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Circular RNA circ-SMAD7 promoted ovarian cancer cell proliferation and metastasis by suppressing KLF6

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Abstract. – OBJECTIVE: Recently, the roles of circular RNAs (circRNAs) in tumor progression have attracted much attention. Currently, circ-SMAD7 has been identified as an oncogene in cancers. The aim of this study was to investigate the function of circ-SMAD7 in the pr[illegible]sion of ovarian cancer.

PATIENTS AND METHODS: Circ-SM[illegible] expression in both ovarian cancer cells a[illegible]ssue samples was detected by quantitative [illegible]al Time-Polymerase Chain reaction (qRT-PC[illegible] Circ-SMAD7 shRNA was constr[illegible] and transfected into the ovarian canc[illegible]o identify the function of circ-SMA[illegible]n ova[illegible] cancer, cell proliferation assay, c[illegible]y forma[illegible]n assay, transwell assay, and M[illegible] assa[illegible]ducted, respectively. In a[illegible] Western blot assay[illegible]ere p[illegible]ed to elucidate the underlyin[illegible]echanism [illegible]en, it was analyzed.

RESULTS: C[illegible]7 expressio[illegible] was remarkably hig[illegible] in o[illegible] cancer tissue samples than in correspond[illegible]rmal tissues. The proliferat[illegible] of the ovarian [illegible] cells was significant[illegible]nhibited after circ-[illegible]AD7 downregulatio[illegible]leanwhile, the migration and invasion of o[illegible]an canc[illegible] cells were significantly inhibited [illegible]cir[illegible]MAD7 d[illegible]wnregulation in vitro. Both t[illegible]A and th[illegible]rotein expressions of the Krüpp[illegible] facto[illegible] (KLF6) were remarkably [illegible]ted af[illegible]MAD7 was knocked down in [illegible]an canc[illegible]lls. Furthermore, the KLF6 expr[illegible]sion level was negatively correlated with circ[illegible]AD7 expression level in ovarian cancer sa[illegible]

[illegible]ONCLUSIONS: Our study suggests that circ-[illegible]D7 promotes the progression of ovarian c[illegible]nd enhances cell metastasis and prolifera[illegible]via suppressing KLF6. In addition, circ-[illegible]AD7 may be[illegible]ovel therapeutic strategy in [illegible]rian cancer.

Key[illegible]
Circ[illegible], Circ-SMAD7, Ovarian cancer, KLF6.

Introduction

Ovarian cancer remains one of the most fatal and common malignancies in women globally, accounting for 5-6% cancer-related deaths[1,2]. In 2017, it was estimated that 22,500 patients were initially diagnosed with ovarian cancer in America, with 14,100 deaths[3,4]. Due to the vagueness of symptoms and a lack of the early detection tests, 70-75% of ovarian cancer patients have already been in advanced stages when first diagnosed[5]. Currently, the standard therapeutic strategy of surgery combined with chemotherapy has been widely used in ovarian cancer. However, the therapy resistance and metastasis still occur in approximately 80% of the patients[6,7]. Therefore, the severe situation underscores the urgency of the early detection and the establishment of new therapeutic interventions for ovarian cancer.

Circular RNAs (circRNAs) are characterized by evolutionary conservation, enormous abundance, and relative stability in the cytoplasm. Recently, circRNAs have been considered as important factors in the regulation of tumorigenesis by sponging microRNAs (miRNAs) to regulate their downstream genes or acting as competing endogenous RNAs (ceRNAs) for en-

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coding RNAs. For example, the up-regulation of hsa_circ_100395 significantly inhibits cell proliferation, migration, and invasion in lung cancer by targeting TCF21[8]. Circ_0067934 functions as an oncogene in cervical cancer by regulating the miR-545/EIF3C axis[9]. The up-regulation of circ-ITCH inhibits the proliferation and metastasis of the triple-negative breast cancer cells by regulating the Wnt/β-catenin pathway[10]. Meanwhile, the expression of hsa_circ_0003159 is negatively associated with the progression of gastric cancer[11]. However, the exact function of circ-SMAD7 in the proliferation and metastasis of ovarian cancer and the underlying mechanism have not been fully elucidated.

In this study, we found that circ-SMAD7 was remarkably upregulated in the ovarian cancer tissues and cells. Circ-SMAD7 enhanced the proliferation and metastasis of the ovarian cancer cells *in vitro*. Moreover, we explored the underlying mechanism of circ-SMAD7 function in ovarian cancer development. The results demonstrated that the function of circ-SMAD7 in tumorigenesis was associated with the Krüppel-like factor 6 (KLF6), which was reported to be a tumor suppressor in many ca[illegible] including ovarian cancer.

Patients and Methods

Tissue Specimens

Paired ovarian cancer tis[illegible] and [illegible]esponding normal tissues were [illegible]quential[illegible] enrolled from 52 ovarian cancer [illegible] und[illegible]gery in the Shanxian [illegible]entra[illegible] [illegible] 2016 to December 2[illegible]. This st[illegible]s approved by the Ethics C[illegible]ittee of Sha[illegible] Central Hospital. Infor[illegible]sent was obta[illegible]d from each subject [illegible]re th[illegible].

Cell Cul[illegible]e

The [illegible]an ovarian cancer c[illegible]l lines (A2780, TOV[illegible]D, OVCA[illegible]R-3, and SKOV3) and the norma[illegible]ian [illegible] line (ISOE80) were cultured in th[illegible]co's M[illegible]ed Eagle's Medium (DMEM; [illegible] Rock[illegible]e, MD, USA) consisting [illegible]% fetal [illegible]erum (FBS; Gibco, Rockvi[illegible]D, USA)[illegible]d penicillin in a humidified incu[illegible]or with 5% CO_2 at 37°C.

[illegible]tivir[illegible]xpressing Short-Hairpin RNA [illegible] Cell Transfection

[illegible]entivirus expressing short-hairpin RNA (shR[illegible]) directed against circ-SMAD7 were provided by GenePharma (Shanghai, China). The complementary DNA encoding ci[illegible] was amplified and inserted into p[illegible]A3.1 (G[illegible]nePharma, Shanghai, China). S[illegible]equently, the cell transfection was conducte[illegible]ording to the instructions of Lipofectamine 3[illegible]vitrogen, Carlsbad, CA, USA). Th[illegible] expres[illegible]f circ-SMAD7 in the transfec[illegible] cells was [illegible] using quantitative Rea[illegible]me Polymerase [illegible] Reaction (qRT-PCR).

RNA Extracti[illegible] and [illegible]CR

The total R[illegible]A in tiss[illegible] c[illegible] was extracted us[illegible] TRIzol rea[illegible]nvitrogen, Carlsbad[illegible]A). The RNA [illegible]oncentration was me[illegible]red b[illegible]g an ultraviolet spectrophotometer (Hitac[illegible]kyo, Japan). Subseque[illegible]he extracted [illegible]RNA was reverse t[illegible]ed into cDNAs [illegible]hrough the Reverse [illegible]anscription Kit (TaKaRa Biotechnology Co., [illegible]d., Dalian, C[illegible]a). The thermocycling con[illegible]ns were as [illegible]lows: 30 s at 95°C, 5s for 4[illegible]les at 95[illegible] and 35 s at 60°C. The relative [illegible] was calculated by the $2^{-\Delta\Delta Ct}$ method. [illegible]in was used as the internal ref[illegible]nce. The experiment was repeated for 3 [illegible] primer sequences used in this study [illegible]ere [illegible]own as follows: circ-SMAD7 forward 5′-TGAGAAGAGAAATCTATTGGAACC-3′, circ-SMAD7 reverse 5′-GGTTTGTC-TC-CGCTGCTTTA-3′; β-actin, forward 5′-GATGGAAATCGTCAGAGGCT-3′ and reverse 5′-TGGCACTTAGTTGGAAATGC-3′.

Western Blot Analysis

The total proteins were collected from cells via radioimmunoprecipitation assay (RIPA) buffer. The concentration of the extracted protein was determined by the bicinchoninic acid method (Beyotime, Shanghai, China). The target proteins were separated by the sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF) membranes (Roche, Basel, Switzerland). Then, the membranes were incubated with primary antibodies overnight. On the next day, the membranes were incubated with the corresponding secondary antibodies of rabbit anti-β-actin (Cell Signaling Technology, CST, Danvers, MA, USA) and rabbit anti-KLF6 (Cell Signaling Technology, CST, Danvers, MA, USA). The immunoreactive bands were visualized by Pierce enhanced chemiluminescence (ECL) (Santa Cruz Biotechnology, Inc, Santa Cruz, CA, USA).

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Cell Counting Kit-8 (CCK-8) Assay

The proliferation of the transfected cells was monitored by the Cell Counting Kit-8 (CCK-8; Beyotime Institute of Biotechnology, Shanghai, China). Briefly, 5 mg/ml CCK-8 was added to each well at each point (0, 24, 48, and 72 h), followed by incubation for 1 h in the dark. The optical density (OD) value at 450 was measured using Spectrophotometer (Thermo Scientific, Waltham, MA, USA).

Colony Formation Assay

To detect the long-term effect of circ-SMAD7 on cell proliferation, the colony formation assay was conducted. 5×10^2 cells were seeded into 6-well plates, and the culture medium was replaced every day. 7 day later, the formed colonies were fixed with 75% ethanol for 30 min and stained with 0.2% crystal violet. Finally, the colonies were photographed and counted.

Wound Healing Assay

After transfection, the cells were seeded into 6-well plates and cultured in DMEM medium overnight. Subsequently, the cells were scratched with a plastic tip and cultured in seru[illegible] DMEM. Each assay was repeated in t[illegible] independently. The relate distance was [illegible]ved under a light microscope (Olympus Corp., [illegible], Japan) at 48 h.

Transwell Assay and Matr[illegible]ay

After transfection, 1×10^5 [illegible]s in [illegible] μL serum-free DMEM were [illegible]ded to [illegible]e upper chamber (Corning, Inc[illegible]ning, [illegible]) with or without 50 μ[illegible] Ma[illegible], [illegible] MA, USA). Meanwhile, DMEM and FBS were added to the lower chamber. Then, the [illegible]tured overnight in an incubator wi[illegible]% CO_2 [illegible] 37°C. Next, the top surface of th[illegible]ambers was treated with methanol for 30 m[illegible]fter wiped by a cotton swab, followed by sta[illegible]ith crystal violet for 20 min. Five [illegible]elds we[illegible]domly selected for each sample [illegible]d the num[illegible] grating and invading [illegible]s was counted u[illegible] Leica DMI4000B m[illegible]scope ([illegible]ica Microsystems, Heidelberg, G[illegible]y).

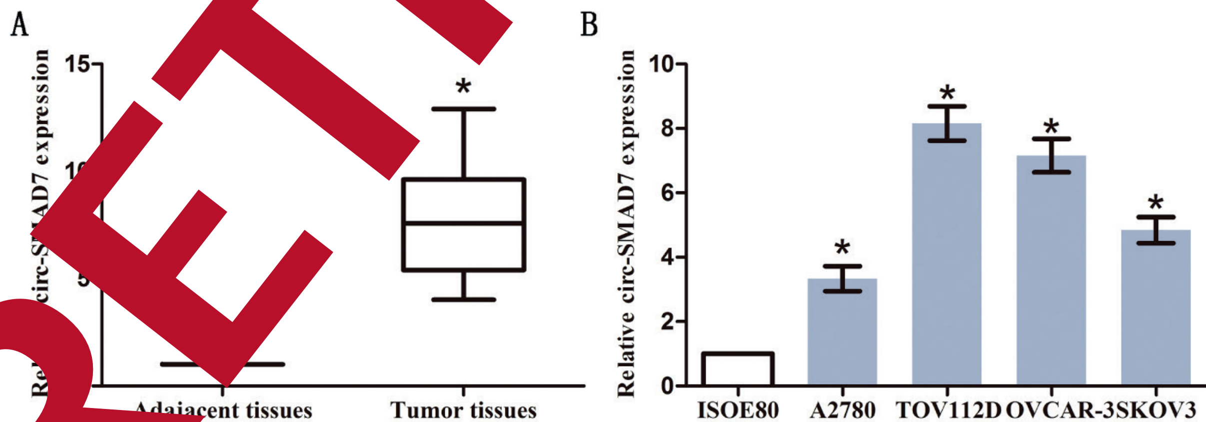
Statistical A[illegible]ysis

The Stati[illegible] Product and [illegible] Solutions (SPSS) 18[illegible]c., Chicago, IL, [illegible]SA) was used for all st[illegible]tical a[illegible]s. The difference between the two groups was co[illegible]d by the Student's *t*-test. $p<0.0$[illegible] considered st[illegible]ally significant.

Results

C[illegible]MAD7 E[illegible]ression Level in Ovarian Ca[illegible] and Cells

The expression of circPSMC3 in 52 ovari[illegible] cancer tissue samples and matched adjacent [illegible]ues was detected via qRT-PCR. Circ-[illegible]MA[illegible] was significantly up-regulated in the ovarian cancer tissues compared with the adjacent tissues (Figure 1A). Moreover, circ-SMAD7 level in the ovarian cancer cells was remarkably higher than that of the normal ovarian cell line (ISOE80) (Figure 1B). The results suggested that the up-regulation of circ-SMAD7 might be associated with ovarian cancer development.



[illegible]re 1. Expression levels of circ-SMAD7 significantly increased in ovarian cancer tissues and cell lines. ***A,*** QRT-PCR results [illegible] that circ-SMAD7 expression was significantly up-regulated in ovarian cancer tissues compared with adjacent tissues. ***B,*** T[illegible]sion levels of circ-SMAD7 relative to β-actin were determined in human ovarian cancer cell lines and normal ovarian cell [illegible]OE80 by qRT-PCR. The data were presented as mean ± standard error of the mean. *$p<0.05$.

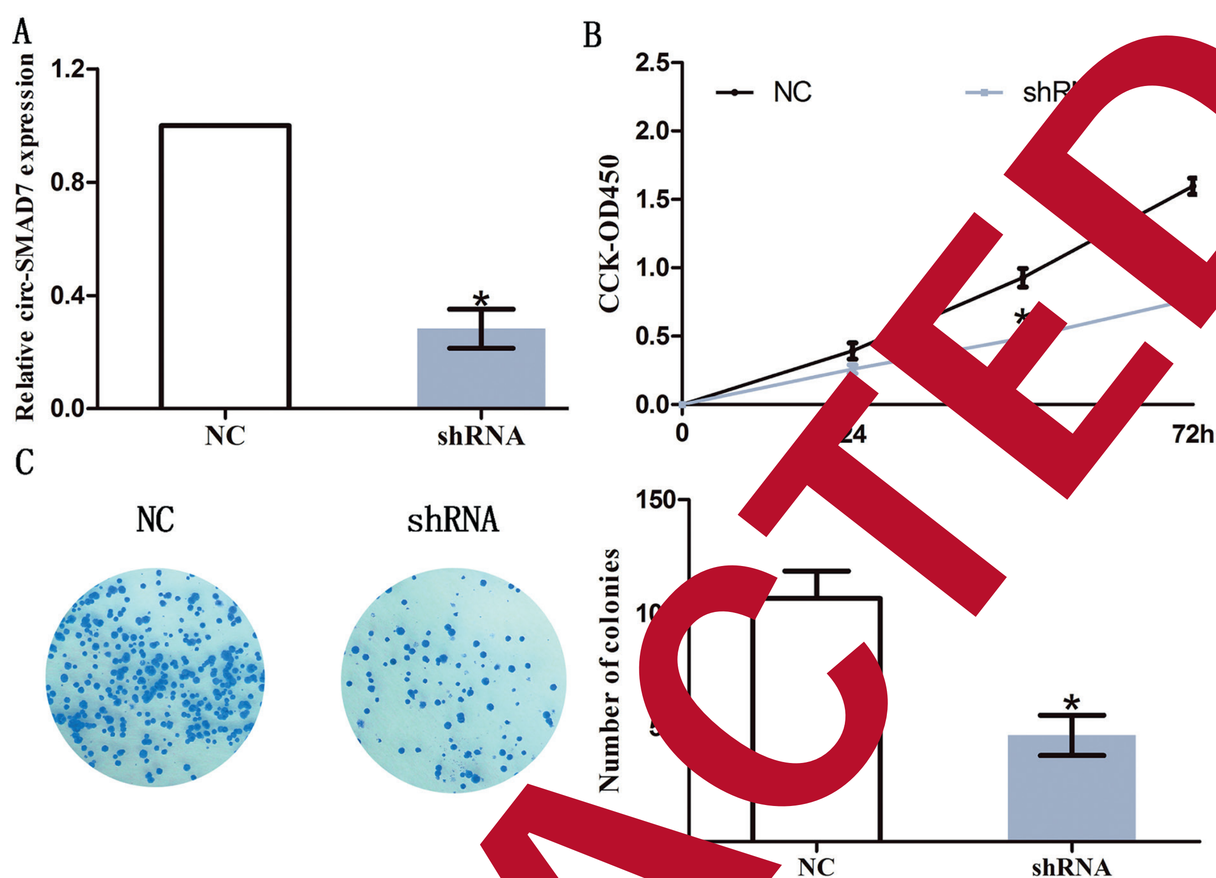


Figure 2. Knockdown of circ-SMAD7 inhibited ova[illegible]an[illegible]ell proliferation. ***A,*** Circ-SMAD7 expression in TOV112D ovarian cancer cells transduced with circ-SMAD7 shR[illegible]NA) and negative control (NC) was detected by qRT-PCR. β-actin was used as an internal control. ***B,*** CCK-8 assay s[illegible] that the knockdown of circ-SMAD7 significantly inhibited the growth of the ovarian cancer cells. ***C*** [illegible]y formati[illegible]y showed that the knockdown of circ-SMAD7 significantly reduced the number of formed col[illegible] in th[illegible]ian cancer[illegible](magnification: 40×). The results represented the average of three independent experiments (m[illegible] ± standa[illegible]ror of the m[illegible]n). *$p<0.05$, as compared with control cells.

Knockdow[illegible]f Ci[illegible]AD7 Inhibited Proliferation of Ovar[illegible]ancer Cells

In ou[illegible]udy, TOV112D[illegible] were chosen for the [illegible]ockdown of circ-S[illegible]AD7 *in vitro.* Then [illegible]RT-PCR was utilized for detecting circ-SM[illegible] expr[illegible]on (Figure 2A). To explore the effect [illegible]SMAD7 [illegible] the proliferation of the ovari[illegible]cer c[illegible], the CCK-8 assay and [illegible]olony [illegible] assay were performed. CC[illegible]assay fo[illegible]that after circ-SMAD7 was kno[illegible]d down, the growth ability of the OV-CA[illegible]s significantly repressed (Figure [illegible] Simila[illegible]y, the colony formation assay indi-[illegible]d that the number of colonies was signifi-ca[illegible]epressed after circ-SMAD7 down-regu-latio[illegible]igure 2C).

Knockdown of Circ-SMAD7 Inhibited Migration and Invasion of Ovarian Cancer Cells

To explore the role of circ-SMAD7 in ovarian cancer metastasis, wound healing assay, transwell assay, and Matrigel assay were performed. The results of the wound healing assay revealed that after circ-SMAD7 was knocked down, the migrated length of the ovarian cancer cells was significantly repressed (Figure 3A). The transwell assay demonstrated that after the circ-SMAD7 knockdown, the migrated ability of the ovarian cancer cells was significantly suppressed (Figure 3B). In addition, the Matrigel assay illustrated that after circ-SMAD7 down-regulation in ovarian cancer cells, the number of the invaded cells remarkably decreased (Figure 3C).

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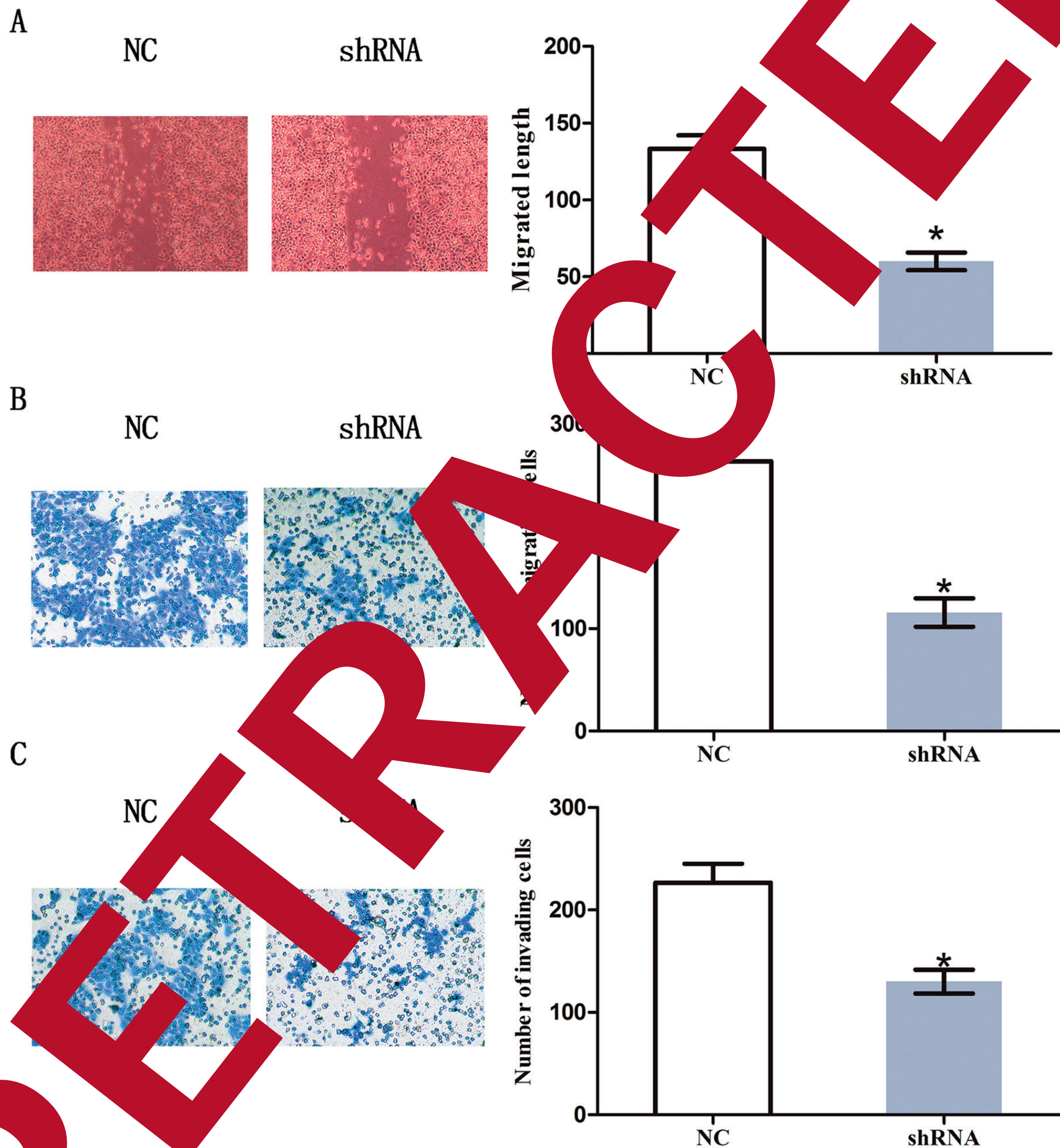
Interaction Between KLF6 and Circ-SMAD7 in Ovarian Cancer

QRT-PCR results showed that the expression level of KLF6 was significantly higher in the ovarian cancer cells of circ-SMAD7 shRNA (shRNA) group when compared with the negative control group (Figure 4A). The Western blot assay found that after circ-SMAD7 was kno[illegible] the protein expression of KLF6 wa[illegible]gnifican[illegible] up-regulated (Figure 4B). Further[illegible]re, we found that KLF6 expression in the o[illegible]n cancer tissues was significantly lower than [illegible]f the adja-



Fig[illegible]own of circ-SMAD7 inhibited ovarian cancer cell migration and invasion. ***A,*** The Wound healing assay sh[illegible]nockdown of circ-SMAD7 significantly reduced migrated length in the ovarian cancer cells (magnification: [illegible]). ***B,*** The transwell assay showed that the knockdown of circ-SMAD7 significantly decreased the migration of the ovarian [illegible]cells (magnification: 40×). ***C,*** The Matrigel assay showed that the number of the invaded cells was significantly reduced vi[illegible]own of circ-SMAD7 in the ovarian cancer cells (magnification: 40×). The results represented the average of three indep[illegible]nt experiments (mean ± standard error of the mean). *p<0.05, as compared with the control cells.

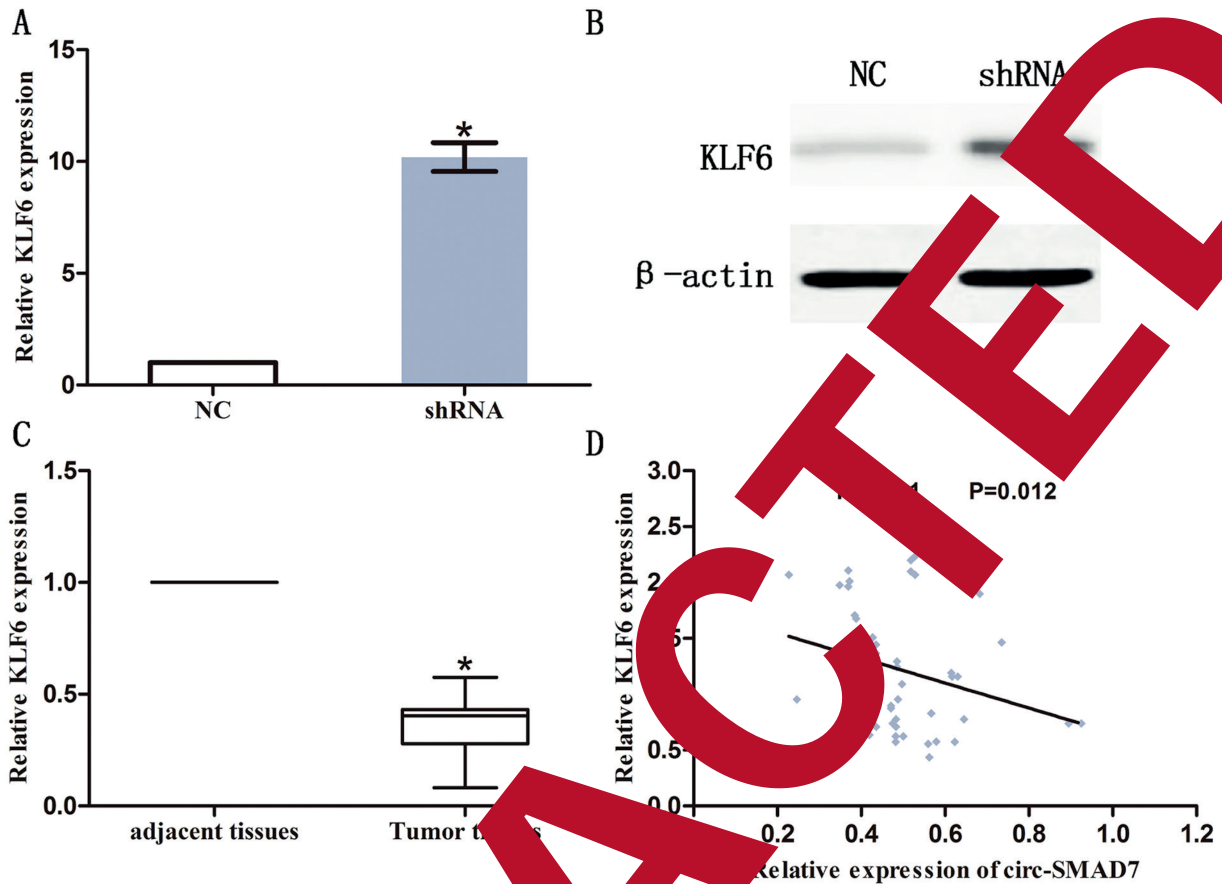


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Figure 4. Interaction between circ-SMAD7 and KLF6 [illegible] cancer tissues and cells. ***A,*** QRT-PCR results showed that the KLF6 expression was significantly higher [illegible] circ-SMAD[illegible]A (shRNA) group compared with NC group. β-actin was used as an internal control. ***B,*** The Wester[illegible] revealed [illegible]e protein expression of KLF6 remarkably increased in circ-SMAD7 shRNA (shRNA) group c[illegible]red w[illegible]e NC grou[illegible] KLF6 was significantly downregulated in the ovarian cancer tissues compared with the adjace[illegible]ssues. ***D,*** [illegible]linear corre[illegible]on between the expression level of KLF6 and circ-SMAD7 in ovarian cancer tissues. The res[illegible] presented [illegible]average of three independent experiments. The data were presented as mean ± standard error of the mean. *p[illegible]

cent normal tis[illegible]ure 4C). The [illegible]relation analysis reve[illegible] that [illegible] expression was negatively correlated with ci[illegible]AD7 expression in the ovari[illegible]ancer tissues (F[illegible]4D).

Discussion

CircR[illegible]AD7 [illegible]generated from chromo[illegible] 18, wh[illegible]orted to be over-expressed in e[illegible]hageal sq[illegible]ous cell carcinoma (ESCC). Mea[illegible]hile, it can also inhibit the prolifera-tio[illegible]on of ESCC[12]. In our research, [illegible] circ-SMAD7 was significantly [illegible]egulated in both ovarian cancer tissues and c[illegible]me studies have proved that circRNAs parti[illegible]ate in the development of ovarian cancer, which can be used as potential indicators and therapeutic target for ovarian cancer. For instance, circ-ITCH suppresses the proliferation and induces apoptosis of the epithelial ovarian cancer cells. Moreover, it is associated with prolonged overall survival[13]. Circ _LARP4 is significantly down-regulated in ovarian cancer, serving as a potential biomarker for the prognosis of patients[14]. By sponging miR-370, the knockdown of hsa_circ_0061140 inhibits cell growth and metastasis in ovarian cancer[15]. In addition, circ VPS13C-has-circ-001567 is up-regulated in ovarian cancer, which also promotes cell proliferation and invasion[16].

In the present study, circ-SMAD7 was first knocked down in the ovarian cancer cells. Ovarian cancer cell proliferation was found significantly

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inhibited after the downregulation of circ-SMAD7. Moreover, ovarian cancer cell migration and invasion were remarkably inhibited after circ-SMAD7 was knocked down *in vitro*. The above results indicated that circ-SMAD7 promoted tumorigenesis of ovarian cancer and might act as an oncogene.

Furthermore, we explored the potential target proteins of circ-SMAD7 using bio-informative methods. The results showed that the potential target protein, Krüppel-like factor 6 (KLF6), was significantly down-regulated in the ovarian cancer tissue samples. Being a tumor suppressor, KLF6 takes part in the regulation of a variety of biological processes in multiple carcinomas. For example, KLF6 has deleted glioblastomas, which is related to poor prognosis of patients by targeting KLF6[17]. KLF6 inhibits the migration and invasion of the oral cancer cells by attenuating the activity of MMP-9 and the expressions of the mesenchymal markers[18]. As a target of miR-630, KLF6 accelerates cell proliferation and invasion in epithelial ovarian cancer[19]. Moreover, KLF6 constrains the progression of hepatocellular carcinoma dissemination by regulating a VAV3-RAC1 signaling axis[20]. In the present work, KLF6 expression was remarkably up-regulated af[illegible] knockdown of circ-SMAD7. However, th[illegible] expression of KLF6 was significantly up-r[illegible]ted after the knockdown of circ-SMAD7. Moreov[illegible] KLF6 expression in the ovarian cancer tissues [illegible] negatively correlated with circ-SMAD7 expressi[illegible] All the above results suggeste[illegible]-SMAD[illegible] might promote tumorigenesis [illegible] ovari[illegible]ncer via suppressing KLF6.

Co[illegible]lusion[illegible]

We found th[illegible]SMAD7 was [illegible]arkably highly expre[illegible] in [illegible]n cancer tissues and cells. Besides, circ-SMA[illegible]uld enhance ovarian canc[illegible]ell proliferation[illegible]ration and invasion [illegible]ough targeting KLF[illegible] These findings sugg[illegible]d that c[illegible]c-SMAD7 might contribute to the[illegible]r ov[illegible]n cancer as a candidate target.

[illegible]ct of I[illegible]

The [illegible]rs declare [illegible]onflicts of interest.

References

1) [illegible]el R, Naishadham D, Jemal A. Cancer statistics, [illegible]. CA Cancer J Clin 2013; 63: 11-30.
2) Luo L, Gao YQ, Sun XF. Circular RNA ITCH suppresses proliferation and promotes a[illegible] human epithelial ovarian cancer cel[illegible]spon[illegible] miR-10a-α. Eur Rev Med Pharma[illegible]Sci 2018; 22: 8119-8126.
3) Siegel RL, Miller KD, Jemal A[illegible]er Statistics, 2017. CA Cancer J Clin 2017; 67[illegible]
4) Lv Y, Li H, Li F, Liu P, Zha[illegible] Long no[illegible] RNA MNX1-AS1 knockdow[illegible]nhibits cell p[illegible] and migration in ov[illegible]n cancer. Cancer [illegible] Radiopharm 2017[illegible] 91-99.
5) Lalwani N, Prasa[illegible]ikra[illegible] Shanbh[illegible]ue AK, Huettner PC, [illegible]asih [illegible]gic, mole[illegible]r, and cytogenetic[illegible]tures o[illegible] canc[illegible] implications for d[illegible]osis and tre[illegible]iographics 2011; 31[illegible]646.
6) Bast [illegible]r, [illegible]sy B, Mills GB. The biology of ova[illegible] cancer[illegible]pportunities for translation. Nat Rev Cancer 2[illegible] 415-428.
7) [illegible]ra SA. Cancer [illegible]ovary. N Engl J Med 20[illegible] 351: 2519-2529.
8) Chen D, Ma [illegible]W, Ke Z, Xie F. CircRNA hsa_circ_100395 [illegible]ulates miR-1228/TCF21 pathway to inhibit lun[illegible]ancer progression. Cell Cycle 2018; 17: 208[illegible]090.
9) [illegible] Wan[illegible] Li A, Zhang J, Xue F, Zhu L. Overex[illegible]rc_0067934 acts as an oncogene to facilitate cervical cancer progression via the miR-545/EIF3C axis. J Cell Physiol 2019; 234: 9225-[illegible]
10) Wa[illegible] ST, Liu LB, Li XM, Wang YF, Xie PJ, Li Q, Wang R, Wei Q, Kang YH, Meng R, Feng XH. Circ-ITCH regulates triple-negative breast cancer progression through the Wnt/β-catenin pathway. Neoplasma 2019; 66: 232-239.
11) Tian M, Chen R, Li T, Xiao B. Reduced expression of circRNA hsa_circ_0003159 in gastric cancer and its clinical significance. J Clin Lab Anal 2018; 32. doi: 10.1002/jcla.22281.
12) Zhang Y, Wang Q, Zhu D, Rong J, Shi W, Cao X. Up-regulation of circ-SMAD7 inhibits tumor proliferation and migration in esophageal squamous cell carcinoma. Biomed Pharmacother 2019; 111: 596-601.
13) Luo L, Gao Y, Sun X. Circ-ITCH correlates with small tumor size, decreased FIGO stage and prolonged overall survival, and it inhibits cells proliferation while promotes cells apoptosis in epithelial ovarian cancer. Cancer Biomark 2018; 23: 505-513.
14) Zou T, Wang PL, Gao Y, Liang WT. Circular RNA_LARP4 is lower expressed and serves as a potential biomarker of ovarian cancer prognosis. Eur Rev Med Pharmacol Sci 2018; 22: 7178-7182.
15) Chen Q, Zhang J, He Y, Wang Y. Hsa_circ_0061140 knockdown reverses FOXM1-mediated cell growth and metastasis in ovarian cancer through miR-370 sponge activity. Mol Ther Nucleic Acids 2018; 13: 55-63.
16) Bao L, Zhong J, Pang L. Upregulation of circular RNA VPS13C-has-circ-001567 promotes ovari-

an cancer cell proliferation and invasion. Cancer Biother Radiopharm 2019; 34: 110-118.

17) Masilamani AP, Ferrarese R, Kling E, Thudi NK, Kim H, Scholtens DM, Dai F, Hadler M, Unterkircher T, Platania L, Weyerbrock A, Prinz M, Gillespie GY, Harsh GI, Bredel M, Carro MS. KLF6 depletion promotes NF-kappaB signaling in glioblastoma. Oncogene 2017; 36: 3562-3575.

18) Hsu LS, Huang RH, Lai HW, Hsu HT, Sung WW, Hsieh MJ, Wu CY, Lin YM, Chen MK, Lo YS, Chen CJ. KLF6 inhibited oral cancer migration and invasion via downregulation of mesenchymal markers and inhibition of MMP-9 activities. Int J Med Sci 2017; 14: 530-535.

19) Zhang S, Zhang JY, Lu LJ, Wang [illegible] Wang [illegible]. MiR-630 promotes epithelial [illegible]rian cancer proliferation and invasion vi[illegible]rgeting KLF6. Eur Rev Med Pharmacol S[illegible]7; 21: 4542-4547.

20) Ahronian LG, Zhu LJ, C[illegible] YW, Chu[illegible]mstra DS, Lewis BC. A nove[illegible]LF6-Rho GT[illegible] regulates hepatoce[illegible]r carcinoma cell [illegible]tion and dissemi[illegible]on. Onc[illegible]gene 2016; [illegible]5: 4653-4662..

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