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The methyltransferase KIAA1429 potentiates cervical cancer tumorigenesis via modulating LARP1 mRNA m^{6}A modification and stability

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Summary. Cervical cancer (CC) is one of the most common gynecological malignancies in the world and poses a great threat to public health. There is inadequate knowledge of the molecular mechanisms underlying CC. This study aimed to explore the prognostic value of KIAA1429 (VIRMA, vir-Like m^{6}A methyltransferase associated) in patients with CC and analyze its molecular mechanisms. The level of KIAA1429 in tumor specimens was tested using RT-qPCR and western blotting. Cellular biological processes were assessed using CCK-8 and Transwell assays. Xenograft experiments were used to verify the function of KIAA1429 in CC *in vivo*. The results manifested that KIAA1429 expression was enhanced in CC. Downregulation of KIAA1429 hindered the viability, migration, and invasion of CC cells. Moreover, LARP1 (La-related protein 1) was uncovered to be positively modulated by KIAA1429. Further, the anti-tumor impacts of KIAA1429 depletion on the phenotype of CC cells were counteracted by LARP1 amplification. Additionally, KIAA1429 deficiency suppressed the stability of LARP1 through methylating LARP1. Collectively, KIAA1429 can boost the tumorigenesis of CC via modifying LARP1 through m^{6}A methylation to promote its stability. This work highlights the promoting effects of KIAA1429 on CC development and presents new targets for its treatment.

Key words: Cervical cancer, KIAA1429, LARP1, N6-methyladenosine, Tumorigenesis

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Introduction

Cervical cancer (CC) is the fourth most common and fatal malignancy among females worldwide, with approximately 604,127 new cases and 341,831 deaths in 2020 (Sung et al., 2021). Human papillomavirus (HPV) infection is regarded as the major risk factor for clinically induced CC (Ferlay et al., 2015). However, recent evidence has attested that HPV infection alone is insufficient to elicit the malignant transformation of normal cervical cells (Hemmat and Bannazadeh Baghi, 2019). Despite surgery, chemotherapy, radiotherapy, and HPV vaccination can effectively fight against CC, the overall prognosis of patients with metastatic or recurrent disease is still poor (Vaccarella et al., 2013; Wright et al., 2015). With the development of molecular biology and genomics, molecular targeted therapy has made a breakthrough in the cure of cancer (Liu et al., 2021). Emerging evidence has manifested that molecular targeted therapy markedly affected cell progression and relapse in CC with few side effects (Lee et al., 2021). Thus, it is imperative to develop new effective diagnostic biomarkers and therapeutic targets for CC patients.

RNA N6-methyladenosine (m^{6}A) modification is the most abundant conserved post-translational modification in eukaryotic organisms (Dai et al., 2018). An abundance of literature has hinted that m^{6}A plays essential roles in RNA splicing, translation, and stability, thus performing significant biological functions in tumors (Pan et al., 2018). For instance, the m^{6}A methyltransferase METTL3 (methyltransferase-like 3) accelerated TGF-β-triggered epithelial-mesenchymal transition (EMT) of lung cancer cells via modulating JUNB expression (Wanna-Udom et al., 2020). Silencing of METTL14 (methyltransferase-like 14) hampered the malignant development of non-small cell lung cancer by lessening Twist expression via activation of AKT signaling (Yang et al., 2021b). Moreover, KIAA1429 (VIRMA, vir-Like m^{6}A methyltransferase associated) has been revealed as an m^{6}A methyltransferase and elucidated to be

implicated in tumor biogenesis and development (Yang et al., 2021a; Zhang et al., 2022). Importantly, Condic et al. implied that higher KIAA1429 was closely associated with a shortened overall survival in CC, indicating that KIAA1429 could be used as biomarkers and indicators in CC (Condic et al., 2022). Nevertheless, the biological function of KIAA1429 and its regulatory mechanisms in CC have not been sufficiently described. La-related protein 1 (*LARP1*) was identified as a novel gene implicated in the tumorigenesis of many cancers (Ye et al., 2016). However, the relationship between KIAA1429 and LARP1 in CC remains unknown. The purpose of this study was to clarify the regulatory mechanism of KIAA1429 in tumor growth and metastasis of CC and provide a potential therapeutic target for CC.

Materials and methods

Tissue specimen

A total of 34 pairs of CC tumor tissues and adjacent non-tumor tissues were provided by patients at the Wujin Hospital Affiliated with Jiangsu University. The histological diagnosis was performed according to the International Federation of Gynecology and Obstetrics (FIGO) classification standard. No patients had received chemotherapy or radiotherapy before the surgery. Authorization of the study was via the Ethics Committee of the Wujin Hospital Affiliated with Jiangsu University and written informed consent was signed by each patient.

Cell culture

Human CC cell lines (C33A, MS751, ME-180, and CaSki) were purchased from ATCC (Manassas, VA, USA) and a normal cervical epithelial cell line (Ect1/E6E7) was obtained from ATCC (Manassas, VA, USA). The cells were cultured in RPMI-1640 (Gibco) containing 10% FBS (Invitrogen) at 37°C with 5% CO_2 in a humidified condition.

Cell transfection

For silencing *KIAA1429*, shRNA (shKIAA1429) was synthesized by Genepharma (Shanghai, China), along with the shNC oligonucleotide as a negative control. *KIAA1429* and *LARP1* were amplified and inserted into the pcDNA3.1 vector (Invitrogen) to obtain the vectors pcDNA3.1/KIAA1429 and pcDNA3.1/LARP1. The empty pcDNA3.1 vector was used as an internal reference. The cultured MS751 and CaSki cells were transfected with plasmids using Lipofectamine 2000 (Invitrogen).

Reverse transcription-quantitative PCR (RT-qPCR)

Total RNA was extracted using the TRIzol method (Invitrogen) and subsequently reverse-transcribed into cDNA using the Reverse Transcription kit (Invitrogen). qPCR was performed to evaluate gene expression on a 7900 FAST real-time PCR instrument using the SYBR Green dye. The reaction conditions were as follows: denaturation at 94°C for 30 s, followed by annealing at 55°C for 30 s, and extension at 72°C for 90 s, for a total of 40 cycles. Gene expression was calculated by the $2^{-\Delta\Delta Cq}$ method and normalized to GAPDH.

Western blotting

Western blotting was carried out as described in the literature (Zhou et al., 2019). Total protein was dissociated in RIPA buffer. Then, 20 μg of protein was separated via 10% SDS-PAGE and transferred to polyvinylidene fluoride membrane membranes (Millipore). After being blocked with 5% nonfat milk, the membranes were incubated with primary antibodies KIAA1429, E-cadherin, N-cadherin, and Vimentin (Abcam) overnight at 4°C. Later, membranes were incubated with the secondary antibodies for 2h. Finally, the protein bands were viewed using an enhanced chemiluminescence reagent (Thermo Scientific, Rockford, USA).

Co-immunoprecipitation (co-IP)

Co-IP was performed as previously described (Wen et al., 2022). Briefly, after being harvested and washed with PBS, cells were lysed with RIPA buffer containing a protease inhibitor (Sigma). After centrifugation, supernatants were incubated with KIAA1429 antibody overnight at 4°C. Finally, western blotting was utilized to test the presence of the indicated protein.

Cell proliferation

Cell proliferation ability was measured by the Cell Counting Kit-8 (CCK-8) assay. MS751 and CaSki cells were plated into a 96-well plate. After 24, 48, and 72h of incubation, CC cells were treated with 10 μL CCK-8 and incubated for another 4h. The absorbance was measured using a microscope (Olympus, Japan) at 450 nm.

Transwell assay

For migration assays, 1×10^5 cells were placed in the upper layer with serum-free medium. The lower chamber was replenished with 500 μL complete medium containing 10% FBS. The cells remaining on the lower surface of the insert were fixed with 4% formaldehyde and stained by DAPI (Roche). For invasion assays, cells were seeded in a Matrigel-coated chamber and pre-incubated at 37°C for 30 min.

Methylated RNA immunoprecipitation (MeRIP)-qPCR

For quantification of m^6A-modified KIAA1429 levels, MeRIP-qPCR was performed. First, total RNA was isolated from cells by TRIzol. Anti-m^6A antibody (Abcam) or anti-IgG interacted with protein A/G

magnetic beads in IP buffer overnight. Then, the RNA was incubated with antibody-coated magnetic beads in an IP buffer. After precipitation and elution, the m^{6}A level was detected by RT-qPCR.

RNA stability

RNA was extracted from CC cells using TRIzol reagent (Beyotime). After 24h transfection, cells were treated with RNA synthesis inhibitor actinomycin D (ActD; 5 μg/mL) and then the LARP1 mRNA level was measured using RT-qPCR at the indicated time point.

Animal experiments

Female BALB/C nude mice (6-8 weeks old) were purchased from Shanghai LAC Laboratory (Shanghai, China). MS751 cells stably transfected with shNC or shKIAA1429 were injected into nude mice. Then, the tumor volumes were detected every seven days. After 28 days, mice were sacrificed and the tumors were weighed. This animal study was performed following the guidelines and regulations of the Ethics Committee of the Wujin Hospital Affiliated with Jiangsu University.

Statistical analysis

Statistics are presented as the mean ± standard deviation and analyzed using SPSS 21.0 software (IBM Corp.). The differences between the two groups were determined using the Student's t-test. Statistical differences between more than two groups were determined using a one-way analysis of variance (ANOVA). $p<0.05$ was considered statistically significant.

Results

KIAA1429 is highly expressed in CC

To check the potential role of KIAA1429 in CC development, the expression of KIAA1429 was examined. Initially, RT-qPCR results implied that KIAA1429 levels were prominently elevated in CC tissues compared with paratumoral tissues (Fig. 1A). Kaplan–Meier survival analysis revealed shorter overall survival (OS) in patients with high KIAA142 expression (Fig. 1B), determining that elevated KIAA1429 expression in CC patients represents a relatively poor prognosis. Simultaneously, KIAA1429 levels were also higher in CC cells (C33A, MS751, ME-180, and CaSki) (Fig. 1C). MS751 and CaSki were selected for subsequent experiments. Similarly, the m^{6}A level of CC cells was also higher than normal cells (Fig. 1D). Collectively, the above results implied that KIAA1429 played an essential function in the tumorigenesis of CC.

Depletion of KIAA1429 suppresses the malignant invasion of CC cells

To evaluate the effects of KIAA1429 on CC development, we designed shRNAs (shNC and shKIAA1429) transfected into MS751 and CaSki cells to reduce KIAA1429 expression. RT-qPCR and western blotting determined that the KIAA1429 level was reduced in CC cells (Fig. 2A,B). The results of the CCK-8 assay disclosed that inhibition of KIAA1429 interfered with the viability of MS751 and CaSki cells (Fig. 2C). Moreover, Transwell assays manifested that suppressed SMYD2 expression reduced MS751 and CaSki cell migration and invasion (Fig. 2D,E). Furthermore, KIAA1429 deficiency elevated the protein level of E-cadherin, and reduced N-cadherin and Vimentin in CC cells (Fig. 2F). These data hinted that knockdown of KIAA1429 could impede CC cell viability and metastasis.

LARP1 is positively related to KIAA1429 in CC

We therefore checked the downstream effectors responsible for the oncogenic roles of KIAA1429 in CC. The correlation of KIAA1429 with all genes in CC tissues was analyzed by the use of linkedOmics. The data showed that LARP1 was strongly correlated with

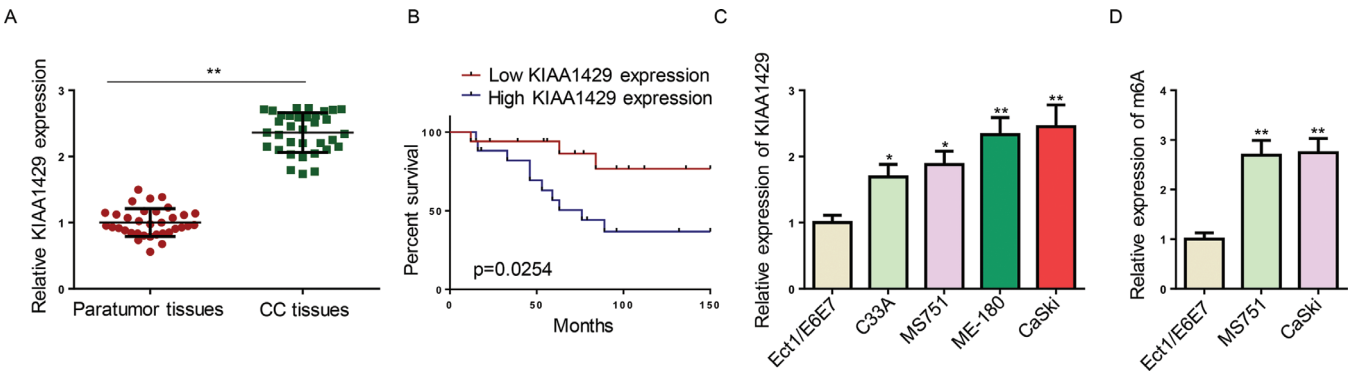

Fig. 1. KIAA1429 is highly expressed in CC. **A.** RT-qPCR showed KIAA1429 mRNA levels in CC tissues and paratumoral tissues. **B.** The OS of patients with high expression of KIAA1429. **C.** RT-qPCR determined KIAA1429 levels in CC cell lines (C33A, MS751, ME-180, and CaSki) in comparison with normal cervical cell lines (Ect1/E6E7). **D.** MeRIP-qPCR revealed Total m6A levels in MS751 and CaSki cells. ** $p<0.01$.

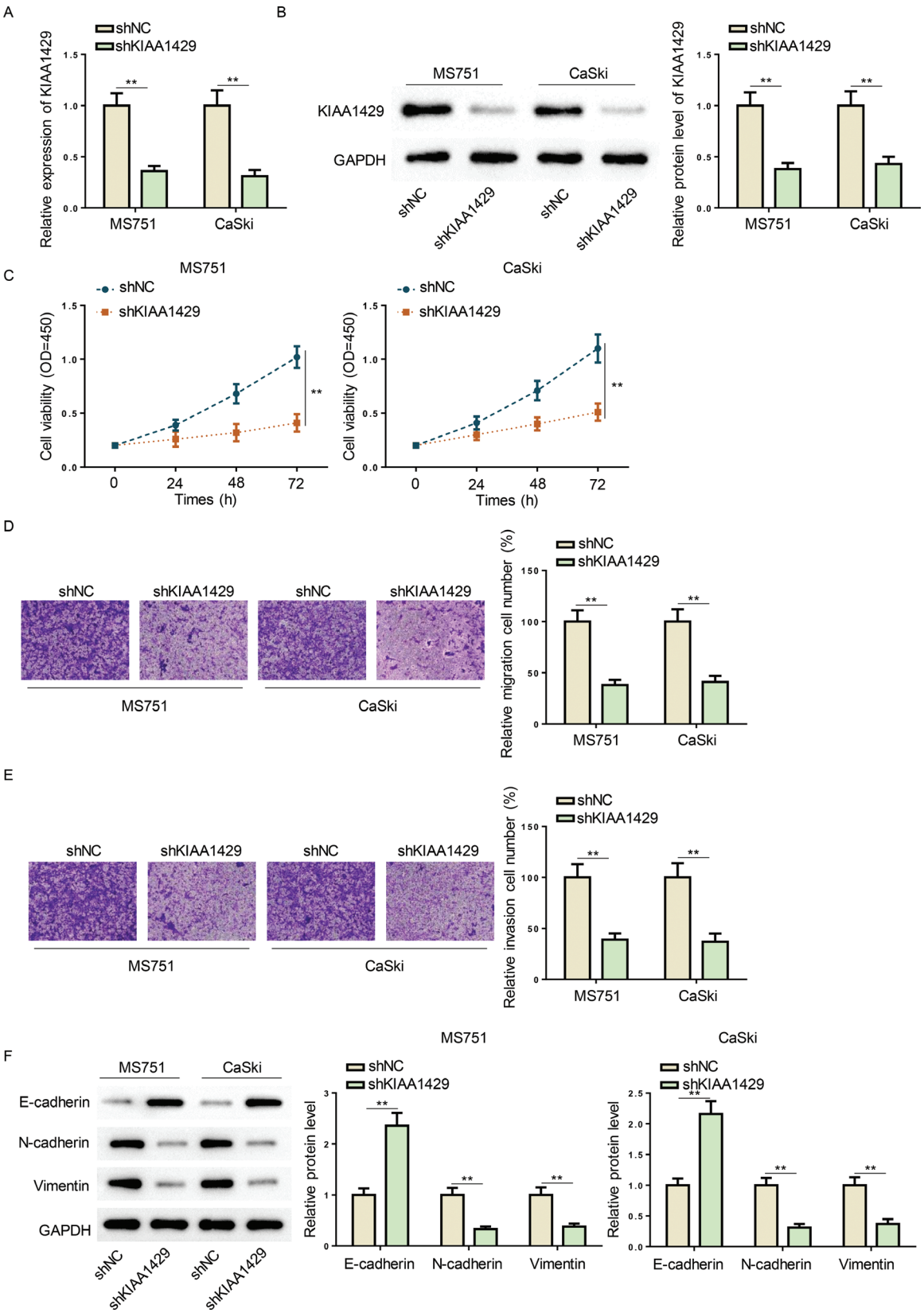

Fig. 2. Depletion of KIAA1429 suppresses the malignant invasion of CC cells. **A, B.** KIAA1429 mRNA and protein levels in MS751 and CaSki cells transfected with shKIAA1429 or shNC. **C.** The CCK-8 assay for cell viability of MS751 and CaSki cells. **D, E.** Transwell assays for MS751 and CaSki cell migration and invasion. **F.** Protein levels of E-cadherin, N-cadherin, and Vimentin in MS751 and CaSki cells. **p<0.01.

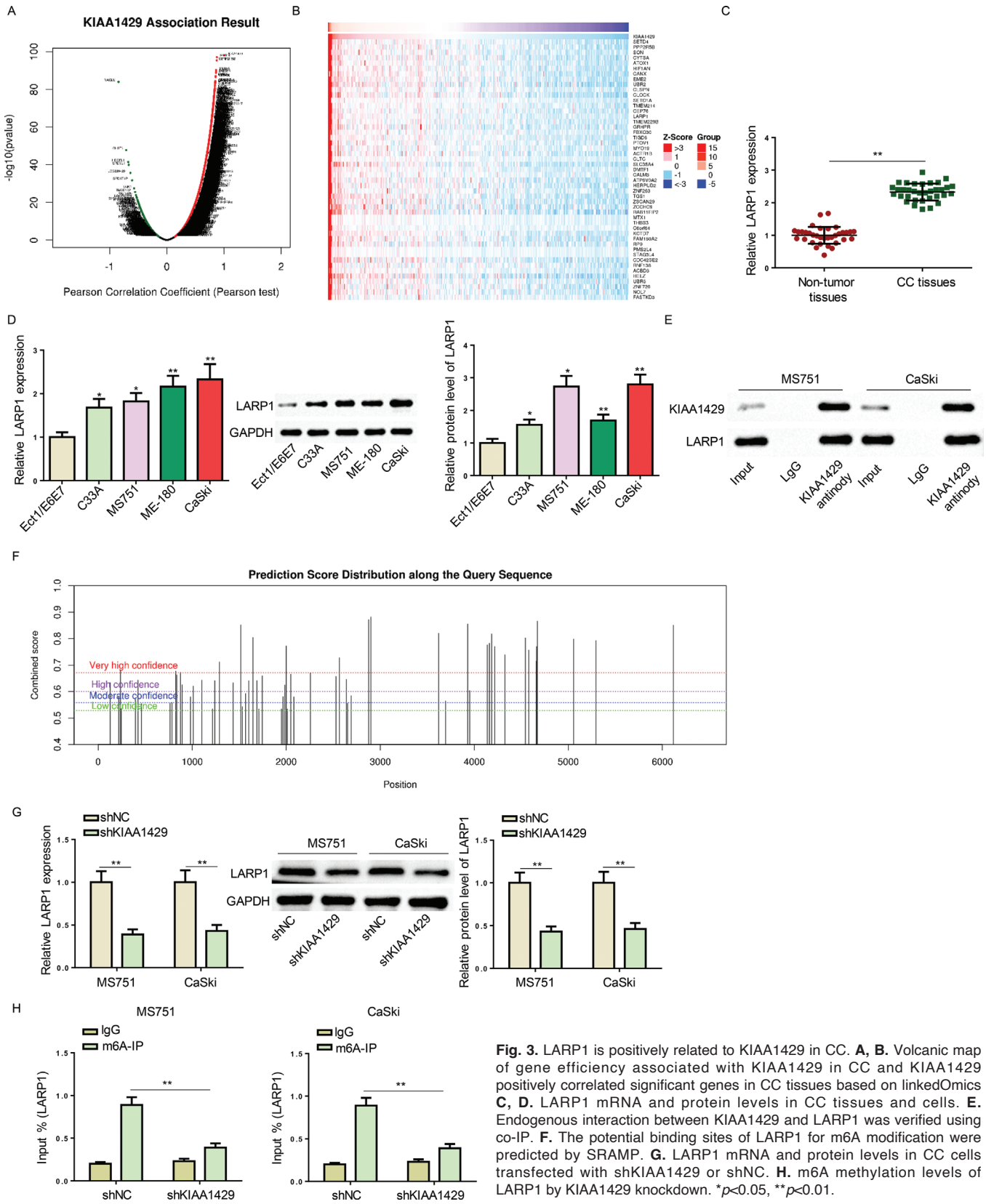

Fig. 3. LARP1 is positively related to KIAA1429 in CC. **A, B.** Volcanic map of gene efficiency associated with KIAA1429 in CC and KIAA1429 positively correlated significant genes in CC tissues based on linkedOmics **C, D.** LARP1 mRNA and protein levels in CC tissues and cells. **E.** Endogenous interaction between KIAA1429 and LARP1 was verified using co-IP. **F.** The potential binding sites of LARP1 for m6A modification were predicted by SRAMP. **G.** LARP1 mRNA and protein levels in CC cells transfected with shKIAA1429 or shNC. **H.** m6A methylation levels of LARP1 by KIAA1429 knockdown. *p<0.05, **p<0.01.

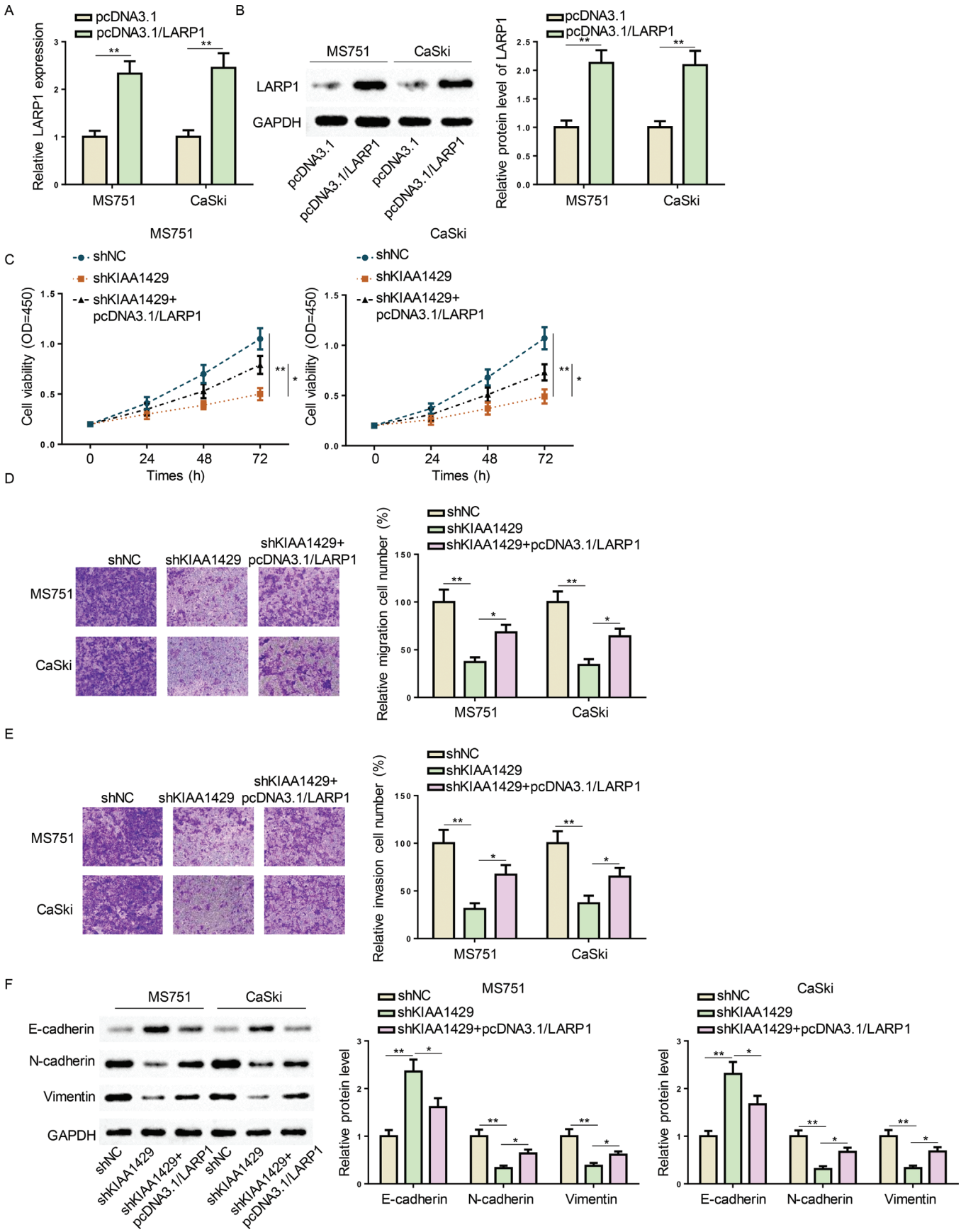

Fig. 4. LARP1 addition ameliorates the potency of KIAA1429 deficiency in CC cell progression. **A, B.** LARP1 mRNA and protein levels in MS751 and CaSki cells transfected with pcDNA3.1/LARP1 or pcDNA3.1. **C.** Cell viability was detected in cells transfected with shNC, shKIAA1429, or shKIAA1429+pcDNA3.1/LARP1. **D, E.** Cell migration and invasion in treated cells. **F.** Protein levels of E-cadherin, N-cadherin, and Vimentin in treated cells. *p<0.05, **p<0.01.

KIAA1429 in CC (Fig. 3A,B). Then, LARP1 expression was measured in CC tissues and cells, and the results revealed that LARP1 expression was heightened in CC tissues and cells (Fig. 3C,D). Moreover, co-IP analysis substantiated the binding interaction between KIAA1429 and LARP1 in MS751 and CaSki cells (Fig. 3E). The potential m^6A sites of LARP1 for m^6A modification were predicted using SRAMP (Fig. 3F). Additionally, we intended to further elaborate the relationship between KIAA1429 and LARP1. It was shown that LARP1 mRNA and protein levels were suppressed by the knockdown of KIAA1429 (Fig. 3G). Besides, m^6A methylation levels of LARP1 were also reduced by KIAA1429 silencing (Fig. 3H). In sum, KIAA1429 was positively correlated with LARP1 in CC.

LARP1 addition ameliorates the potency of KIAA1429 deficiency on CC cell progression

We further assessed whether KIAA1429 exerted its function in CC via targeting LARP1. As illustrated in Figure 4A,B, LARP1 mRNA and protein levels were augmented by LARP1 addition in MS751 and CaSki cells. Moreover, cell viability was hindered by KIAA1429 downregulation, which was restored owing to upregulation of LARP1 (Fig. 4C). Further, LARP1 amplification counteracted the repressive impact of KIAA1429 depletion on migration and invasion of MS751 and CaSki cells (Fig. 4D,E). Consistently, amplification of LARP1 neutralized the influences of KIAA1429 ablation on the levels of EMT-associated markers (Fig. 4F). Taken together, KIAA1429 accelerated CC malignant progression by upregulating LARP1.

KIAA1429 methylates LARP1 to enhance its stability

To understand the mechanism by which KIAA1429 regulated LARP1 expression in CC cells. RT-qPCR results revealed that inhibition of KIAA1429 caused a decrease in mature LARP1 mRNA expression, whereas the precursor LARP1 mRNA level remained unchanged (Fig. 5A,B). Moreover, ablation of KIAA1429 facilitated the degradation of the remaining LARP1 mRNA caused by ActD in both MS751 and CaSki cells (Fig. 5C). These findings supported the notion that KIAA1429 upregulates LARP1 expression by increasing its mRNA stability.

KIAA1429 depletion restrains tumor growth of CC in vivo

To elaborate on the functional role of KIAA1429 in CC cell growth *in vivo*, animal experiments were performed. As illustrated in Figure 6A-C, KIAA1429

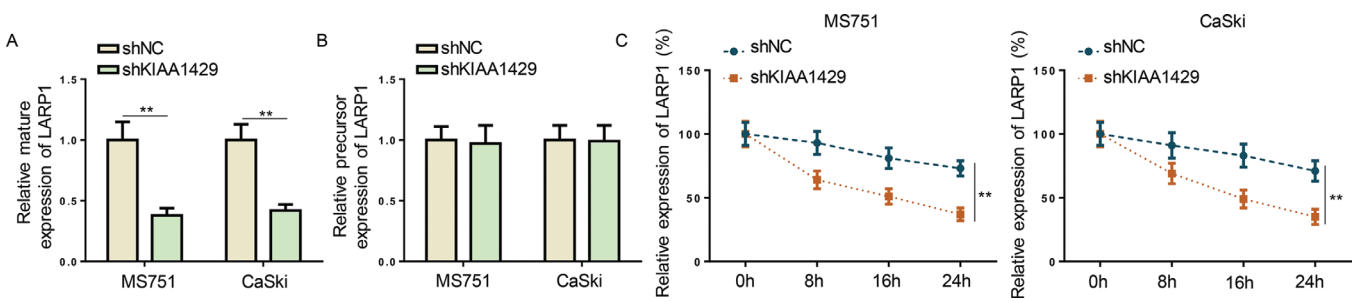

Fig. 5. KIAA1429 methylates LARP1 to enhance the stability of LARP1. **A, B.** RT-qPCR determined the levels of LARP1 precursor and mature mRNA in MS751 and CaSki cells transfected with shKIAA1429 or shNC. **C.** LARP1 mRNA stability was analyzed. $^{**}p<0.01$.

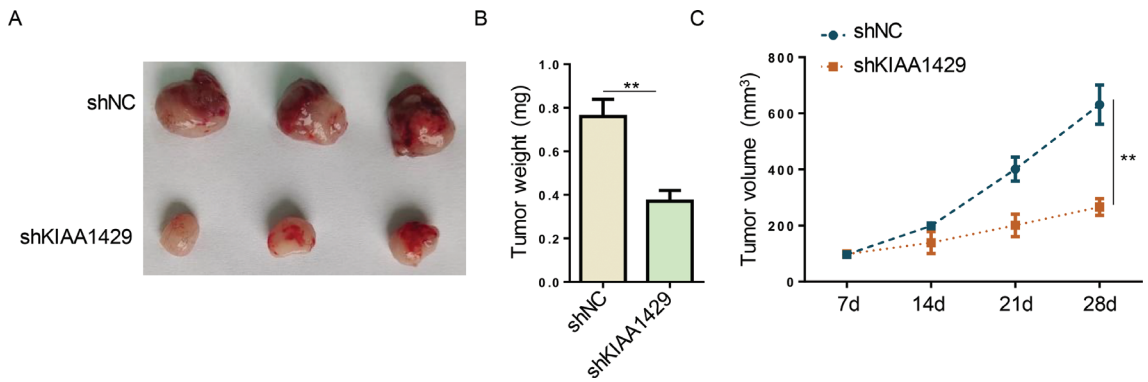

Fig. 6. KIAA1429 depletion restrains tumor growth of CC *in vivo*. **A-C.** Volume and weight of xenograft tumors in the KIAA1429 knockdown group. $^{**}p<0.01$.

knockdown repressed both tumor volume and weight. All these results consolidate the conclusion that KIAA1429 plays a pivotal role in promoting CC progression *in vivo*.

Discussion

The pathogenesis of CC is complex. Several oncogenes and tumor suppressor genes have been identified in CC, however, only a few of these can be applied to the early diagnosis of CC and gene target therapy. Consequently, it is of great significance to continue to find and identify additional oncogenes and tumor suppressor genes associated with the occurrence and development of CC. In our research, we certified that KIAA1429 expression was augmented in CC and exerted its oncogenic function in CC progression. Mechanistically, KIAA1429 can promote the stability of LARP1 in an m^{6}A-dependent manner. LARP1 was a potential carcinogen that promoted the growth and metastasis of multiple tumors. It is important to investigate the m^{6}A modification of LARP1 for its carcinogenesis.

Recent reports have shown that m^{6}A modification plays imperative and diverse biological functions in the occurrence and development of human cancers (Chen et al., 2020b; Hou et al., 2021). Among the m^{6}A modulators, KIAA1429 is thoroughly and widely studied in various cancer types. Lan et al. elaborated that KIAA1429 facilitated liver cancer cell viability and metastasis by mediating the m^{6}A modification of GATA binding protein 3 (GATA3) precursor mRNA (Lan et al., 2019). Zhou et al. revealed that upregulated KIAA1429 stabilized the silent mating-type information regulation 2 homolog 1 (SIRT1) mRNA in an m^{6}A-dependent manner, which consequently boosted colorectal cancer development (Zhou et al., 2022). Zhao et al. elucidated that the m^{6}A methyltransferase KIAA1429 increased Mucin 3A (MUC3A) levels via m^{6}A modification to modulate lung adenocarcinoma cell viability and metastasis (Zhao and Xie, 2021). In the current work, we found that the KIAA1429 level was elevated in CC tissues and cells. Depletion of KIAA1429 retarded the viability and metastasis of CC cells. Furthermore, silencing KIAA1429 restrained CC cell growth *in vivo*.

An extensive body of studies has demonstrated that the EMT and migration of cancer cells are two important biological phenomena during the tumorigenic process. Moreover, it was implied that changes in m^{6}A levels can affect metastasis in CC progression (Ji et al., 2021; Wang et al., 2021). Thus, whether KIAA1429 can enhance the level of related genes via m^{6}A modification, thereby activating EMT in CC is the problem that should be explored. It has been suggested that LARP1 served as an oncogene, playing an important role in tumorigenesis. Chen et al. manifested that LINC01969 augmented LARP1 levels through sponging miR-144-5p and facilitated the malignant phenotypes of ovarian cancer cells (Chen et al., 2020a). Kato et al. elucidated that enhancement of LARP1 expression promoted the tumorigenicity of prostate cancer cells (Kato et al., 2015). In this study, we uncovered a positive correlation between KIAA1429 and LARP1 in CC, and amplified LARP1 alleviated the suppressive impacts of KIAA1429 deficiency on cell viability, metastasis, and EMT-associated markers in CC. KIAA1429 could enhance the stability of LARP1. Moreover, further investigations revealed that KIAA1429 repaired the stability of LARP1 to exert tumor-promoting behaviors.

Conclusions

In sum, these discoveries illuminated the critical roles of KIAA1429 in CC carcinogenesis, by promoting cancer cell viability and metastasis. KIAA1429 facilitated malignant CC progression by modifying LARP1 via m^{6}A methylation to promote its stability. These findings demonstrated that KIAA1429 could be considered a potential target for molecular therapy of CC. However, details of the strategy that targets the KIAA1429/LARP1 axis in CC require further investigation.

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