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MiR-1179 is downregulated in cervical cancer and its overexpression suppresses cancer cells invasion by targeting CHAF1A/ZEB1

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The anticancer effect of miR-1179 has been extensively studied in many tumors. The mechanism of miR-1179 action in cervical cancer, however, remains largely unknown. In the present study, miR-1179 was downregulated in both cervical cancer cell lines and cancer tissues. In addition, miR-1179 mimic suppressed cancer cells invasion and epithelial-mesenchymal transition (EMT) in cervical cancer SiHa and Caski cells. We found that chromatin assembly factor 1 subunit A (CHAF1A) might be a direct target of miR-1179 and could be regulated by miR-1179. Furthermore, CHAF1A shRNA suppressed the cervical cancer cells invasion and the expression of EMT-promoted proteins. Reversely, CHAF1A overexpression not only promoted cervical cancer cells invasion but also upregulated the level of Zinc finger E-box binding protein 1 (ZEB1), an EMT-related protein. The induction of ZEB1 could be counteracted by miR-1179 overexpression. It was observed that in cervical cancer patients' tissues, miR-1179 was downregulated while the pathway of CHAF1A/ZEB1 was upregulated. In summary, our research indicated that the miR-1179 might regulate CHAF1A/ZEB1 axis and inhibit the invasion of cervical cancer cells.

Keywords: cervical cancer, miR-1179, epithelial-mesenchymal transition, CHAF1A/ZEB1

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Abbreviations: CHAF1A, chromatin assembly factor 1 subunit A; EMT, epithelial-mesenchymal transition; HPV, human papillomavirus; ZEB1, Zinc finger E-box binding protein 1

INTRODUCTION

Cervical cancer is one of the most common gynecological malignancies caused by human papillomavirus (HPV) infection. Clinical trials has validated that HPV vaccines reduce the risk of cervical cancer with HPV type 16 and 18 by 70% and by and 86–95% for other HPV-associated cancers (Markham *et al.,* 2020). However, new cases of cervical cancer still account for 10% of all gynecological cancers and approximately 5% of all tumors (Hovland *et al.,* 2010), second only to breast cancer (Ferlay *et al.,* 2010; De Martel *et al.,* 2012), with more than 85% of cervical cancers prevalent in developing countries and more than 80% of all cases (Arbyn *et al.,* 2011). Epithelial-mesenchymal transition (EMT) and cancer cells invasion might be the main reasons for cervical cancer malignancy. Therefore, in addition to the prevention of cervical cancer with HPV vaccines, biological biomarkers and therapeutic targets have gained increasing interest as there is still the demand for the treatment of cervical cancer.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by inhibiting post-transcriptional translation of mRNA. The relationship between miRNA and tumors has been extensively studied, and many studies found that various miRNAs play an important regulatory role in the occurrence and development of cervical cancer (Wilting *et al.,* 2010; Wang *et al.,* 2011; Liu *et al.,* 2012; Xie *et al.,* 2012; Zhu *et al.,* 2013). The anticancer effect of miR-1179 has been extensively studied in many tumors (Lin *et al.,* 2018; Song *et al.,* 2018; Gao *et al.,* 2019; Li & Qin 2019), but its pro-oncogenic effect was also reported (Jiang *et al.,* 2015; Zhihong *et al.,* 2019). However, the effect as well as the underlying mechanism of miR-1179 action in cervical cancer remain unknown. Therefore, we aimed to investigate the expression level and the effect of miR-1179 in cervical cancer.

Chromatin assembly factor 1 subunit A (CHAF1A) is a pro-oncogene that plays a role in a variety of tumors, such as colon cancer (Wu *et al.,* 2014), glioblastoma (Peng *et al.,* 2016), ovarian cancer (Xia *et al.,* 2017) and gastric cancer (Zheng *et al.,* 2018). In addition, studies showed that the expression of CHAF1A was increased in cervical cancer and was positively correlated with tumor malignancy (Luo *et al.,* 2017). However, the specific mechanism of its action in cervical cancer needs to be further studied. Interestingly, in the present study, we found that miR-1179 could bind to the 3'UTR of CHAF1A. Furthermore, CHAF1A overexpression promoted EMT and invasion. Thus, we speculated that CHAF1A might be a regulatory target of miR-1179 in cervical cancer. Zinc finger E-box binding protein 1 (ZEB1) was reported as EMT-activator in cancer biology (Zhang *et al.,* 2015). In previous studies, CHAF1A was demonstrated to interact with TCF4, which promotes gastric carcinogenesis (Zheng *et al.,* 2018), while β-catenin/TCF4 complex can induce the EMT-activator ZEB1 to regulate tumor invasion (Sánchez-Tilló *et al.,* 2011). Moreover, TCF4 can regulate ZEB1/ZEB2 expression in drug resistance and stemness of colorectal cancer (Sun *et al.,* 2020). These studies indicated that a regulatory mechanism might exist for CHAF1A and ZEB1. In summary, we aimed to clarify the action of miR-1179/CHAF1A/ZEB1 axis in cervical cancer and this study might provide a new target for cervical cancer therapy.

MATERIALS AND METHODS

Cell lines and culture

The cervical cancer cell lines SiHa and Caski were purchased from the American type culture collection (ATCC; Rockville, MD, USA). SiHa cells were cultured in Eagle's Minimum Essential Medium (EMEM, Gibco, Grand Island, NY, USA) and Caski cells were cultured in RPMI-1640 Medium (Gibco), respectively, supplemented with 10% FBS (Gibco) in an incubator at 37°C with 5% CO_2.

Cell transfection

MiR-1179 mimic (miR-1179 overexpression), negative control (NC mimic), pGL3-CHAF1A-wild type (WT), pGL3-CHAF1A-mutant (MUT), negative control (shNC), shCHAF1A (CHAF1A knockdown) and pcDNA3.1-CHAF1A (CHAF1A overexpression) were obtained from GenePharma Co., Ltd. (Shanghai, China). The vectors were separately transfected into cells using Lipofectamine 3000 (Invitrogen, Carlsbad, USA) strictly according to the manufacturer's instruction. After transfection, cells were cultured for 48 h and quantitative polymerase chain reaction (qPCR) was conducted to assess the transfection efficiency, and cells with satisfactory transfection efficiency were used for the subsequent experiments.

qPCR

Total RNA of SiHa and Caski cells and cervical cancer tissues was extracted with TRIzol reagent according to the manufacturer's protocols (Invitrogen). Briefly, 2 μg of RNA was reversely transcribed into cDNA with SuperScriptII Reverse Transcriptase kit (Invitrogen). Then the expression levels of miR-1179 and CHAF1A were quantified using SYBR Green supermix (Bio-Rad Corp.,USA) in the PCR 7300 System (Applied Biosystems, Foster City, USA). Primers for miR-1179, snRNA U6, β-actin, ZEB1 and CHAF1A were synthesized by Sangon Biotech (Shanghai, China). Primers were as follows: ZEB1 (Peña *et al.,* 2006): forward primer: 5'-GCCAATAAGCAAACGATTCTG-3' and reverse primer: 5'-TTTGGCTGGATCACTTTCAAG-3'; miR-1179: forward primer: 5'-GGCTGGAAAGGAAGAAG-3'; reverse primer: 5'-GTTAACCCGGCGGTGA-3'; CHAF1A (Liu *et al.,* 2017): forward primer: 5'-AGGGAAGGTGCCTATGGTG-3' and reverse primer: 5'-CAGGGACGAATGGCTGAGTA-3'; U6: forward primer: 5'-CTCGCTTCGGCA GCACA-3' and reverse primer: 5'-AACGCTTCACGAATTTGCGT-3'; β-actin (Li *et al.,* 2016): forward primer: 5'-GAGCTACGAGCTGCCTGACG-3' and reverse primer: 5'- GTAGTTTCGTGGATGCCACAG-3'. The qPCR data were analyzed by comparative Ct method and $2^{-\Delta\Delta CT}$ method. For control, miR-1179 expression was normalized to U6 while CHAF1A and ZEB1 expression was normalized to β-actin.

Transwell assay

SiHa and Caski cells were inoculated into the upper Transwell chambers filled with serum-free EMEM and RPMI-1640, respectively, at a density of 5×10^4/200 μL. At the same time, 500 μL EMEM and RPMI-1640, respectively, containing 10% FBS were placed in the lower Transwell chambers (Chen *et al.,* 2019) . After 24 h of culture, the cells in lower chambers were fixed with 95% ethanol and stained with crystal violet. Finally, the invasive cells were counted under a light microscope. The experiments were repeated 3 times.

Western blot assay

48 Hours after transfection, the protein expression of EMT markers (E-cadherin, N-cadherin), CHAF1A, ZEB1 and β-actin (Abcam, Cambridge, UK) was detected via Western blot. The expression level of target proteins was normalized to the expression of β-actin. The Western blot protocol was performed according to the literature (Lee & Hwang 2017). Target blots were visualized using the Chemiluminescent ECL Reagent Kit (Millipore, Bedford, MA, USA).

Luciferase reporter assay

The CHAF1A 3'UTR wild-type (WT) sequence or mutant binding sites (MUT) complementary to miR-1179 were amplified by PCR and cloned to pGL3-Basic vector. For luciferase reporter assays, pRL-TK and WT or MUT versions reporter plasmid vectors or miR-1179 mimics were co-transfected into Caski cells using Lipofectamine 3000 reagent. Cells were cultured for 48 h, and then the relative luciferase intensity was detected by the dual-luciferase reporter assay system (Promega, WI, USA) using a standard protocol. The relative luciferase intensity was normalized to Renilla luciferase intensity.

Immunohistochemical staining (IHC)

The study protocol was approved by the Ethics Committee of The No.2 People's Hospital of Hefei and performed in accordance with the revised version of the Declaration of Helsinki principles. All cervical cancer patients agreed to the use of their tumor tissues for IHC, and written consent was obtained from all the patients. 3-μm thick tissue sections from cervical cancer patients (including cervical cancer and normal cervical tissue) were prepared. After fixation with formalin and embedding in paraffin, tissue sections were submitted to standard immunohistochemistry processing with anti-CHAF1A and anti-ZEB1 antibodies (Abcam). The samples were observed and (×400) photographed under an optical microscope (Olympus).

Statistical analysis

Statistical analysis was performed using the statistical software (SPSS; version 17.0; Inc., Chicago, IL). The data were presented as means ± SD. Statistical differences were analyzed using paired t-test or one-way ANOVA followed by Tukey's posthoc test. P values < 0.05 were considered statistically significant.

RESULTS

Overexpression of miR-1179 inhibited EMT-upregulated proteins and invasion of cervical cancer cells

In both Caski and SiHa cells, miR-1179 mimic upregulated the expression of miR-1179 compared to NC mimic (Fig. 1A). Overexpression of miR-1179 *via* miR-1179 mimic significantly reduced the number of cells that passed through the Transwell basement membrane (Fig. 1B). Additionally, the N-cadherin protein expression was reduced, whereas the E-cadherin protein expression was increased after miR-1179 mimic transfec-

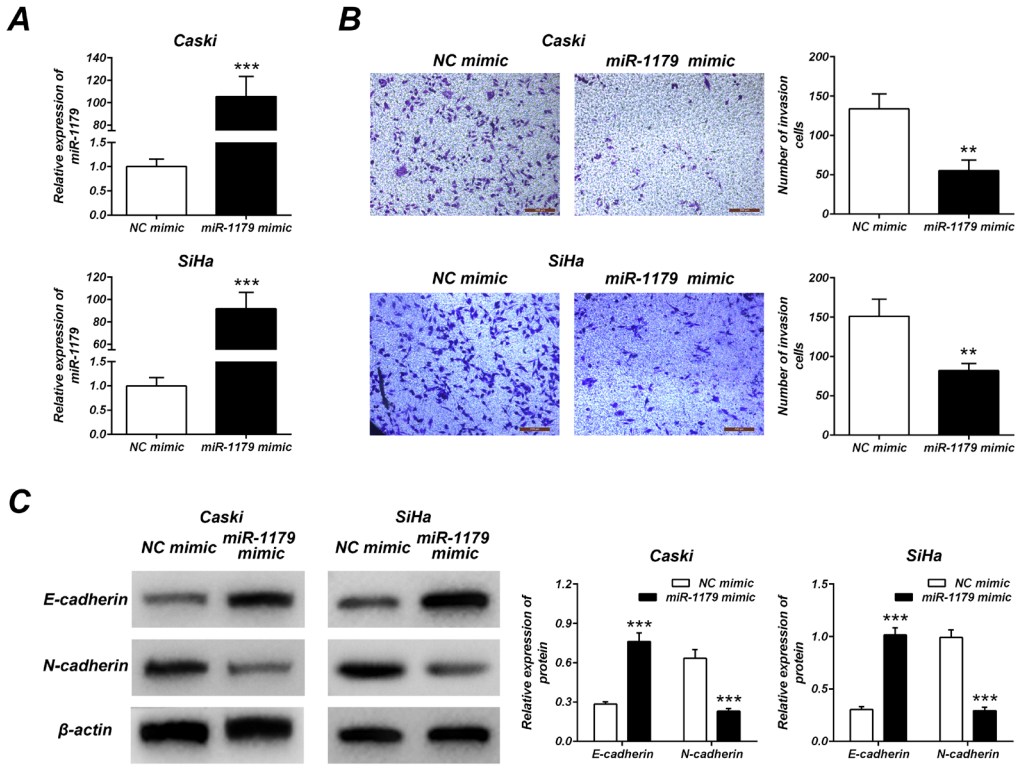

Figure 1. Overexpression of miR-1179 inhibited the invasion of cervical cancer cells.
Caski and SiHa cells were transfected with NC mimic or miR-1179 mimic. (**A**) qPCR was used to detect the expression of miR-1179 in Caski and SiHa cells. (**B**) Transwell assay was performed to assess the invasion of Caski and SiHa cells. (**C**) Western blot assay was performed to detect the protein expression of EMT-related proteins. The experiments were repeated three times. $^{**}p<0.01$, $^{***}p<0.001$ compared to the NC mimic group.

tion (Fig. 1C). These results indicated that overexpression of miR-1179 inhibited the invasion ability and EMT-upregulated proteins of Caski and SiHa cells.

Targeted binding of miR-1179 to CHAF1A

During the investigation of the potential targets of miR-1179 using TargetScan, miR-1179 was predicted to bind to the CHAF1A 3'UTR (Fig. 2A). MiR-1179 targeting CHAF1A was then verified by double-luciferase reporting assay (Fig. 2B). The expression of miR-1179 was vastly inhibited by miR-1179 inhibitor (Fig. 2C). In addition, the mRNA level of CHAF1A was decreased upon the treatment with miR-1179 mimic but was increased by miR-1179 inhibitor (Fig. 2D). The same trends were found at the protein level (Fig. 2E). These results suggested that CHAF1A was a target gene of miR-1179 and it could be regulated by miR-1179.

CHAF1A knockdown inhibited ZEB1 expression

To reveal the regulatory mechanism of CHAF1A and ZEB1, we performed CHAF1A knockdown using shCHAF1A to detect the level of ZEB1 in Caski and SiHa cells. In both Caski and SiHa cells, CHAF1A knockdown inhibited ZEB1 expression both at the mRNA and protein level (Fig. 3A–B).

CHAF1A overexpression reversed the effect of miR-1179 mimic on cell invasion

To further explore the mechanism of miR-1179/CHAF1A axis in cervical cancer, both Caski and SiHa cells were transfected with miR-1179 mimic, CHAF1A -pcDNA-3.1 vector, or miR-1179 mimic+CHAF1A -pcDNA-3.1 vector. Consequently, miR-1179 mimic decreased the levels of CHAF1A, ZEB1 and N-cadherin, but upregulated E-cadherin expression. On the contrary, CHAF1A overexpression significantly upregulated CHAF1A, ZEB1 and N-cadherin, but downregulated E-cadherin (Fig. 4A). As expected, the CHAF1A overexpressing cells treated with miR-1179 mimic showed no such effects (Fig. 4A), suggesting that miR-1179 might inhibit EMT-upregulated proteins by suppressing CHAF1A and ZEB1 expression. Additionally, the inhibitory effect of miR-1179 on the invasion of both Caski and SiHa cells was reversed by CHAF1A overexpression (Fig. 4B), which further confirmed that miR-1179 might inhibit cell invasion by downregulating the expression of CHAF1A and ZEB1.

MiR-1179 was downregulated in tumor tissues and negatively correlated with the expression of CHAF1A and ZEB1

As shown in Fig. 5 A&C, the relative mRNA level of miR-1179 was decreased in cervical cancer tissues compared to the normal tissues of patients. Conversely, the relative expression of CHAF1A and ZEB1 was elevated in cervical cancer tissues compared to the normal tissues of patients. In addition, the Pearson analysis revealed a negative correlation between the expression of CHAF1A1 and miR-1179 (Fig. 5B, r=0.7108, $P<0.001$), and a negative correlation between the expression of ZEB1 and miR-1179 (Fig. 5B, r=0.5196, $P<0.001$) in cervical cancer tissues. On the other hand, a positive correlation between the expression of ZEB1 and

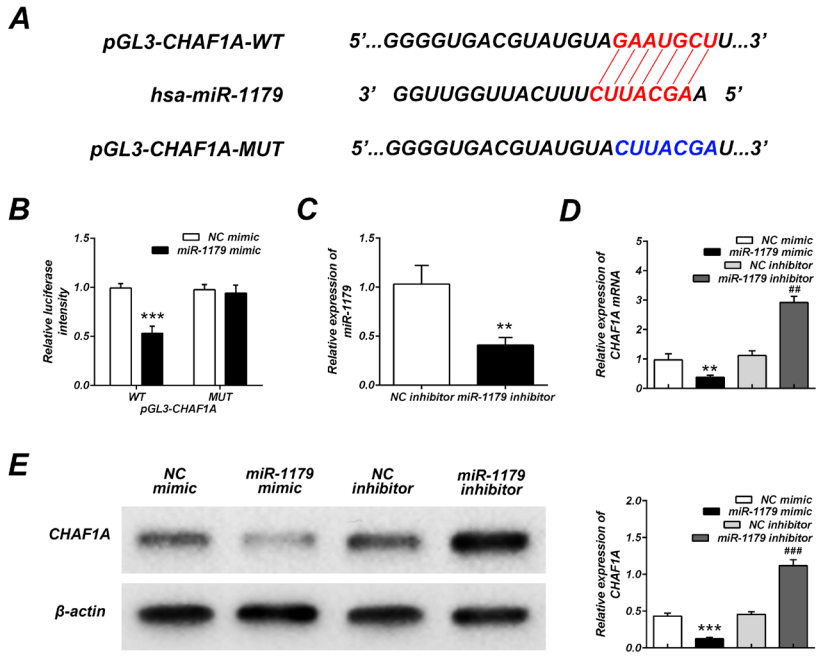

Figure 2. Targeted binding of miR-1179 to CHAF1A.
(**A**) Target prediction was conducted using the TargetScan website. (**B**) Caski cells were divided into NC mimic + pGL3-CHAF1A-WT, miR-1179 mimic + pGL3-CHAF1A-WT-NC mimic + pGL3-CHAF1A-MUT and miR-1179 mimic + pGL3-CHAF1A-MUT groups. Luciferase reporter assay was performed to confirm the target relationship between miR-1179 and CHAF1A. (**C–D**) qPCR was used to detect the expression of miR-1179 and CHAF1A in Caski cells. (**E**) Western blot assay was performed to detect the expression of CHAF1A protein in Caski cells. The experiments were repeated three times. $^{**}p<0.01$, $^{***}p<0.001$ compared to the NC mimic group; $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$, compared to the NC inhibitor group.

CHAF1A1 (Fig. 5B, r=0.7378, $P<0.001$) was observed in cervical cancer tissues. All these results indicated that CHAF1A might be a target of miR-1179 and the expression of ZEB1 and CHAF1A1 in cervical cancer could be regulated by the miR-1179 level.

DISCUSSION

The acquisition of EMT features has been demonstrated to be an important contributor to the metastasis of cancer cells (Li *et al.,* 2016). In cervical cancer, EMT was identified to play a major role in promoting invasion (Xiao *et al.,* 2018), which is also an essential prerequisite for cancer cell invasion and migration (Li *et al.,* 2016). In this study, we explored the influence of miR-1179 in cervical cancer and the regulatory mechanism behind the invasion of cervical cancer cells.

MiRNAs, small non-coding RNAs, have been extensively studied in terms of its association with cancer biology (Wilting *et al.,* 2010; Wang *et al.,* 2011; Liu *et al.,* 2012; Xie *et al.,* 2012; Zhu *et al.,* 2013). In the present study, we found that miR-1179 was downregulated in cervical cancer cells as well as cervical cancer patient tis-

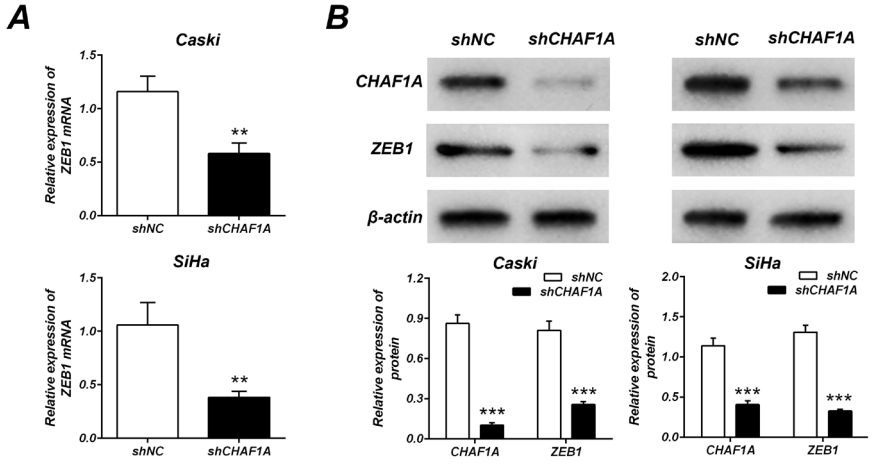

Figure 3. CHAF1A knockdown inhibited ZEB1 expression.
Caski and SiHa cells were transfected with shRNA NC (shNC) or shRNA CHAF1A (shCHAF1A). (**A**) qPCR was used to detect the expression of ZEB1 in Caski and SiHa cells. (**B**) Western blot assay was performed to detect the protein expression of ZEB1 and CHAF1A. The experiments were repeated three times. $^{**}p<0.01$, $^{***}p<0.001$ compared to the NC mimic group.

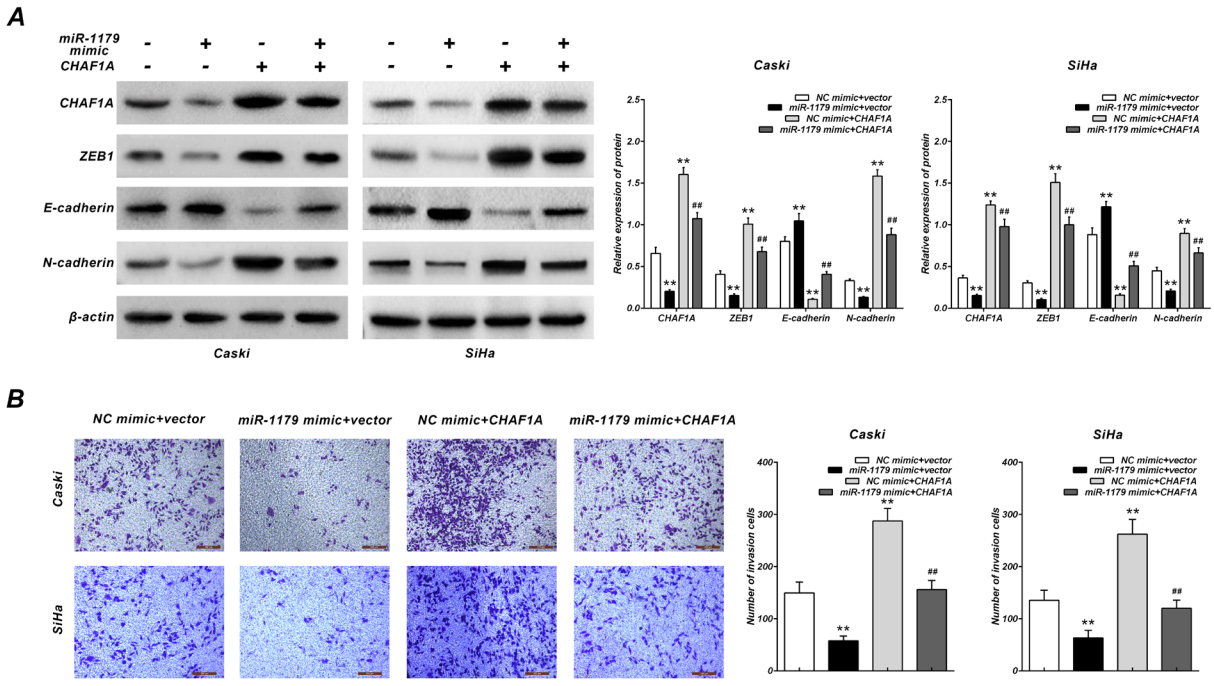

Figure 4. CHAF1A overexpression reversed the effect of miR-1179 mimic on the cells invasion.
Caski and SiHa cells were divided into NC mimic, miR-1179 mimic, NC inhibitor, miR-1179 inhibitor groups. (**A**) Western blot assay was performed to detect the protein expression. (**B**) Transwell assay was performed to assess the invasion of Caski and SiHa cells. The experiments were repeated three times. $^{**}p<0.01$ compared to the NC mimic + vector group; $^{\#\#}p<0.01$ compared to the NC mimic + CHAF1A group.

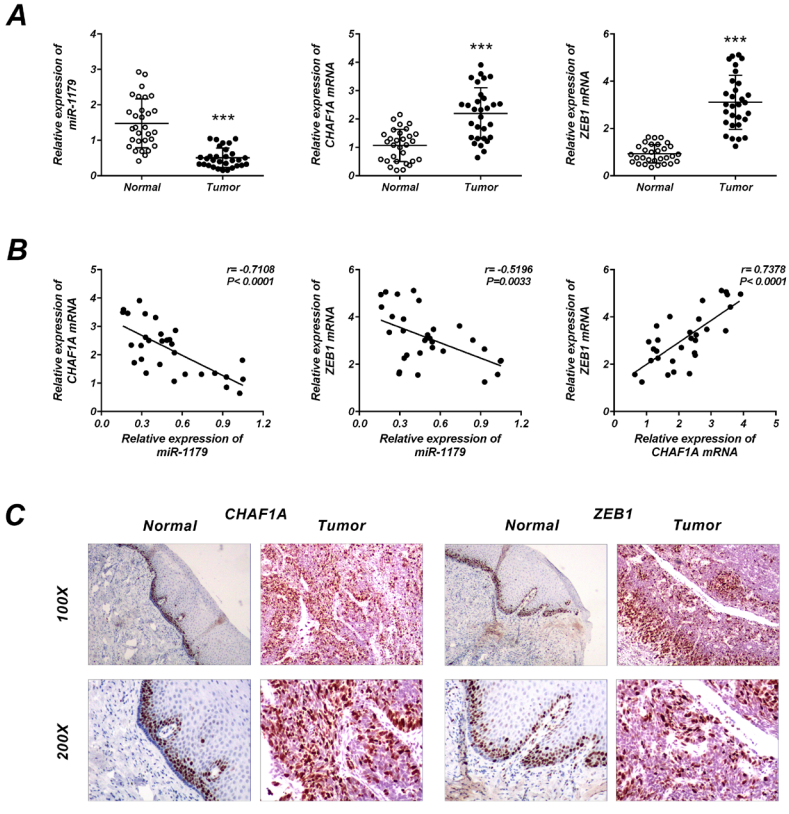

Figure 5. MiR-1179 was downregulated in tumor tissues and negatively correlated with the expression of CHAF1A and ZEB1.
(**A**) The expression levels of miR-1179, CHAF1A and ZEB1 were detected by qPCR in cervical cancer and normal cervical tissue. $^{***}p<0.001$ compared to the normal tissues. (**B**) Correlation of miR-1179 and CHAF1A was assessed using Pearson analysis. (**C**) CHAF1A and ZEB1 distribution detected using IHC. The experiments were repeated three times.

sues. However, contradictory results regarding the effects in cancers were previously obtained for miR-1179. Some researchers indicated that miR-1179 promoted cell invasion in esophageal squamous cell carcinoma (Jiang *et al.,* 2015). MiR-1179 has been also identified as a suppressor in several cancers such as human non-small cell lung cancer (Heller *et al.,* 2018), gastric cancer (Song *et al.,* 2018), papillary thyroid carcinoma (Ye *et al.,* 2020) and cervical cancer (Qu *et al.,* 2020). Interestingly, consistently with the effect of miR-1179 in other cancers, our study also supports the inhibitory role of miR-1179 in cervical cancer, as miR-1179 suppressed the cervical cancer cells invasion. Thus, this result further verified the anti-cancer role of miR-1179 in cervical cancer and suggested that the loss of miR-1179 might induce the malignancy of cervical cancer including cells invasion.

In addition, CHAF1A was predicted as a putative target gene of miR-1179 using TargetScan website, and miR-1179 mimic significantly reduced the mRNA and protein level of CHAF1A. CHAF1A is the main functional subunit of CHAF1 protein (Liu *et al.,* 2017), which is involved in deoxyribonucleic acid (DNA) replication, gene expression regulation and DNA mismatch repair (Cai *et al.,* 2018). It was found that CHAF1A plays an essential role in the occurrence and development of various malignant tumors, and is related to a poor prognosis of cancers. Most importantly, CHAF1A overexpression promotes the migration and invasion of cancer cells (Liu *et al.,* 2017; Zheng *et al.,* 2018). Therefore, CHAF1A, acting as an oncogene, may be a target for the diagnosis and therapy in malignant cancers. CHAF1A overexpression was proved to be positively correlated with the malignancy of cervical squamous cell carcinoma (Luo *et al.,* 2017). We also found that CHAF1A could directly bind miR-1179 in cervical cancer cells.CHAF1A was also significantly upregulated in cervical cancer cells and patient tissues. Consistently with the previous studies, a negative correlation was found between CHAF1A expression and miR-1179 expression. Expectedly, CHAF1A overexpression effectively reversed the inhibitory effect of miR-1179 on the invasion of cervical cancer cells. All these results indicated that the inhibitory effect of miR-1179 on cervical cancer invasion was achieved by inhibiting the expression of CHAF1A. ZEB1 was found to play a key role in tumorigenesis and tumor progression. In addition, previous studies demonstrated that ZEB1 contributed to the promotion of EMT (Yu *et al.,* 2018). In this study, similarly to CHAF1A, ZEB1 was overexpressed in cervical cancer cells and tumor tissues. Along with this, a negative correlation was found between ZEB1 expression and miR-1179 expression, while we revealed a positive correlation between the expression of ZEB1 and CHAF1A. However, the mechanism of ZEB1 regulation by CHAF1A is uncertain and needs to be further investigated.

In summary, the current research revealed that miR-1179 was downregulated in cervical cancer and its overexpression suppressed cancer cells invasion, while CHAF1A overexpression reversed this inhibitory effect. Moreover, CHAF1A was identified as a direct target of miR-1179 and miR-1179 might regulate cervical cancer through CHAF1A/ZEB1 axis. The present study revealed for the first time the critical role of the miR-1179/CHAF1A/ZEB1 axis in cervical cancer and might provide new targets and theoretical basis for cervical cancer therapy.

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Competing interests

The authors state that there are no conflicts of interest to disclose.

Ethics approval

Ethical approval was obtained from the Ethics Committee of The No.2 People's Hospital of Hefei.

Statement of Informed Consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials

All data generated or analyzed during this study were included in this published article.

Authors' contributions

Fahui Lv designed the study, supervised the data collection, YouWen Zhong analyzed the data, interpreted the data, Ling Sang and XiaoLing Wu prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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