identified by performing p[illegible]eratio[illegible]ssay and colony formation assay[illegible]eover, t[illegible]function of circular RNA_LARP4 i[illegible]m[illegible] measured by perfor[illegible]g s[illegible]ound[illegible]y and transwell ass[illegible] *in vitro*. [illegible]rmore, the underlying mec[illegible]m was exp[illegible] through Western blot a[illegible]y[illegible] RT-qPCR.

RESULTS: [illegible]rcula[illegible]A_LARP4 expression was signi[illegible]antly lowe[illegible] NPC tissues compared to [illegible]t in adjacent s[illegible]es. Cell proliferation o[illegible]PC was inhibited a[illegible] overexpression of ci[illegible]ar RNA_LARP4 *in vitro.* Cell migration an[illegible]sion [illegible]PC was inhibited after overexpress[illegible]f [illegible]cular R[illegible]_LARP4 *in vitro*. Furthermo[illegible] resul[illegible]of further experiments [illegible]led t[illegible]o-[illegible]ociated kinase 1 (ROCK1) w[illegible]ownreg[illegible] *via* overexpression of circular [illegible]A_LARP4[illegible]nd was also a direct target of cir[illegible]r RNA_LARP4 in NPC.

[illegible]NS: This study suggests that cir[illegible]lar RNA_LARP4 inhibits NPC cell prolifera[illegible] and metastasis via targeting ROCK1 *in vitro*.

Ke[illegible]rds:
Circular RNA_LARP4, Nasopharyngeal carcinoma, ROCK1.

[illegible]troduction

[illegible]sopharyng[illegible] carcinoma (NPC), which is a ma[illegible] ari[illegible]g from the nasopharynx epithelium, is [illegible] the most common head and neck [illegible]ithelial cancers globally, especially in Southern [illegible]d Southeast Asia[1]. Despite the advance [illegible]otherapy technique and chemotherapy strategies, approximately 30% of NPC cases suffered from treatment failure[2]. Moreover, the majority of patients with NPC cases are predisposed to metastasis at initial diagnosis which contributes to the poor prognosis, with a median survival of about 12 months[3,4]. Therefore, it is urgent to identify the cellular and molecular mechanisms of NPC and promote the development of effective individualized therapy for NPC.

Recently, although much technological progress has been made in human genome sequencing, the molecular mechanisms of NPC remain unclear. With the development of technology, it is widely known that the majority of human DNA is converted into noncoding RNAs (ncRNAs). Circular RNAs (circRNAs) is a subtype of ncRNAs, which has caught much attention in recent years for the crucial function in the progression of cancers. For example, by downregulating the expression of RhoA and circRNA_000839, miR-200b inhibits cell invasion and cell migration in hepatocellular carcinoma[5]. Through the sponging of miR-370, the knockdown of hsa_circ_0061140 inhibits cell growth and cell metastasis in ovarian cancer[6]. Through miR-506 sponging, silencing of circRNA-000284 inhibits cell proliferation and cell invasion in cervical can-

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cer[7]. By regulating the expression of miR-29a, circ MYLK functions as an oncogene and promotes prostate cancer progression[8].

Circular RNA_LARP4 was a newly discovered circRNA in human diseases. Although the association between circular RNA_LARP4 and tumorigenesis has been reported in some malignant tumors, the function of circular RNA_LARP4 in NPC remains unstudied. In our research, by performing bioinformatics analysis and functional experiments, we discovered that circular RNA_LARP4 may also act as a tumor suppressor in NPC, which was associated with the oncogene Rho-associated kinase 1 (ROCK1). This work aims to uncover the role of circular RNA_LARP4 in NPC.

Patients and Methods

Tissue Specimens

58 paired tumor tissues and adjacent non-tumor tissues were sequentially gathered from NPC patients who underwent surgery at Haining People's Hospital. All cases were diagnosed with [illegible] by two independent pathologists without [illegible]troversy. This investigation was approved [illegible] the Ethics Committee of Haining People's Ho[illegible]l. Signed written informed consents were obta[illegible] from all participants before the st[illegible].

Cell culture

Four NPC cancer ce[illegible]es (CN[illegible], CNE1, 5-8F, and 6-18B), and imm[illegible]ze[illegible]sopharyngeal epith[illegible] cell [illegible]NP69) were purchased from t[illegible]hinese Acad[illegible]f Science (Shanghai, Chi[illegible] were maint[illegible] in 10% fetal bovine [illegible]um ([illegible] Invitrogen, Carlsbad, CA, USA) [illegible]oswell Park [illegible]orial Institute 1640 (RPMI-1[illegible]0; Invitrogen, Ca[illegible]d, CA, USA), as well [illegible]% penicillin/strepto[illegible]ycin (Sigma-Aldri[illegible]t. Loui[illegible]MO, USA). Besides, cells were cult[illegible] incubato[illegible] containing 5% CO_2 at 37°C.

C[illegible]ransfe[illegible]

[illegible]tivirus di[illegible]ectly against circular RNA_L[illegible] provided by GenePharma (Shanghai, [illegible]. [illegible] empty vector was also synthesized. [illegible]n, circular RNA_LARP4 lentivirus or emp[illegible]tor was transfected into 6-18B NPC cells thr[illegible]h Lipofectamine 2000 reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol.

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

Total RNA was extracted from ce[illegible]sues by using TRIzol reagent (Tak[illegible]Bio, Inc. Otsu, Shiga, Japan) and then reve[illegible]-transcribed to complementary deoxyribos[illegible]leic acids (cDNAs) through the reverse Tra[illegible]ion Kit (TaKaRa, Otsu, Shiga, Ja[illegible]). The [illegible] sequences used for RT-[illegible]R were as [illegible] circular RNA_LARP[illegible]orward: 5′-GGG[illegible]-CAGGAGCAAACT[illegible] and [illegible]erse: 5′-CTG-GCGAATTAAA[illegible]CCA[illegible] glycer[illegible]hyde 3-phosphate de[illegible]rogenase [illegible]PDH[illegible]orward: 5′-GCACCG[illegible]AGGCTGA[illegible] and reverse: 5′-T[illegible]GACGCCA[illegible]GA-3′. PCR was performed th[illegible]mes in the following sequence: pre-denatura[illegible]t 95°C for 1 min, follow[illegible]0 cycles at 95[illegible] 15 s, 60°C for 30 s, a[illegible]2°C for 30 s. The $2^{-\Delta\Delta Ct}$ method was utilized [illegible]alculate relati[illegible] expression.

C[illegible]Proliferat[illegible] Assay

[illegible]ing th[illegible]manufacturer's protocol, 2 ×10^3 transfe[illegible] were seeded in 96-well plates and [illegible]ll proliferation was assessed by the Cell Prolifer[illegible]gent Kit I (MTT; Roche, Basel, Switzer[illegible]nd) [illegible] h, 24 h, 48 h, and 72 h. The absorbance at 490 nm was assessed using an enzyme-linked immunosorbent assay (ELISA) reader system (Multiskan Ascent, LabSystems, Helsinki, Finland).

Ethynyl Deoxyuridine (EdU) Incorporation Assay

According to the manufacturer's manual, an EdU Kit (Roche Diagnostics, 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.

Cell Cycle Assay

The 2×10^5/mL cells were diluted by RNase A in 75% ice-cold ethanol overnight. These cells were stained with propidium iodide (PI; 50 mg/mL; MultiSciences Biotech Co., Ltd, Hangzhou, China) in the dark for 30 min at 4°C. Then, they were measured with a flow cytometer (FACScan, BD Biosciences, Franklin Lakes, NJ, USA).

Scratch Wound Assay

The cells, transferred into 6-well plates, were cultured in RPMI-1640 medium overnight. Once scratched with a plastic tip, cells were cultured

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in serum-free RPMI-1640. Wound closure was viewed at 48 h. Each assay was independently repeated three times.

Transwell Assay

Transwell chambers with 8 µm pores were provided by Corning (Corning, NY, USA). The membrane was precoated with or without 50 µL Matrigel (BD Biosciences, Franklin Lakes, NJ, 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. The number of migrated cells was counted by a light microscope (Olympus, Tokyo, Japan).

Western Blot Analysis

Reagent radioimmunoprecipitation assay (RIPA; Beyotime, Shanghai, China) was utilized to extract protein from cells. Bicinchoninic acid (BCA) protein assay kit (Pierce, Rockford, IL, USA) was chosen for quantifying protein concentrations. The target proteins were sep[illegible] by sodium dodecyl sulphate-polyacrylam[illegible] g[illegible] electrophoresis (SDS-PAGE). Then they [illegible]ere incubated with antibodies after replaced [illegible]e polyvinylidene difluoride (PVDF) membra[illegible] (Roche, Basel, Switzerland). Cell [illegible]aling Tec[illegible]nology (CST, Danvers, MA [illegible] vided u[illegible] rabbit anti-GAPDH and r[illegible]t anti-[illegible]CK1, as well as goat anti-rabbit [illegible]dary an[illegible]ody. Image J software (NIH, Beth[illegible] M[illegible] s applied for the asses[illegible]ent of p[illegible] expression.

Statistical Analysis

All statistical analyses were performed by Statistical Product and Service Solutions (SPSS) 21.0 (IBM Corp., Armonk, NY, USA). [illegible]dent-sample *t*-test was used to compa[illegible]he differ[illegible]ence between the two groups. M[illegible]over, $p<0.05$ was considered a statistically s[illegible]ant difference.

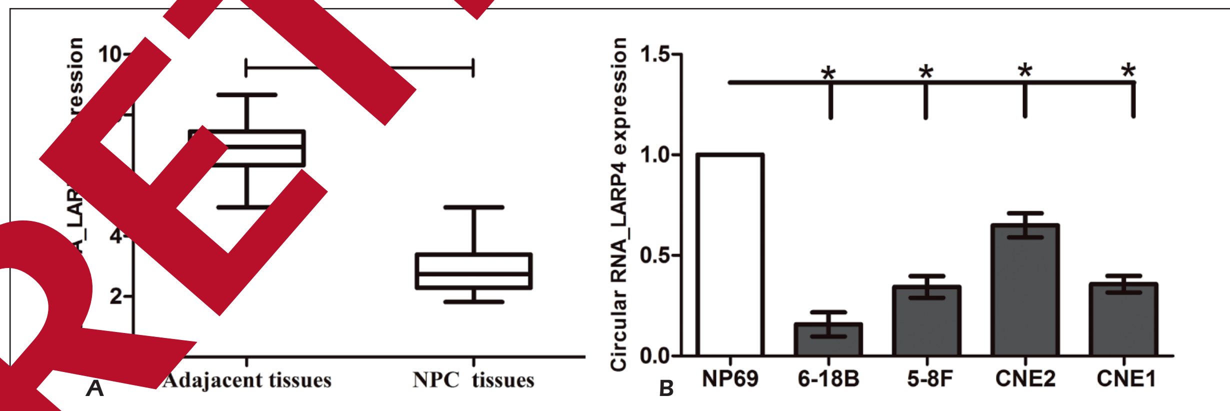
Res[illegible]s

Expression Level [illegible]rcula[illegible] RNA_LARP4 in Tissu[illegible] Cells o[illegible] PC

We perform[illegible] RT-qPC[illegible] 58 p[illegible]d NPC patients' tiss[illegible]amples and [illegible] lines. As was shown [illegible] 1A, downre[illegible]ated circular RNA_LA[illegible]P4 was [illegible]rved in tumor tissue samples compared to tha[illegible]djacent tissues. Compar[illegible]e expression [illegible]69, circular RNA_L[illegible]RP4 level was significantly lower in NPC cells [illegible]gure 1B).

O[illegible]expressi[illegible] of Circular RN[illegible]ARP4 [illegible]pressed Cell Prolife[illegible] in 6-18B NPC Cells

To determine whether circular RNA_LARP4 [illegible]lly play a vital role in NPC, we upregulat[illegible] c[illegible]ar RNA_LARP4 expression level in 6-18B cells by using lentivirus. As shown in Figure 2A, circular RNA_LARP4 expression was remarkably upregulated in RNA level after transfection of 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 repression of cell proliferation *via* overexpression



Fi[illegible]. Expression levels of circular RNA_LARP4 were decreased in NPC tissues and cell lines. **A**, Circular RNA_LARP4 expre[illegible]sion was significantly decreased in the NPC tissues compared with adjacent tissues. **B**, Expression levels of circular RNA_LARP4 relative to GAPDH were determined in the human NPC cell lines and immortalized normal nasopharyngeal epithelial cell line (NP69) by RT-qPCR. Data are presented as the mean ± standard error of the mean. $*p<0.05$.

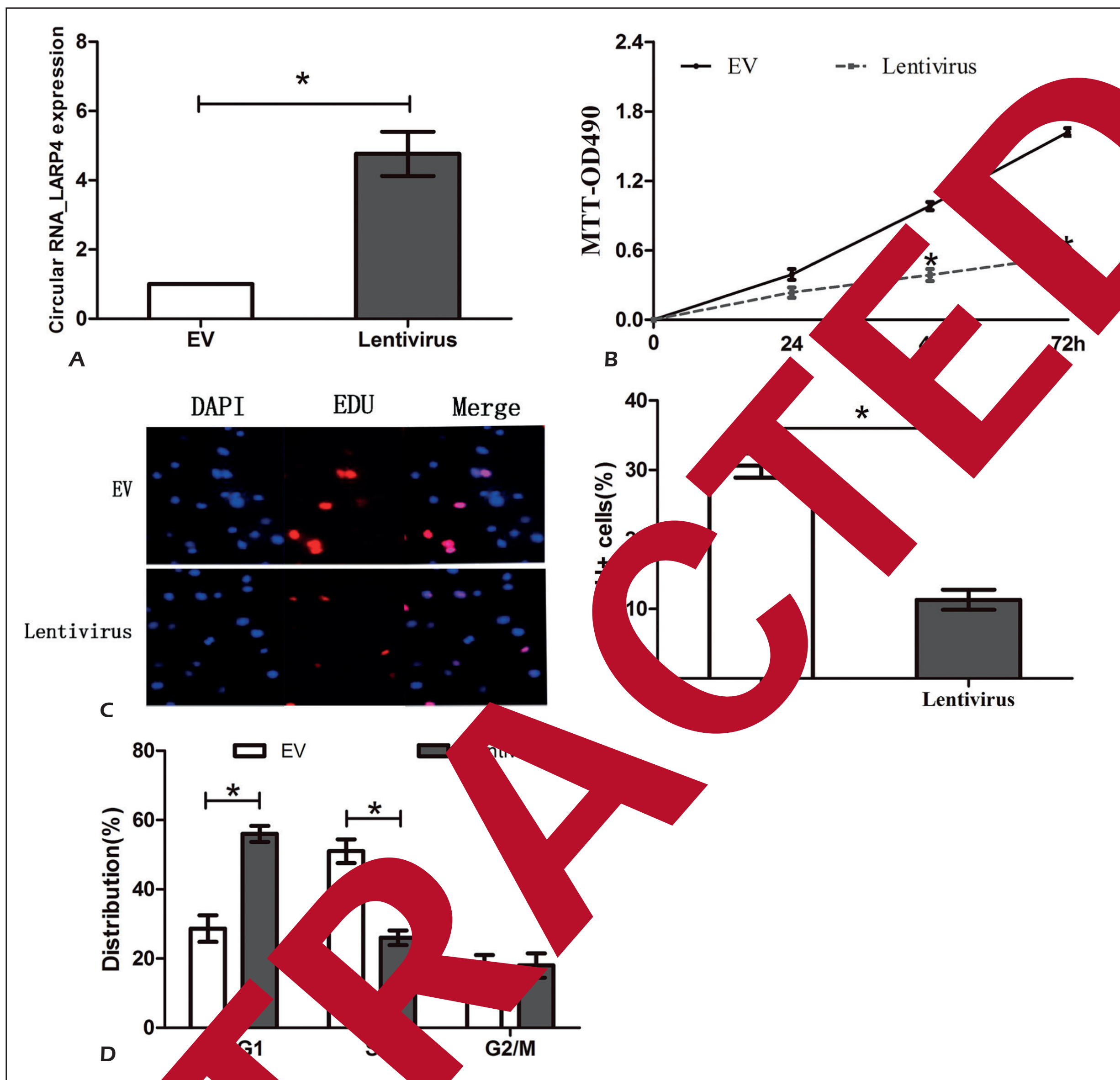


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Figure 2. Overexpression o... ar RNA_LARP4 inhibited 6-18B NPC cell proliferation. **A**, Circular RNA_LARP4 expression in NPC cell... nsfected with em... tor (EV) or circular RNA_LARP4 lentivirus (Lentivirus) was detected by RT-qPCR. GAPDH was u... as an internal control. ...T assay showed that overexpression of circular RNA_LARP4 significantly repressed cell prolifer... in NPC cells. **C**, EdU assay showed that the EdU positive cells were reduced in circular RNA_LARP4 lentivirus (Lentivir... oup comp... d with EV group in NPC cells. **D**, Cell cycle assay revealed that the percentage of G0/G1 cells was increased and t... nta... S cells was reduced after overexpression of circular RNA_LARP4 in 6-18B cells. The results represent the average o... pendent ex... ments (mean ± standard error of the mean). *$p<0.05$, as compared with the control cells.

of ...ular R... ARP4 (transfection with lentivi...) compared to the EV (transfection with em... ...tor) was viewed in 6-18B cells ($p<0.05$). T... ...ur... ...nfirm the outcome of the methyl thi... ...lyl tetrazolium (MTT) assay, we performed ... ...ssays in 6-18B cells. As shown in Figure 2C, Ed... ...ositive cells were also reduced by circular RNA_LARP4 overexpression ($p<0.05$), which was consistent with the results of MTT assays. To detect the effect of circular RNA_LARP4 on NPC cell cycle, the cell cycle assay was performed. The outcome of the cell cycle assay also revealed that the percentage of G0/G1 cells was increased and the percentage of S cells was reduced after overexpression of circular RNA_LARP4 in 6-18B cells (Figure 2D). Together they suggested circular RNA_LARP4 as a new suppressor in proliferation and cell cycle of NPC.

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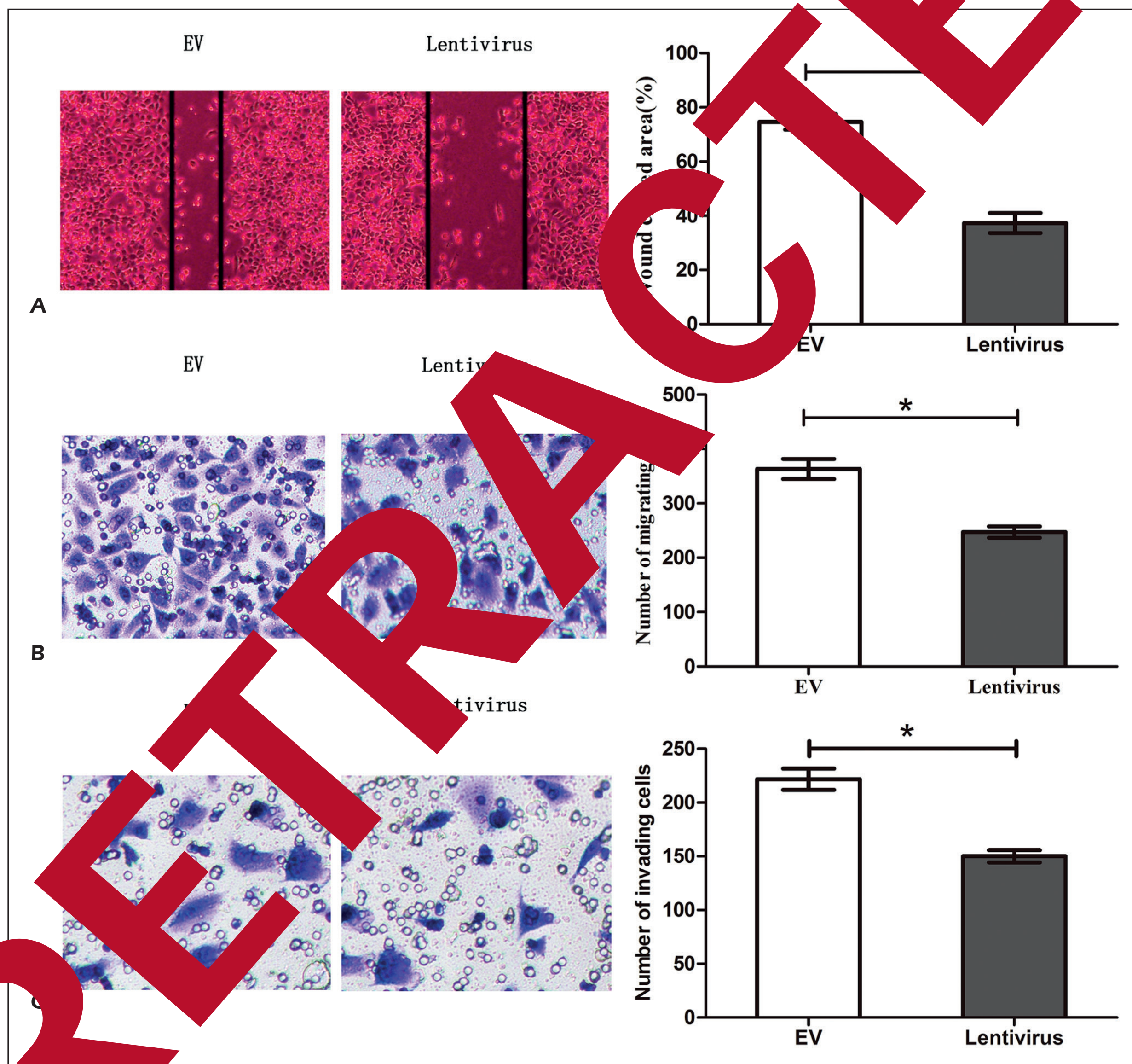
Overexpression of Circular RNA_LARP4 Repressed Cell Migration and Invasion in 6-18B NPC Cells

To explore the function of circular RNA_LARP4 in the migrated and invaded abilities of NPC cells, scratch wound assay and transwell assay were performed. Scratch wound assay showed that the wound closure was significantly reduced in 6-18B cells transfected with circular RNA_LARP4 lentivirus (Figure 3A). Transwell assay showed that a significant decrease was observed in the number of migrated and invaded 6-18B cells transfected with circular RNA_LARP4 lentivirus (Figures 3B and 3C). These together suggest circular RNA_LARP4 as a new s... in metastasis of NPC.

The Interaction Between R...4 and Circular RNA_LARP4 in N...

Starbase v2.0 (http://st...se.sysu...../starbase2/rbpCircRNA.php) ...used to find th... proteins of circular R..._LARP... ROCK1 ...s



...ure 3. Overexpression of circular RNA_LARP4 inhibited 6-18B NPC cell migration and invasion. **A**, Scratch wound assay ... that overexpression of circular RNA_LARP4 significantly reduced wound closure in NPC cells (magnification: 10×). **B**, Tr... assay showed that overexpression of circular RNA_LARP4 significantly repressed cell migration in NPC cells (magnification: 40×). **C**, Transwell assay showed that overexpression of circular RNA_LARP4 significantly repressed cell invasion in NPC cells (magnification: 40×). The results represent the average of three independent experiments (mean ± standard error of the mean). $*p<0.05$, as compared with the control cells.

selected from these proteins which were interacted with circular RNA_LARP4. As was shown in Figure 4A, the RT-qPCR assay showed that an evident downregulation of ROCK1 was observed after the overexpression of circular RNA_LARP4. Western blot assay revealed that the expression of ROCK1 was downregulated after the overexpression of circular RNA_LARP4 (Figure 4B). As was shown in Figure 4C, upregulated ROCK1 was observed in tumor tissue samples compared to that in adjacent tissues. Compared with the expression in NP69, ROCK1 level was significantly higher in NPC cells (Figure 4D). Meanwhile, the results of the linear correlation analysis showed that the expression of ROCK1 was negatively correlated with circular RNA_LARP4 expression in NPC tissues (Figure 4E).

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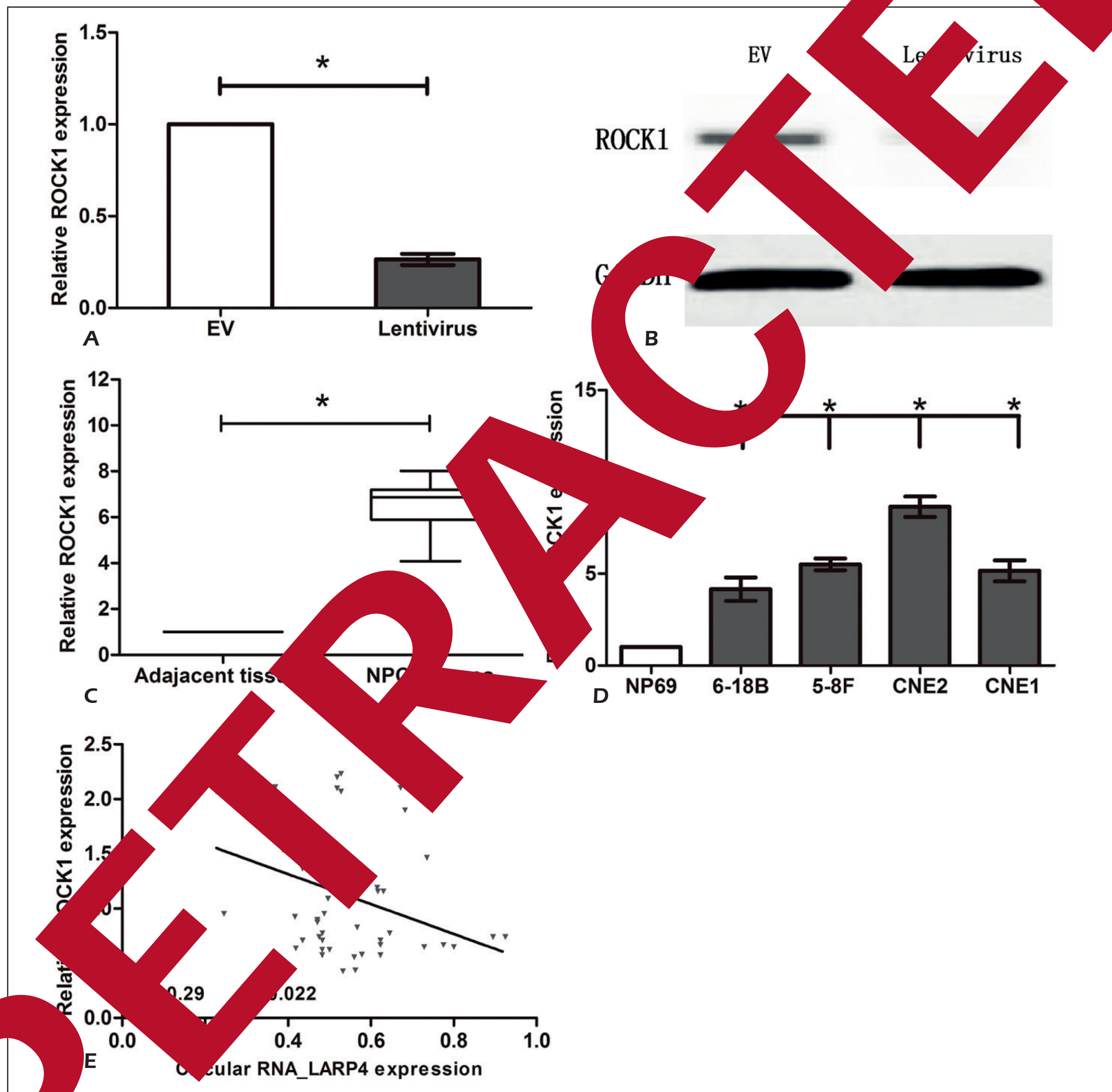

Figure 4. Association between circular RNA_LARP4 and ROCK1 in NPC. **A**, RT-qPCR results showed that the ROCK1 expression was decreased in circular RNA_LARP4 lentivirus (Lentivirus) group compared with empty vector (EV) group. **B**, Western blot assay results showed that the ROCK1 expression was decreased in circular RNA_LARP4 lentivirus (Lentivirus) group compared with empty vector (EV) group. **C**, Upregulated ROCK1 was observed in tumor tissue samples compared with that in adjacent tissues. **D**, Compared with the expression in NP69, ROCK1 level was significantly higher in NPC cells. **E**, Linear correlation between the expression level of ROCK1 and circular RNA_LARP4 in NPC tissues. The results represent the average of three independent experiments. Data are presented as the mean ± standard error of the mean. $^*p<0.05$.

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Discussion

CircRNAs are recently discovered as a large class of noncoding RNAs which are tissue-specific and ubiquitously expressed. The majority of circRNAs are located in the cytoplasm which is more stable than linear RNA due to their resistance to exonucleolytic degradation[9].

CircRNAs have been reported to be potential prognostic biomarkers and therapeutic targets for many cancers, which may offer a clinical tool for predicting the treatment response, assessing the disease state and clinical outcome, including the progression of NPC. Serving as miRNA sponges is the vital function of cellular circRNAs. For instance, circRNA_0000285 is overexpressed in patients with radioresistant NPC which may serve as a prognostic biomarker for NPC[10]. CircRNA_000543 decreases irradiation sensibility of NPC by targeting miR-9/platelet-derived growth factor receptor B axis[11].

Derived from LARP4 gene locus, circular RNA_LARP4 has been revealed recently to inhibit cancer cell migration and invasion by serving as a La-related RNA-binding protein. Mor[illegible] circular RNA_LARP4 is significantly d[illegible]ulated in ovarian cancer which may be us[illegible]s a potential biomarker for prognosis of ovarian c[illegible]r patients[12]. Through the sponging of miR-42[illegible] and the modulation of LATS1 ex[illegible]on, circu[illegible] RNA_LARP4 suppresses cell [illegible]n and ce[illegible] invasion in gastric cancer[13][illegible] the pr[illegible]t study, circular RNA_LARP4 w[illegible]nd to b[illegible]ownregulated in both NPC tis[illegible]ue a[illegible]lls[illegible], after circular RNA[illegible]RP4 w[illegible]erexpressed, the ability of NPC[illegible] growth, mi[illegible] and invasion were supp[illegible]hese results i[illegible]ted that circular RNA[illegible]ARP[illegible]tioned as a tumor suppressor an[illegible]epressed the [illegible]rigenesis of NPC.

Rho-[illegible]ociated kinase 1 [illegible]CK1) is a protein serine[illegible]eonine kinase which [illegible]as been reported to p[illegible]ipate i[illegible] variety of biological and pathologic[illegible] c[illegible]s, inclu[illegible]ing cell motility, tumor metasta[illegible]d epith[illegible]-to-mesenchymal transi[illegible] (EM[illegible] For[illegible]ance, silencing of URG11 re[illegible]es the c[illegible]iferation and EMT in benign pro[illegible]ic hyperp[illegible]sia cells through the RhoA/R[illegible]thway[15]. Mst1 regulates cell apoptosis i[illegible] cell lung cancer through ROCK1/[illegible]tin pathways that induced mitochondrial dam[illegible] [illegible]ncRNA LOC441178 inhibits cell invasion an[illegible]ll migration in oral squamous carcinoma *via* targeting ROCK1[17]. Through miR-124 sponging, circular RNA HIPK3 enhances the progression of gallbladder cancer *via* ROCK1 and CDK6 pathway[18]. Moreover, ROCK1 expression could be downregulated through the overexpression of circular RNA_LARP4. The expression o[illegible] is upregulated in NPC cells and ti[illegible]es, whic[illegible] correlate negatively to circular R[illegible]LARP4 expression in NPC tissues. All the[illegible]lts showed that ROCK1 was downregulated b[illegible]expression of circular RNA_LAR[illegible]in NPC.

Co[illegible]ion[illegible]

Circular R[illegible]_LARP4 [illegible]d in[illegible]t NPC cell prolifera[illegible]and metastas[illegible]wnregulating ROCK[illegible]ndings impl[illegible]that circular RNA_LA[illegible]P4 co[illegible]ve as a promising marker for NPC.

[illegible]nflict of Inter[illegible]sts

[illegible]authors declare[illegible]at they have no conflict of interests.

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