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Hsa_circ_0072008 regulates cell proliferation, migration, and invasion in cervical squamous cell carcinoma via miR-1305/helicase, lymphoid specific (HELLS) axis

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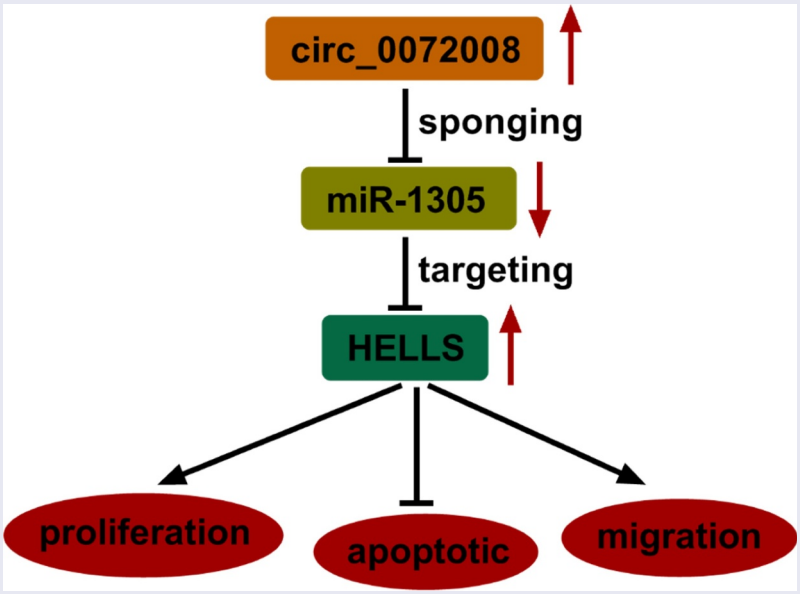
ABSTRACT

Cervical squamous cell carcinoma (CESC) is one of the most common cancers in women. Recent studies have proved that circular RNAs (circRNAs) could regulate the progress of CESC, but the mechanism is still indistinct. In this work, we explored the roles of circ_0072008 in CESC. The expression levels of circ_0072008, microRNA-1305 (miR-1305) and mRNA of HELLS (helicase, lymphoid specific) were detected by quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) in CESC tissues. Meanwhile, the level of HELLS was quantified by western blot analysis. Besides, the cell functions were examined by colony formation assay, 5-Ethynyl-2′-deoxyuridine (EdU) assay, wound healing assay, flow cytometry assay and western blot. Furthermore, the interaction between miR-1305 and circ_0072008 or HELLS was detected by dual-luciferase reporter assay. The function of circ_0072008 in CESC has also been further verified *in vivo* by xenograft model experiments. The levels of circ_0072008 and HELLS were upregulated, and the miR-1305 level was decreased in CESC tissues in contrast to that in normal tissues. For functional analysis, silencing circ_0072008 inhibited cell proliferation and cell migration, whereas enhanced cell apoptosis in CESC cells. In mechanism, circ_0072008 acted as a miR-1305 sponge to regulate the level of HELLS. Moreover, miR-1305 was confirmed to repress the progression of CESC cells by suppressing HELLS. Meanwhile, knockdown of circ_0072008 inhibited CESC cells growth *in vivo*. In conclusion, circ_0072008 facilitated CESC cell proliferation, migration, and invasion through increasing HELLS expression by regulating miR-1305, which also offered an underlying targeted therapy for CESC treatment.



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Supplemental data for this article can be accessed here

1 Introduction

Cervical squamous cell carcinoma (CESC) is a common cause of cancer-related death in women [1]. *Human papillomavirus* (HPV) is the causative agent of CESC, and its continuous and repeated infection is the main cause of CESC [2]. In recent years, with the widespread implementation of CESC screening, the incidence and mortality of CESC have decreased significantly [1]. However, for patients with terminal stages of CESC, the current treatment is not ideal. Therefore, we urgently need to find a new way to treat CESC.

Circular RNAs (circRNAs) are a type of RNAs that have no 5'-caps and 3'-tails, which could stabilize existence in plentiful types of organisms and regulate a variety of cellular biological functions [3,4]. For instance, circ-myosin X (MYO10) regulates cell proliferation in osteosarcoma progression [5]. Besides, circ-DNA polymerase alpha 2 (POLA2) takes part in the cell migration and invasion in CESC [6]. Moreover, circ_0101996 acts as a biomarker for CESC [7]. In addition, circ-ATPase family AAA domain containing 1 (ATAD1) participates in cell proliferation and apoptosis in CESC [8]. An article analyzing the circRNA/miRNA/mRNA network in CESC showed that circ_0072008 was up-regulated in CESC [9], but the function of circ_0072008 in CESC has not been confirmed.

MicroRNAs (miRNAs) are a class of small RNAs that inhibit the target genes expressed to regulate the subsequent biology processes [3,4]. For example, miR-1305 is related to cell metastasis in bladder cancer [10]. Besides, miR-1305 takes part in regulating cell adhesion and cell apoptosis in esophageal squamous cell carcinoma cells [11]. Moreover, miR-1305 acts as a vital regulator in hepatocellular carcinoma [12]. However, the understanding of the influence of miR-1305 in CESC is still restricted.

HELLS (helicase, lymphoid specific), a member of the SNF2-like family, is important for DNA methylation [13]. In addition, HELLS is highly expressed in glioblastoma and can regulate glioma progression [14]. Moreover, HELLS plays an important role in normal development [15]. In mouse models, HELLS mutated mice showed signs of growth retardation and premature aging [16]. However, the relationship between HELLS and the CESC is still indistinct, which is worth studying in detail.

In this study, we aimed to figure out the action and regulation mechanism of circ_0072008 in CESC. The research revealed that circ_0072008 facilitates CESC cell proliferation, migration, and invasion. Our results may provide new ideas for targeted therapy of CESC and provide a molecular theoretical basis for subsequent clinical treatment.

2 Materials and methods

2.1. Clinical tissue samples

The study was approved by the Ethics Committee of Jingmen NO. 1 People's Hospital (2020JMY-012-03). We collected 49 pairs of CESC tumor tissues and adjacent normal cervix tissues, which were gathered from Jingmen NO. 1 People's Hospital. In addition, normal epithelium samples (n = 10), cervical intraepithelial neoplasia (CIN) 1 samples (n = 13), CIN 2 samples (n = 11), CIN 3 samples (n = 15) were obtained in the same hospital. The subject samples were obtained in compliance with the Declaration of Helsinki. All patients and volunteers have written the informed consent, and all samples were conserved at −80°C.

2.2. Cell lines and cell culture

The CESC cell lines (SW756 and SiHa) and the control cell line (Ect1/E6E7) were acquired from American type culture collection (ATCC, Manassas, VA, USA). All cells were cultured with 5% CO_2. The SW756 cell line was cultured in Leibovitz's L-15 Medium (ATCC) supplemented with 10% FBS (Thermo Fisher Scientific, Waltham, MA, USA) at 37°C with 100% air. The SiHa cell line was cultured in Eagle's Minimum Essential Medium (EMEM) (ATCC) supplemented with 10% FBS (Thermo Fisher Scientific) at 37°C with 95% air and 5% CO_2. The Ect1/E6E7 cell line was maintained in keratinocyte-Serum Free medium (Thermo Fisher Scientific) supplemented with calcium chloride 44.1 mg/L (Sigma) at 37°C with 95% air and 5% CO_2.

2.3. Quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR)

All tissues and cells RNA was extracted by a Trizol reagent (Sigma). The Prime Script RT reagent kit (Thermo Fisher Scientific) was applied for circ_0072008 and HELLS reverse transcription. Meanwhile, miRNA was reverse transcribed using a miRNA First-Strand Synthesis kit (Takara, Tokyo, Japan) for miR-1305. Next, cDNA was synthesized and used for qRT-PCR with an SYBR Green kit (Takara). GAPDH and RNU6 (U6) were used as endogenous controls to standardize circRNA and miRNA expression levels, respectively. The primer as follow: circ_0072008, F: 5'-GTTTCAAGCCGCAACAACCA-3' and R: 5'-TCAAAGCAGCACGCATACAG-3'; MYO10 mRNA, F: 5'-AGCTGTCTCCACTGCTCTTG-3' and R: 5'-CTTTGGGGCTGACATAGGGG-3'; miR-1305, F: 5'-GCCGAGTTTTCAACTCTAATGG-3' and R: 5'-CTCAACTGGTGTCGTGGA-3'; HELLS, F: 5'-TGAGGGCTTCTTTGAAGGCAA-3' and R: 5'-GTACGGTTCACAATGGCTGT-3'; GAPDH, F: 5'-TCCCATCACCATCTTCCAGG-3' and R: 5'-GATGACCCTTTTGGCTCCC-3'; U6, F: 5'-CTCGCTTCGGCAGCACATATACT-3' and R: 5'-ACGCTTCACGAATTTGCGTGTC-3'. Relative expressions were calculated with the $2^{-\Delta\Delta Ct}$ method [17].

2.4. Western blot

The method of Western blot was as previously reported [18]. The antibodies as follows: anti-HELLS (ab3851; 1:1,000; Abcam, Cambridge, MA, USA), anti-PCNA (ab29; 1:500; Abcam), anti-Bax (ab32503; 1:1,000; Abcam) and and anti-β-actin (ab8227; 1:1000; Abcam).

2.5. RNase R degradation assay

The RNA was treated with RNase R (Epicenter Technologies, Madison, WI, USA) as described previously [19]. Moreover, the MYO10 mRNA was employed as a control. At that moment, the levels of circ_0072008 and MYO10 mRNA were detected.

2.6. Cell transfection

The si-circ_0072008, sh-circ_0072008, the control (si-NC, sh-NC), miR-1305 mimic, miR-1305 inhibitor and controls, the HELLS and control (pcDNA) were acquired from Ribobio (Guangzhou, China). These plasmids or oligonucleotides were transferred in into CESC cells by using Lipofectamine 2000 (Thermo Fisher Scientific).

2.7. Colony formation assay

The procedure for this experiment was as previously reported [20]. After post-transfection, the CESC cells were plated on the 6-well plates. After 14 days, the cells were fixed and stained, and the colony number was photographed and counted under a microscope (Olympus, Tokyo, Japan)

2.8. Cell proliferation assay

In this experiment, the Cell-Light 5-Ethynyl-2'-deoxyuridine (EdU) Apollo488 kit (RiboBio, Guangzhou, China) was used to analyze cell proliferation following the operating procedures. EdU positive cells showed green light and nuclei were stained using DAPI solution (Thermo Scientific) with blue light. Images were acquired using a fluorescence photomicroscope (Carl Zeiss, Oberkochen, Germany).

2.9. Wound-healing assay

After post-transfection, the CESC cells were plated on the 6-well plates. In simple terms, the cells were scraped and treated with FBS-free media for 24 h. Next, the distances between two cell edges were measured by Image J. This experiment was done as previously reported [21].

2.10 Flow cytometry assay

The CESC cells after varied transfection were seeded in 6-well plates. As described by Wang *et al.*, the Annexin V-FITC Apoptosis Detection Kit (Sigma) was used to treat every group of cells [22]. The apoptosis cells were observed under a flow cytometry.

2.11. Dual-luciferase reporter assay

The binding site between miR-1305 and circ_0072008 or HELLS was estimated by starbase (http://starbase.sysu.edu.cn). Then, the wild and mutant circ_0072008 and HELLS were synthesized from Ribobio (circ_0072008 wt, HELLS 3 UTR wt or circ_0072008 mut, HELLS 3 UTR mut). The luciferase activity was tested with a dual-luciferase reporter assay system (Promega, Madison, WI, USA) based on the user's manual.

2.12. RNA pull-down

The Bio-miR-1305 and Bio-miR-NC were synthesized from RiboBio. A Pierce Magnetic RNA-Protein Pull-Down Kit (Sigma) was used to recognize the interaction between miR-1305 and circ_0072008 following the user's manual. After post-transfection, CESC cells were nurtured with the probe-bead complex for 3 h. After, the beads were collected, and removed the protein and DNA, respectively. Lastly, the level of circ_0072008 was measured.

2.13. Xenograft models

The research abided by the direction of the Animal Care and Use Committee of Jingmen NO. 1 People's Hospital. This study was conducted in full accordance with the ARRIVE guidelines [23]. All female nude mice were gotten from Beijing Vital River Laboratory Animal Technology (Beijing, China). SW756 cells (1×10^6) with sh-circ_0072008 or the sh-NC were inoculated into mice (two groups, n = 6/group, 6 weeks of age; 18–22 g). Lastly, tumor volume was registered once a week suitable for the formula: Tumor volume = length × width^2 × 0.5. After 35 days, these tumor tissues were carved for further experiment.

2.14. Immunohistochemistry (IHC) assay

Firstly, the tumor specimens were made into paraffin slides, followed by antigen retrieval. Afterward, tissue slides incubated at 4°C overnight with anti-Ki67 (ab92742; 1:1,000; Abcam). Then, the tumor slides were nurtured with HRP-conjugated secondary antibody (ab205718; 1:1,000; Abcam). Eventually, the slides were stained using diaminobenzidine (Sigma) and observed [24].

2.15 Statistical assay

All data were gotten from no less than three independent reiterations and investigated using SPSS 23.0 (SPSS, USA). Student's *t*-test was employed to examine the statistical differences between two groups, and ANOVA was administrated to compare the statistical differences among multiple groups. $P < 0.05$ was significant.

3. Results

3.1. The expression of circ_0072008 was upregulated in CESC tissues and cells

An article analyzing the circRNA/miRNA/mRNA network in CESC showed that circ_0072008 was up-regulated in CESC [9]. To figure out the function of circ_0072008 in CESC, we detected circ_0072008 expression in CESC tissues. qRT-PCR assay showed that the expression of circ_0072008 was significantly increased in CESC tissues (n = 49) relative to paracancer tissues (n = 49) (Figure 1(a)). Also, circ_0072008 expression levels were higher in tumor samples at stages II, III, and IV than that in tumor samples at stage I (supplementary Fig. 1A). In addition, circ_0072008 was highly expressed in CIN3 samples compared to normal samples, but there was no marked change in CIN1 and CIN2 samples (supplementary Fig. 1B). Besides, circ_0072008 was significantly upregulated in SW756 and SiHa cells in comparison to the Ect1/E6E7 cells (Figure 1(b)). RNase R and Act D assays were done to determine the stability of circ_0072008. The expression of MYO10 mRNA was significantly reduced, while circ_0072008 was resistant to RNase R digestion (Figure 1(c,d)). Moreover, the half-life of circ_0072008 was longer than linear MYO10 (Figure 1(e,f)). In a word, the circ_0072008 is more outstanding upregulated in CESC tissues and cells, which might take effects in CESC progression. In addition, circ_0072008 structure pattern was verified as a circular RNA.

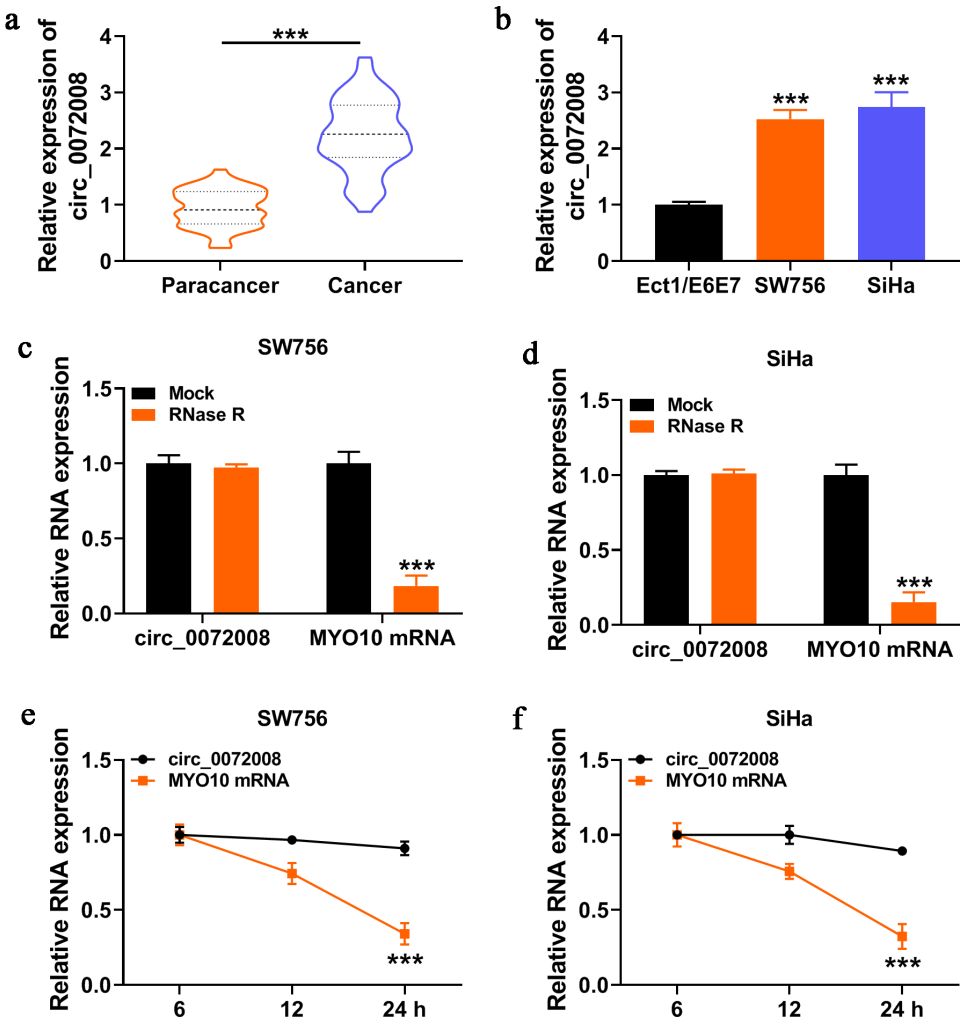

Figure 1. Circ_0072008 expression was enhanced in CESC tissues. (a) The expression of circ_0072008 in CESC tissues was detected by qRT-PCR. (b) The relative levels of circ_0072008 in CESC cells were detected by qRT-PCR. (c and d) The levels of circ_0072008 and MYO10 mRNA after RNase R treatment were detected by qRT-PCR. (e and f) The levels of circ_0072008 and MYO10 mRNA after Act D treatment were detected by qRT-PCR. ***$P < 0.001$.

3.2. Silencing circ_0072008 inhibited cell proliferation and cell migration, whereas enhanced cell apoptosis in CESC cells

Transfection efficiency of si-circ_0072008 was detected by qRT-PCR. The results specified that circ_0072008 expression was restricted in CESC cells transfected with si-circ_0072008 compared to the si-NC group (Figure 2(a)). Functionally, the results of colony formation assay and EdU assay revealed that the si-circ_0072008 inhibited cell proliferation (Figure 2(b,c)). Figure 2(d) displayed that silence of circ_0072008 decreased the cell migration. In addition, the results of flow cytometry assay suggested that the si-circ_0072008 transfection promoted cell apoptosis (Figure 2(e)). The PCNA and Bax are vital to cell proliferation and apoptosis. The downregulation of circ_0072008 dramatically restrained the expression of PCNA, but enhanced the expression of Bax (Figure 2(f,g)). Our results demonstrated that circ_0072008 deficiency inhibited cell proliferation and cell migration, whereas enhanced cell apoptosis in CESC cells.

3.3 MiR-1305 acted as the target of circ_0072008 in CESC cells

Starbase predicted that the miR-1305 is a target of circ_0072008 (Figure 3(a)). In addition, level of miR-1305 was obviously impeded in CESC tissues

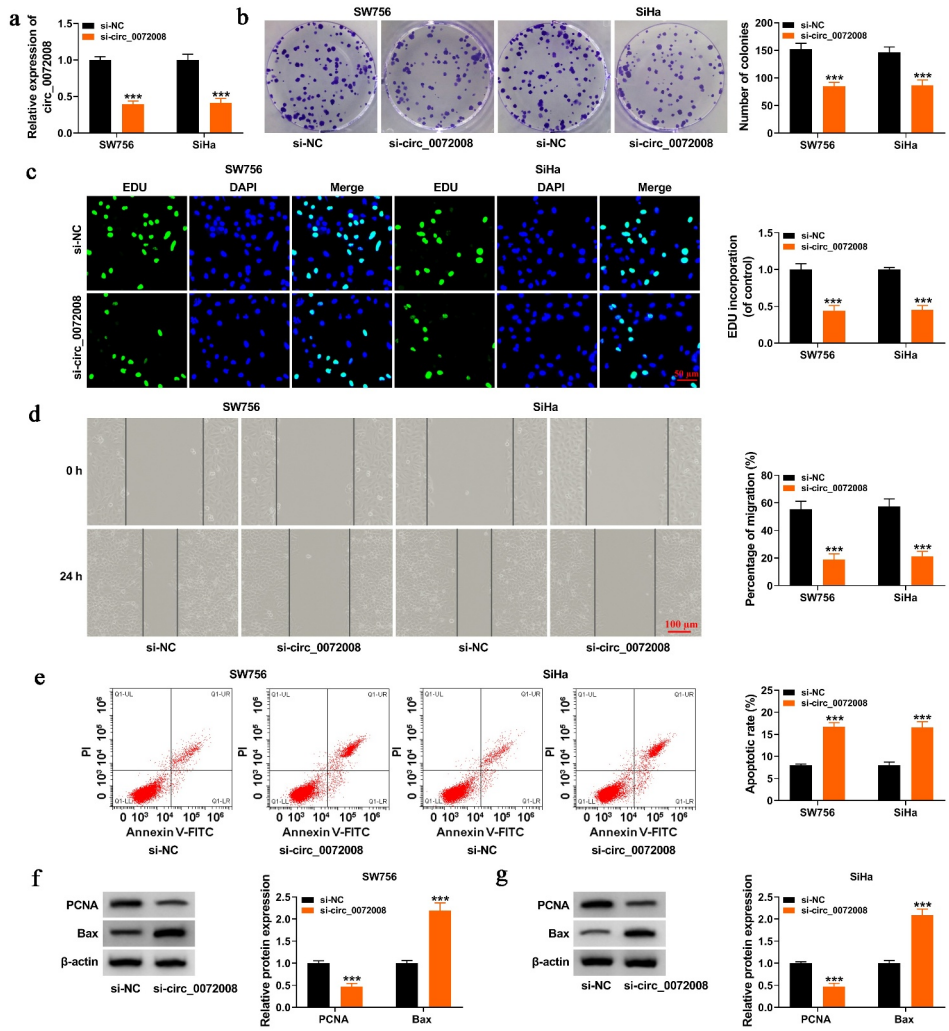

Figure 2. Circ_0072008 knockdown inhibited CESC progression. (a) The silencing efficiency of si-circ_0072008 was measured by qRT-PCR. (b) The colony formation assay revealed the cell proliferation. (c) The EdU assay unfolded the cell proliferation. (d) The wound healing assay measured the cell migration. (e) The flow cytometry assay showed the cell apoptosis. (f and g) The protein level of PCNA and Bax were examined by Western blot. ***$P < 0.001$.

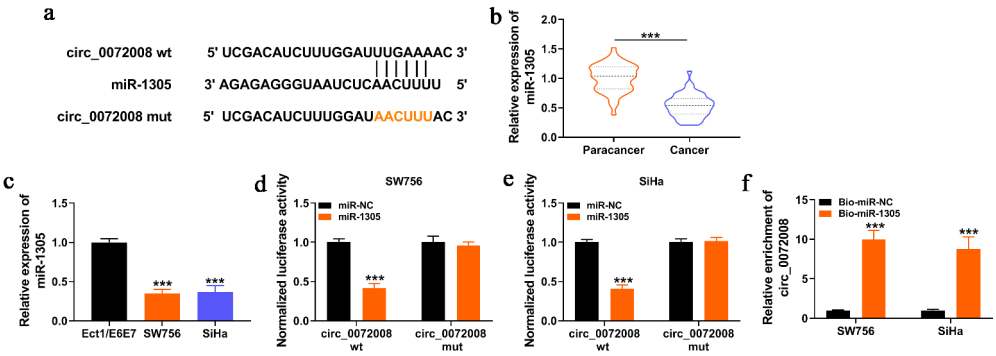

Figure 3. Circ_0072008 acted as a sponge for miR-1305. (a) The targeted miRNAs of circ_0072008 were forecast by starbase. (b and c) The expression of miR-1305 in CESC tissues and cells was measured by qRT-PCR. (d and e) Dual-luciferase reporter assay was used to verify the relationship between circ_0072008 and miR-1305. (f) RNA pull-down assay was used to verify the relationship between circ_0072008 and miR-1305. ***$P < 0.001$.

(n = 49) with respect to paracancer tissues (n = 49) (Figure 3(b)). Also, miR-1305 was downregulated in tumor samples at stages II, III, and IV compared with tumor samples at stage I (supplementary Fig. 1C), and its expression was lower in CIN3 samples than that in normal samples, while there was no significant difference in CIN1 and CIN2 samples (supplementary Fig. 1D). Moreover, our data also manifested that miR-1305 was downregulated in SW756 and SiHa cells in comparison to the Ect1/E6E7 cells (Figure 3(c)). Figure 3(d,e) implicated that the luciferase activity was greatly decreased in circ_0072008 wt and miR-1305 co-transfected in CESC cells compared to circ_0072008 wt and miR-NC co-transfected groups even though no difference was found between circ_0072008 mut and miR-1305 co-transfection groups. The RNA-pulldown assay elucidated the direct reciprocity between miR-1305 and circ_0072008 in CESC cells (Figure 3(f)). In

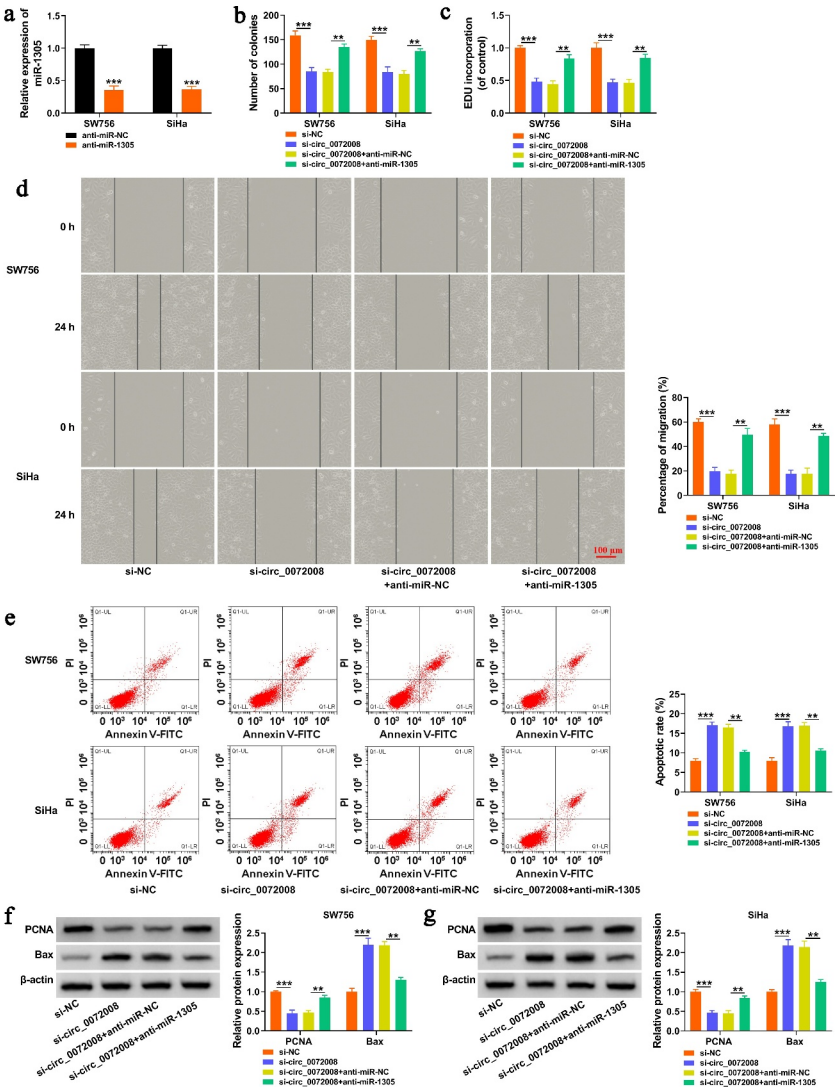

Figure 4. Circ_0072008 facilitated the progression of CESC by sponging miR-1305. (a) The expression of miR-1305 was detected by qRT-PCR. (b and c) The cell proliferation, (d) the cell migration, (e) the cell apoptosis, (f and g) the protein levels of PCNA and Bax were detected by colony formation assay, EdU assay, wound healing assay, flow cytometry assay, and western blot. $^{**}P < 0.01$, $^{***}P < 0.001$.

a word, these results indicated that circ_0072008 acted as a sponge for miR-1305 in CESC, and it may play an important role in CESC development.

3.4 MiR-1305 knock-down reversed si-circ_0072008 effect in CESC cells

Figure 4(a) demonstrated that the level of miR-1305 expression was drastically hindered by miR-1305 inhibitor in CESC cells. Functionally, si-circ_0072008 constrained cell proliferation, but miR-1305 inhibitor reduced the impact in CESC cells (Figure 4(b,c)). Moreover, the miR-1305 knock-down relieved the effect of si-circ_0072008 on cell migration and apoptosis of CESC cells (Figure 4(d,e)). In addition, miR-1305 inhibitor could inhibit the effect of si-circ_0072008 on the level of PCNA and Bax in CESC cells (Figure 4(f, g)). Our results manifested that circ_0072008 knockdown inhibited the progression of CESC, whereas miR-1305 inhibitor could lessen the impact.

3.5 MiR-1305 targeted HELLS in CESC cells

Starbase was applied to predict the binding sites of miR-1305 in HELLS 3 UTR (Figure 5(a)). Figure 5(b,c) unfolded that the mRNA and protein level of HELLS was obviously upregulated in CESC tissues with respect to paracancer tissues. We also observed an overt elevation in HELLS expression in tumor samples at stages II, III, and IV relative to tumor samples at stage I (supplementary Fig. 1E), and the expression of HELLS mRNA was higher in CIN3 samples than that in normal samples (supplementary Fig. 1F). Moreover, the levels of HELLS were enhanced in SW756 and SiHa cells in comparison to the Ect1/E6E7 cells (Figure 5(d,e)). Meanwhile, the luciferase activity of HELLS 3 UTR wt group

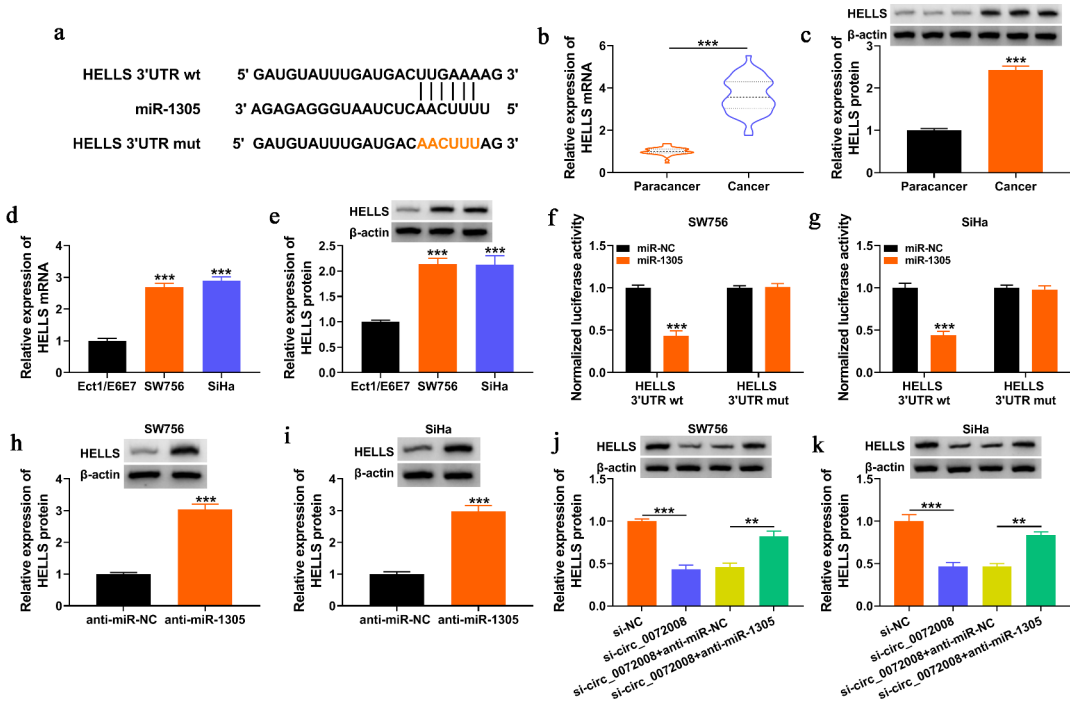

Figure 5. MiR-1305 targeted HELLS in CESC cells. (a) The binding site between miR-1305 and HELLS was analyzed by starbase. (b–e) The expression of HELLS was detected by qRT-PCR and western blot. (f and g) Dual-luciferase reporter assay was used to confirm the relationship between miR-1305 and HELLS. (h–k) The expression of HELLS was detected by western blot. $^{**}P < 0.01$, $^{***}P < 0.001$.

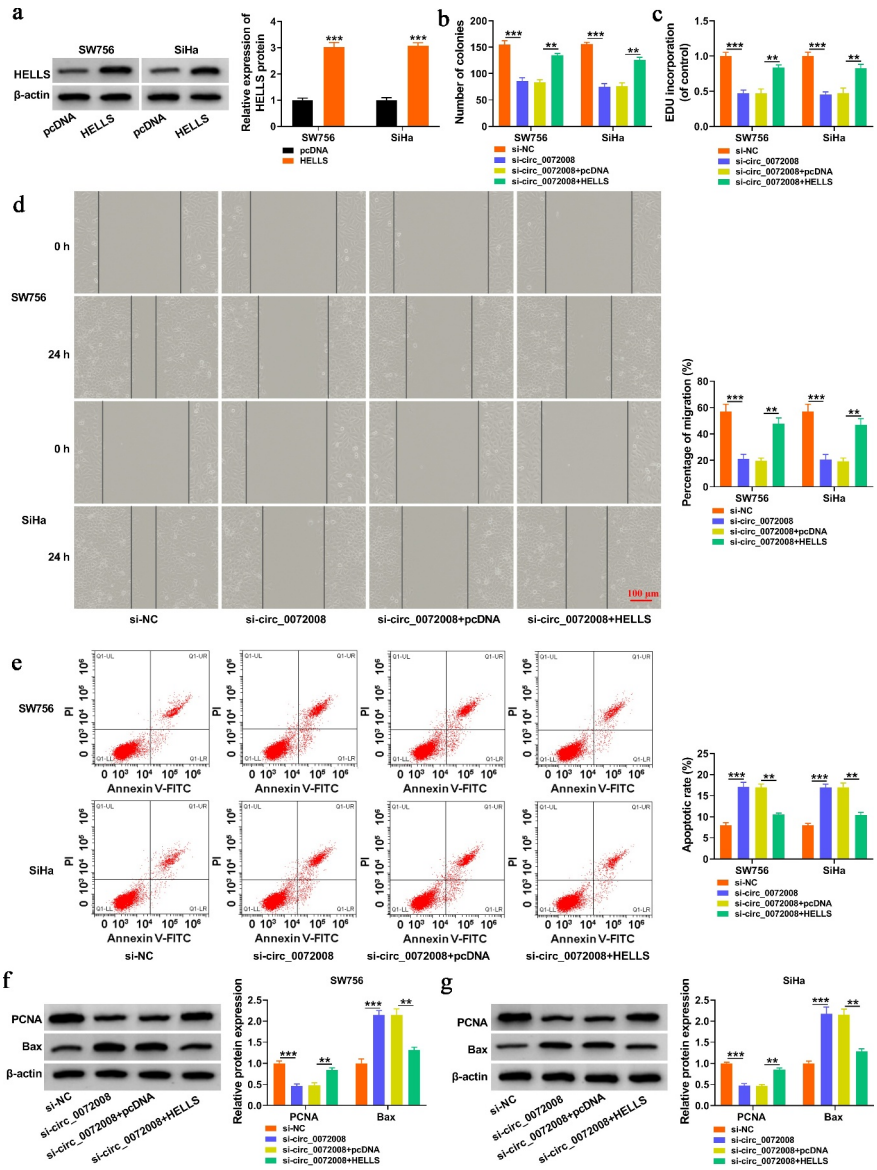

Figure 6. Circ_0072008 regulated the progression of CESC by targeting HELLS. (a) The expression of HELLS was detected by western blot. (b and c) The cell proliferation, (d) the cell migration, (e) the cell apoptosis, (f and g) the protein level of PCNA and Bax were detected by colony formation assay, EdU assay, wound healing assay, flow cytometry assay, and western blot. $^{**}P < 0.01$, $^{***}P < 0.001$.

was notably downregulated after miR-1305 mimic transfection. However, the luciferase activity of HELLS 3 UTR mut group was not significantly changed by miR-1305 (Figure 5(f, g)). Besides, the level of HELLS was significantly increased by miR-1305 inhibitor (Figure 5(h,i)). Moreover, the expression of HELLS was significantly decreased by si-circ_072008, but increased by transfected miR-1305 inhibitor (Figure 5(j, k)). Collectively, these discoveries suggested that miR-1305 could interact with HELLS to inhibit its expression.

3.6 HELLS reversed si-circ_0072008 effect in CESC cells

The HELLS expression was markedly increased by HELLS overexpression in CESC cells (Figure 6(a)). Functionally, si-circ_0072008 inhibited cell proliferation was reversed by HELLS (Figure 6(b,c)).

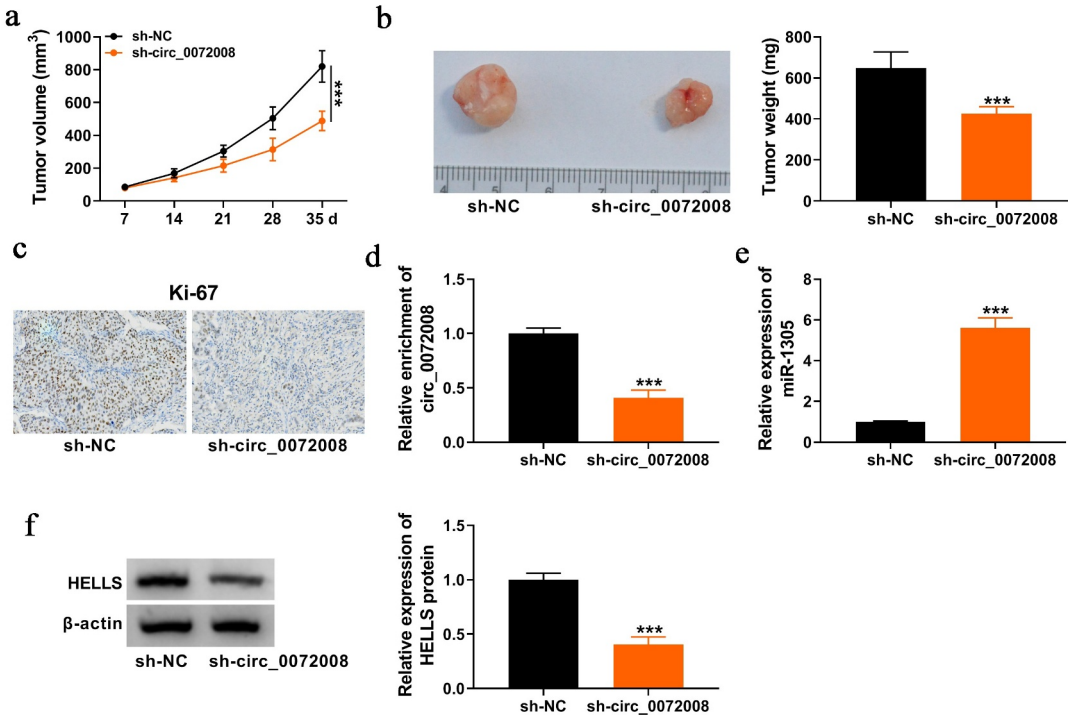

Figure 7. Circ_0072008 restricted tumor growth *in vivo*. (a) The tumor volume was measured every week. (b) Tumor weight was measured after 35 days when the mice were killed. (c) IHC analysis was implemented to examine the expression of Ki-67 in tumor tissues from different groups. (d–f) The expression of circ_0072008, miR-1305, and HELLS in these excised tumor tissues was detected by qRT-PCR. ***$P < 0.001$.

Moreover, the HELLS overexpression relieved the effect of si-circ_0072008 on cell migration and apoptosis of CESC cells (Figure 6(d,e)). In addition, HELLS could inhibit the effect of si-circ_0072008 on the level of PCNA and Bax in CESC cells (Figure 6(f,g)). Our results indicated that si-circ_0072008 inhibited the progression of CESC, whereas HELLS overexpression could lessen the impact.

3.7 *Sh-circ_0072008 restricted tumor growth* in vivo

As shown in Figure 7(a,b), sh-circ_0072008 treatment repressed tumor volume and weight. The results from IHC revealed that the expression levels of Ki-67 were lower in the sh-circ_0072008 group compared with that in the sh-NC group (Figure 7(c)). Then, the tumor tissues were examined by qRT-PCR and western blot. The results showed that sh-circ_0072008 decreased the level of circ_0072008 and HELLS, but increased the expression of miR-1305 (Figure 7(d-f)). These results indicate that circ_0072008 knockdown inhibited xenograft tumor growth.

4 Discussion

Current clinical screening encourages cytology every three years for women ages 21 to 29 and high-risk HPV testing every five years for women ages 30 to 65 [25]. There are many molecules that behave abnormally during the development of CESC, and understanding the mechanisms of action of these molecules is crucial for their potential therapeutic uses [26]. Whereas, the functions of circ_0072008 in CESC are still uncertain. Hence, our study investigated the character of circ_0072008.

Circ_0072008 has been proved was an oncogene in osteosarcoma [5]. In our paper, we determined the circ_0072008 was upregulated in the CESC.

Our consequences signposted that silencing circ_0072008 inhibited cell proliferation and cell migration, whereas enhanced cell apoptosis in CESC cells. The circRNAs could competitively sponge for miRNAs, like circ-ATAD1 could target miR-218 in CESC cells [8]. In this study, circ_0072008 facilitates the progression of CESC by sponging miR-1305, which is parallel to former discoveries.

According to preceding information, miR-1305 was closely related to the progress of bladder cancer, esophageal squamous cell carcinoma cells, and hepatocellular carcinoma [10–12]. In this study, we discovered that miR-1305 suppressed the progress of CESC by targeting HELLS, which is parallel to former discoveries [27]. At present, many researchers have proved that HELLS could regulate the cell proliferation in colorectal cancer cells [28]. In this paper, the expression of HELLS was upregulated in CESC. Even more important, we observed that miR-1305 inhibitor reversed the suppressive effect of si-circ_0072008 on HELLS level in CESC cells. These outcomes additionally supported the control circuit of the circ_0072008/miR-1305/HELLS in CESC cells.

5 Conclusion

The paper determined that circ_0072008 and HELLS were upregulated and miR-1305 was downregulated in CESC cells. Furthermore, our study manifested that silencing circ_0072008 inhibited cell proliferation and cell migration, whereas enhanced cell apoptosis in CESC cells via miR-1305/HELLS axis. There are still some limitations to the study, such as the results need further studied in clinical practice. Overall, this study provides clues to the regulatory mechanisms of CESC and opens up new potential therapeutic avenues for future clinical targeted therapy.

Data Availability Statement

The data used to support the findings of this study are included within the article.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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