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MiR-221 and miR-222 simultaneously target ARID1A and enhance proliferation and invasion of cervical cancer cells

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Abstract. – OBJECTIVE: Increased miR-221 and miR-222 expression were found in cervical cancer. In this study, we investigated the regulative role of miR-221 and miR-222 on ARID1A and further studied their roles in proliferation and invasion of cervical cancer cells.

MATERIALS AND METHODS: The expression of miR-221/222 and ARID1A were detected in cervical cancer tissues and normal cervical tissues. Then, human cervical cancer cell lines, including Hela and siHa cells were used for in vitro studies. The cells were transfected with miR-221 or miR-222 mimics alone or in combination with pcDNA3.1-ARID1A expression vector with mutant miR-221 and miR-222 binding sequence. Then, cell viability, cell cycle distribution and invasion were measured.

RESULTS: MiR-221/222 were significantly upregulated, while ARID1A was significantly downregulated in cervical cancer tissues. MiR-221 and miR-222 have nearly the same binding site in the 3'UTR of ARID1A and could suppress its expression at protein level. Functionally, miR-221 and miR-222 overexpression significantly increased cell viability, increased the proportion of cells in S phase and enhanced invasion of both Hela and siHa cells. In contrast, ARID1A overexpression abrogated these effects of miR-221 and miR-222.

CONCLUSIONS: MiR-221 and miR-222 upregulation partly contribute ARID1A loss in cervical cancer. The miR-221/222-ARID1A axis can modulate proliferation and invasion of cervical cancer cells. These findings revealed a novel mechanism of ARID1A loss and a potential therapeutic target in cervical cancer.

Key Words:
miR-221, miR-222, ARID1A, Cervical cancer.

Introduction

Cervical cancer is a common female malignancy and also a leading cause of malignancy-related death in women[1]. Previous studies suggest that persistent infection of high-risk human papillomavirus (HR-HPV) is the leading cause of cervical cancer[2,3]. The viral infection induces cell neoplastic transformation after viral DNA is incorporated into the host DNA[4,5]. After the viral E6 and E7 genes are incorporated into the host DNA, they become persistently overexpressed[6]. The E6 protein binds to E6-associated protein (E6AP) and then induces degradation of tumor suppressor gene p53 through the ubiquitin-proteasome system[7]. The E7 protein is involved in degradation of Rb family proteins, which are necessary for cell cycle progression[6]. In fact, the viral infection also results in consistently altered miRNAs expression[8].

Increased miR-221 and miR-222 expression after HPV infection were observed in previous studies[9,10]. One previous study reported that miR-222 exerts tumorigenic role by reducing the expression of PTEN and p27 in cervical cancer[11]. In addition, miR-221 can also reduce the sensitivity of cervical cancer cells to gefitinib through the PI3K/Akt signaling pathway by targeting PTEN[12]. Actually, miRNAs may participate in multiple signaling pathways via targeting several genes simultaneously. Therefore, whether other mechanisms are involved in miR-221 and miR-222's effects on tumorigenesis of cervical cancer is not clear.

ARID1A (AT-rich interactive domain-containing protein 1A) is a member of the SWI/SNF family[13]. One previous study reported that the loss of ARID1A protein expression is quite common in cervical adenocarcinomas/adenosquamous carcinoma[13]. Another recent study found that the ARID1A downregulation is partly due to an miR-31 elevation in cervical cancer[14]. ARID1A was verified as a direct target of miR-31. Through suppressing ARID1A expression, miR-31 can enhance cell proliferation, colony formation, and cell migration and invasion of cervical cancer cells *in vitro*[14]. However, whether other miRNAs

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are involved in its downregulation in cervical cancer has not been reported.

In this study, we investigated the regulative role of miR-221 and miR-222 on ARID1A and further studied their role in proliferation and invasion of cervical cancer cells.

Materials and Methods

Human Tissue Collection

This study was approved by the Ethics Committee of Civil Aviation General Hospital, China. Cervical cancer tissues were obtained from the patients with cervical cancer (all squamous cell carcinomas in IB and IIA) and received surgical resections in the hospital in 2014. The staging was performed by pathologists according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer. All of the patients never received preoperative radiotherapy and/or chemotherapy before this study. 10 cases of healthy cervical tissue controls were obtained from the patients received hysterectomy due to benign gynecologic diseases.

Cell Culture and Cell Transfection

Human cervical cancer cell lines HeLa and siHa cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) (HyClone, Logan, UT, USA) in a cell incubator with humidified atmosphere and 5% CO_2 at 37˚C.

The miR-221 and miR-222 mimics, ARID1A si-RNA and the scramble negative controls were all purchased from Ribobio (Shanghai, China). pcDNA3.1-ARID1A expression vector with mutant miR-221 and miR-222 binding sequence was obtained from Biomics (Nantong, Jiangsu, China). Hela and siHa cells were transfected with 50 nM miR-221 or 50 nM miR-222 mimics for overexpression using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). To overexpress ARID1A, the cells were transfected with the pcDNA3.1-ARID1A plasmids using Lipofectamine 2000 (Invitrogen).

QRT-PCR analysis miR-221/222 and ARID1A expression

Total RNAs in the tumor tissue and cell samples were extracted using the TRIzol reagent (Invitrogen) following manufacturer's instruction. Then, the first strand cDNA was synthesized using the First Strand Synthesis kit (Invitrogen). To assess the expression of ARID1A mRNA, QRT-PCR analysis was performed using the following primers: (forward, 5'-AGAACTCGAACGGGAACGCG-3', reverse, 5'-CGGCGACGGCAGACGGGC-3') and Power SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA). β-actin was used as internal control gene.

To quantify miR-221 and miR-222 expression, miRNAs specific cDNA was synthesized using the stem-loop primers and the TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems). Then, the miR-221 and miR-222 level were quantified by using the TaqMan MicroRNA Assays Kit (Applied Biosystems), with RNU6B as a control gene (Applied Biosystems).

All qRT-PCR analysis was performed in an ABI Prism 7500 (Applied Biosystems), and the $2^{-\Delta\Delta Ct}$ method was used to calculate relative mRNA and miRNAs expression.

Western blot Analysis

Western blot analysis followed a conventional method as described in one previous study[15]. The primary antibody against ARID1A (ab97995, 1:1000 dilution) and the HRP conjugated secondary antibody were both purchased from Abcam (Cambridge, MA, USA). The blot signals were visualized using the ECL Western blotting substrate (Beyotime, Shanghai, China). The signal intensity was quantified using ImageQuant TL (GE Healthcare, Piscataway, NJ, USA). To compare the expression difference, the relative gray-scale value of ARID1A *vs.* GAPDH of the miR-NC group was set as 1.

Immunohistochemical (IHC) Staining

Firstly, the 5 μM tissue sections were prepared for immunohistochemical staining according to the methods introduced in one previous study[16]. Then, the sections were incubated with primary antibodies to anti-ARID1A (ab182561, 1:1000, Abcam) at 4°C in a humidified chamber overnight. The sections then were incubated with biotinylated anti-rabbit secondary antibody for 30 minutes and then washed using phosphate buffered saline (PBS) for 5 minutes. Then, the samples were incubated with streptavidin-horseradish peroxidase (HRP) solution for another 30 minutes. The antigen-antibody binding was demonstrated via detecting HRP activity using DAB as substrate. Counterstaining was performed using Harris hematoxylin. Negative control tissue sections were incubated with PBS without the presence of primary antibody. Then, the slides were examined under a transmission light microscope.

Dual Luciferase Assay

The possible binding site between miR-221/222 and the 3'UTR of ARID1A was predicted using TargetScan 6.3. The prediction showed that miR-221 and miR-222 target nearly the same sequence in the 3'UTR of ARID1A. Therefore, the 3'UTR of ARID1A with wild-type or mutant miR-221/222 binding site were chemically synthesized and cloned into the downstream of renilla luciferase gene of the pmirGLO Dual-Luciferase miRNA Target Expression Vector (Promega, Madison, WI, USA) respectively. The recombinant plasmids were named as pGL-ARID1A-WT and pGL-ARID1A-MT respectively. To detect the suppressive effect of miR-221/222 on luciferase expression, Hela and siHa cells were co-transfected with 200 ng recombinant plasmids and 50 nM miR-221 or miR-22 mimics or the scramble negative control using Lipofectamine 2000 (Invitrogen). 24 hours after transfection, luciferase activity was analyzed using the Dual-Luciferase Reporter Assay System (Promega) with a GloMax 20/20 luminometer (Promega). Firefly luciferase activity was normalized to that of Renilla luciferase.

WST-8 Assay of Cell Viability

Hela and siHa cells transfected with miR-221 (50 nM) or miR-222 (50 nM) or co-transfected with miR-221 or miR-222 and ARID1A were seeded in a 96-well plate at a density of 3000 cells/well. Cell viability at indicating time points were measured using the WST-8 assay using Cell Counting Kit-8 (CCK-8, Dojindo, Rockville, MD, USA) according to manufacturer's instruction. Cell viability was reflected by the absorbance at 450 nm measured by a 96-well spectrophotometry.

Flow Cytometry Analysis of Cell Cycle Distribution

Hela and siHa cells transfected with miR-221 (50 nM) or miR-222 (50 nM) or co-transfected with miR-221 or miR-222 and ARID1A were further incubated for 48 hours. Then the cells were fixed using 70% ethanol at −20°C. After that, the cells were firstly incubated with 100 μg/mL RNase A in PBS for 30 min at 37°C and then 10 μg/mL propidium iodide (PI) (Sigma-Aldrich, St Louis, MO, USA) was added for a following 30 min incubation in dark. Then, DNA content was analyzed using a FACSCaliber (BD Biosciences, San Jose, CA, USA).

Transwell Analysis of Cell Invasion

Cell invasion assay was performed using the Transwell insert chamber coated with Matrigel (BD Biosciences). Briefly, 1×10^5 Hela or siHa cells after transfection were suspended in 200 μL serum-free RPMI-1640 medium and then seeded into the upper chamber. The lower chamber was filled with RPMI-1640 with 20% FBS to form a chemoattractant environment. The chamber was maintained in a cell incubator for 24 hours. Then, cells on the top surface of the insert were removed with a cotton swab. The cells on the bottom surface were fixed with 4% polyoxymethylene and stained with 0.1% crystal violet. Then, the number of invading cells were counted under a transmission light microscope.

Statistical Analysis

Data was given in the form of mean ± SD with at least three repeats. Statistical analysis was performed using the SPSS 18.0 software package (IBM, Chicago, IL, USA). A two-sided p value of <0.05 was considered statistically significant.

Results

MiR-221/222 are Significantly Upregulated, while ARID1A is Significantly Downregulated in Cervical Cancer

Dysregulated miR-221/222 in cervical cancer were reported in previous studies[9,11]. However, their oncogenic roles in cervical cancer have not been fully revealed. We firstly compared miR-221 and miR-222 expression between cervical cancer tissues and normal cervical tissues. QRT-PCR results showed that the expression of miR-221 and miR-222 were significantly higher in cancerous tissues than in normal tissues (1 A-B). We also observed that the expression of ARID1A, a tumor suppressor in several types of cancer[17,18], substantially decreased in the cervical cancerous tissues at both mRNA and protein level (Figure 1 C-D). By performing IHC staining, we further confirmed that ARID1A expression was lower in cancerous tissues than in normal tissues (Figure 1E). Therefore, we decided to further detect their association in cervical cancer.

MiR-221 and miR-222 Directly Target 3'UTR of ARID1A and Downregulate its Expression

By performing bioinformatics analysis using TargetScan 6.3, we observed that miR-221 and miR-222 might target nearly the same region in the 3'UTR of

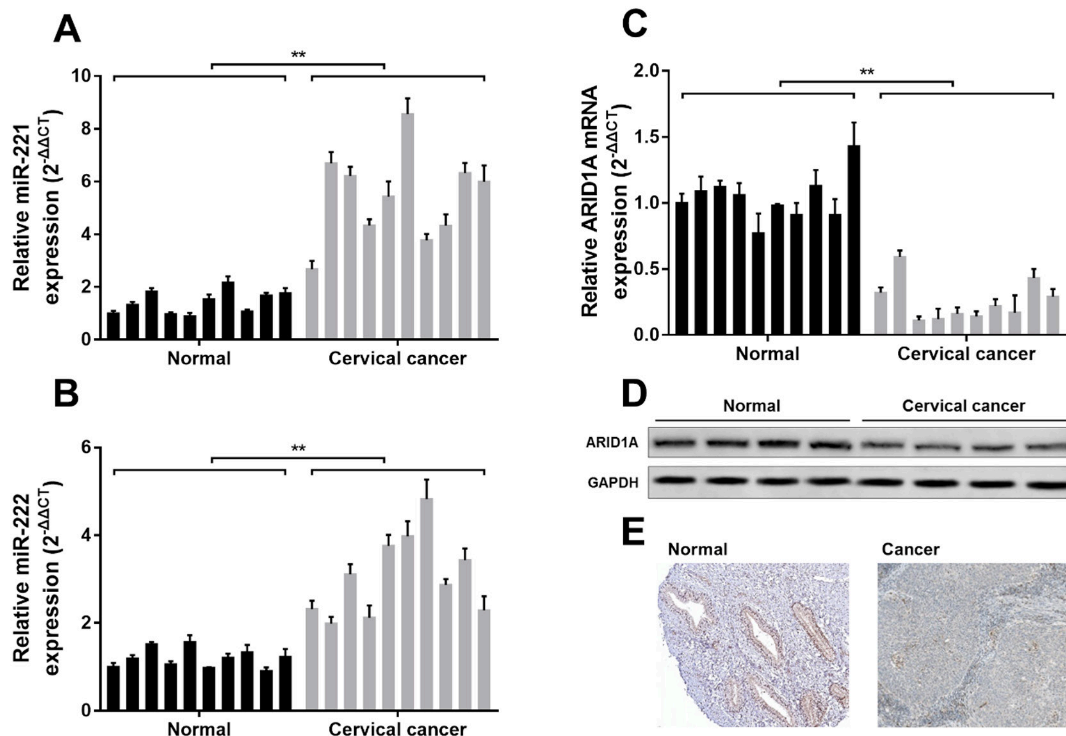

Figure 1. MiR-221/222 are significantly upregulated, while ARID1A is significantly downregulated in cervical cancer. ***A-C,*** QRT-PCR analysis of miR-221 ***(A)***, miR-222 ***(B)*** and ARID1A mRNA ***(C)*** expression in 10 cases cervical cancer tissues and 10 healthy normal controls. ***D)*** Western blot analysis of ARID1A protein expression in 4 randomly selected cervical cancer tissues and 4 healthy normal controls. ***E***, Expression of ARID1A was examined by immunohistochemical (IHC) staining in cervical cancer tissues and healthy normal controls. *$p<0.05$, **$p<0.01$.

ARID1A (Figure 2A). Therefore, we produced two reconstructed dual luciferase reporters carrying the predicted wide type or mutant binding sequences. Both Hela and siHa cells co-transfected miR-221 or miR-222 and the pGL-ARID1A-WT had significantly suppressed luciferase expression (Figure 2 B-C). In contrast, miR-221 or miR-222 had not suppressive effects on the pGL-ARID1A-MT reporter (Figure 2 B-C). These results suggest that there are direct interactions between miR-221 and miR-222 and the 3'UTR of ARID1A. Then, we investigated how miR-221 and miR-222 modulate ARID1A expression in both Hela and siHa cells. Western blot analysis confirmed that the cells transfected with miR-221 and miR-222 had significantly lower ARID1A protein expression (Figure 2 D-E). These results suggest that MiR-221 and miR-222 directly target 3'UTR of ARID1A and downregulate its expression.

MiR-221 and miR-222 Modulate Proliferation and Invasion of Cervical Cancer Cells Through ARID1A

To investigate the influence of miR-221/222-ARID1A axis on cervical cancer cells, Hela and siHa cells were firstly transfected with miR-221 or miR-222 alone or co-transfected miR-221 or miR-222 and the ARID1A expression vector with mutant miR-221 and miR-222 binding sequence. Then, cell proliferation was measured by CCK-8 assay. The results showed that miR-221 and miR-222 overexpression significantly increased cell viability of both Hela and siHa cells (Figure 3A-B). In contrast, ARID1A overexpression abrogated the growth enhancing effects of miR-221 and miR-222 (Figure 3A-B). Then, we investigated the influence of miR-221/222-ARID1A axis on cell cycle and the ability of cell invasion. MiR-221 and miR-222 overexpression significantly increased the proportion of cells in S phase (Figure 3 C-D) and the number of invading cells (Figure 4 E-F). However, ARID1A overexpression reversed the effects of miR-221 and miR-222 on promoting S phase accumulation (Figure 3 C-D) and cell invasion (Figure 4 E-F). These results suggest that miR-221 and miR-222 modulate proliferation and invasion of cervical cancer cells at least partly through ARID1A.

Discussion

Dysregulated miRNAs might be involved in some important signaling pathways in the pathological development of cervical cancer. Some miRNAs might be associated with poor prognosis of cancer. For example, miR-155 can promote proliferation of cervical cancer cells by targeting and reducing LKB1[19]. MiR-17-5p can regulate cell proliferation and apoptosis of cervical cancer cells via targeting TP53INP1[20]. MiR-506 acts as a suppressor of cervical cancer via targeting the hedgehog pathway transcription factor Gli3[21]. Reduced expression of miR-503 is associated with poor prognosis in cervical cancer[22].

MiR-221 and miR-222 are two miRNAs significantly upregulated in cervical cancer[9,10]. One previous study reported that miR-221 might be a useful predictive and prognostic biomarker of cervical cancer due to its close association with squamous cell carcinoma and FIGO stages[9]. In addition, miR-221 upregulation directly decreases PTEN level, leading to following enhanced pAkt and BCL-2 expression[12]. This mechanism is observed in acquired in gefitinib resistance in cervical cancer[12]. MiR-222 is also a miRNA significantly upregulated in cervical cancer[11]. Its upregulation is associated with the extent and depth of the cancer invasion[11]. In addition, miR-222 can also target PTEN, as well as p27, leading to increased proliferation and migration of cervical cancer cells[11]. In fact, one miRNA may involve in regulation of multiple signaling pathways since it may target several genes at the same time. Therefore, we decided to further investigate their regulative roles in cervical cancer.

Our preliminary studies showed that miR-221/222 and ARID1A showed inverse expressions in the cervical cancer tissues. In fact, ARID1A was considered as a tumor suppressor in cancer through several pathways. ARID1A can bind to the promoter of c-Myc and decrease its expression, thereby indirectly enhancing p21 expression[23]. By the same time, p21 initiates cell cycle arrest at G1 phase through inhibiting the activity of CDK2/CDK4 complex[23]. ARID1A can also bind with transcript inhibitors, such as E2F4 and E2F5, leading to suppressed expression of cell cycle proteins[24]. In addition, ARID1A can form a complex with p53, promoting the expression of DNA repair-related protein-CDKN1A and signal transduction molecule-SMAD3 and exerting tumor suppressing effect[25]. The loss of ARID1A protein expression was reported in cervical adenocarcinomas/adenosquamous carcinoma[13]. Actually, the loss of ARID1A/BAF250a expression is associated with tumor progression and adverse prognosis in cervical cancer[26]. However, the

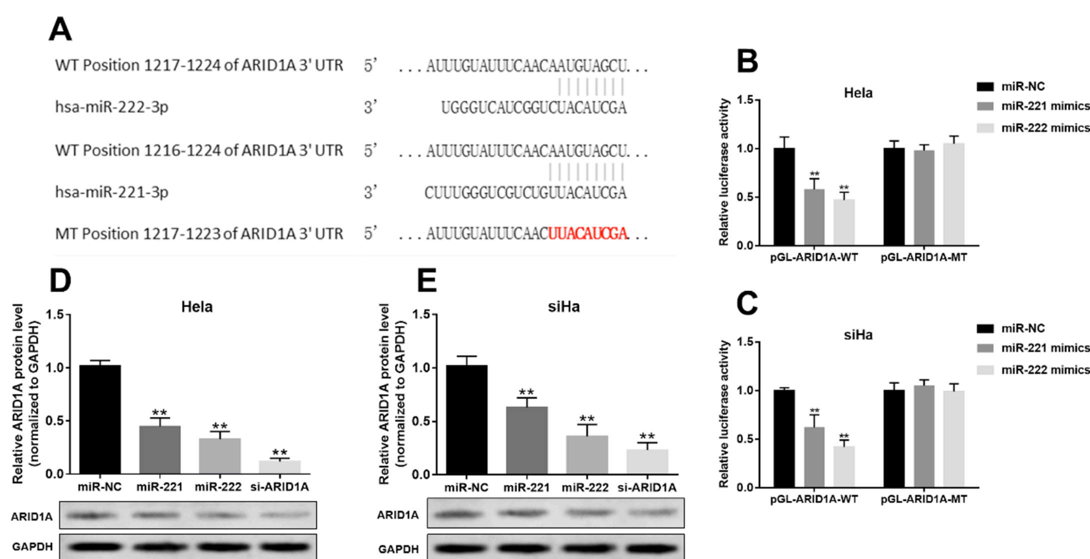

Figure 2. MiR-221 and miR-222 directly target 3'UTR of ARID1A and downregulate its expression. ***A,*** The predicted binding site between miR-221/222 and ARID1A. B and C, Hela ***(B)*** and siHa ***(C)*** cells were co-transfected with 50 nM miR-221 or miR-222 mimics and pGL-ARID1A-WT or pGL-ARID1A-MT. The relative luciferase activity was measured 24 hours after transfection. ***D*** and ***E***, Western blot analysis of ARID1A expression in Hela ***(D)*** and siHa ***(E)*** cells 48 hours after transfection of miR-221 mimics (50 nM), miR-222 mimics (50 nM) or ARID1A siRNA (50 nM). $^{*}p<0.05$, $^{**}p<0.01$

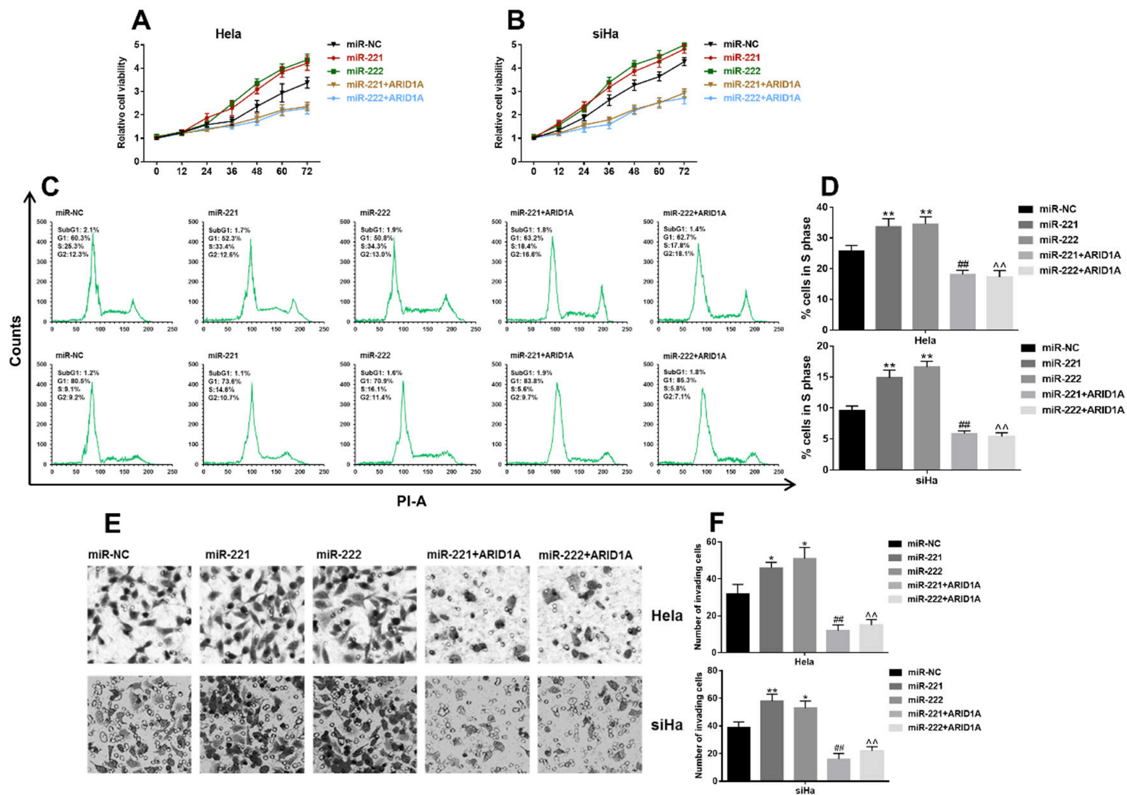

Figure 3. MiR-221 and miR-222 modulate proliferation and invasion of cervical cancer cells through ARID1A. A and B, CCK-8 assay of cell viability of Hela ***(A)*** and siHa ***(B)*** at indicating time points up to 72 hours after transfection of miR-221 mimics (50 nM), miR-222 mimics (50 nM) or co-transfected with miR-221 mimics or miR-222 mimics and pcDNA3.1-ARID1A expression vector with mutant miR-221/222 binding site. ***C*** and ***D***, Representative images ***(C)*** and quantification ***(D)*** of cell cycle distribution of Hela and siHa cells with 48 hours after the indicating treatments. ***E*** and ***F***, Representative images ***(E)*** and quantification ***(F)*** of invading Hela and siHa cells in the Matrigel after the indicating treatments. * indicates comparison with miR-NC, # indicates comparison with miR-221, ^ indicates comparison with miR-222. *,$^{\#}$and ^$p < 0.05$, **, $^{\#\#}$and ^^$p < 0.01$.

exact mechanism of ARID1A downregulation in cervical cancer is not quite clear. One previous study found that ARID1A downregulation is partly due to miR-31 elevation in cervical cancer. Through suppressing ARID1A expression, miR-31 can enhance cell proliferation, colony formation, and cell migration and invasion of cervical cancer cells *in vitro*[14]. Considering the important tumor suppressive effect of ARID1A, we decided to further detect the association between miR-221/222 and ARID1A. By performing bioinformatics analysis and following dual luciferase and western blot analysis, we confirmed that miR-221 and miR-222 can simultaneously target 3'UTR of ARID1A and suppress its expression at protein level. Functionally, we also demonstrated that miR-221 and miR-222 can enhance proliferation and invasion of cervical cancer cells at least partly through suppressing ARID1A. These findings revealed a novel mechanism of ARID1A loss in cervical cancer and further confirmed the oncogenic role of miR-221/222.

Conclusion

MiR-221 and miR-222 upregulation partly contribute ARID1A loss in cervical cancer. The miR-221/222-ARID1A axis can modulate proliferation and invasion of cervical cancer cells, which represents a potential therapeutic target for the treatment of cervical cancer.

Conflicts of interest

The authors declareno conflicts of interest.

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