Revista Argentina de Clínica Psicológica
2020, Vol. XXIX, N°3, 953-963
DOI: 10.24205/03276716.2020.921

# Dihydroartemisinin Inhibits Proliferation and Migration of Cervical Cancer Cells Depending on Mir-214/PTEN Signal Axis

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**Abstract**

**Objective:** This study was designed to probe into the inhibition of dihydroartemisinin on proliferation and migration of cervical cancer (CC) cells by miR-214/PTEN signal axis.

**Methods:** Sixty-nine CC patients who were admitted in our hospital and 78 healthy people in the same period were selected as the research objects for prospective analysis. CC patients were included into a research group (RG), and healthy people were enrolled to a control group (CG). Human CC cells were purchased for biological analysis. The miR-214, PTEN expression and their predictive value in CC, and the relationship between the two were detected. The effects of miR-214 and PTEN on CC cells, and the changes of miR-214, PTEN and biological behavior in those cells after dihydroartemisinin treatment were assessed.

**Results:** The miR-214 and PTEN levels in CC patients in the RG were lower than those in the CG ($p<0.05$), and both of them had good predictive value. There was a positive correlation between miR-214 and PTEN. The migration rate of the miR-214 group was higher than that of the miR-214 group and the miR-NC group ($p<0.05$), and the apoptosis rate was lower ($p<0.05$). The PTEN and Bax expression in the miR-214 group was lower than that in the other two groups ($p<0.05$), and Bcl-2 was higher ($p<0.05$). The proliferation and migration rate of the PTEN-inhibition group were higher than those of the PTEN group and the NC group ($p<0.05$), and the apoptosis rate was lower ($p<0.05$). The PTEN and Bax expression in the miR-214 group was lower than that in other two groups ($p<0.05$), and Bcl-2 was higher ($p<0.05$). The miR-214 and PTEN expression in CC cells increased after dihydroartemisinin treatment ($p<0.05$), while cell proliferation and mobility decreased ($p<0.05$).

**Conclusion:** Dihydroartemisinin depends on miR-214/PTEN signal axis, which can inhibit the proliferation and migration of CC cells and has great application prospect in future diagnosis and treatment.

**Keywords:** dihydroartemisinin, miR-214/PTEN, cervical cancer

## Introduction

Cervical cancer (CC) is the fourth most familiar malignancy diagnosed by women all over the world, canceration or adenocarcinoma of cervix. If not treated in time, most women will slowly change and it is also one of the main causes of cancer death among women (Cohen et al.,2019). Globally, more than 500,000 new cases and 40% CC patients die every year (Ramirez et al., 2018). In some cases, persistent infection of cervix will lead to from atypical hyperplasia to invasive cancer (Curry et al., 2018). At the moment, the treatment methods are mainly surgery, radiotherapy, chemotherapy and other comprehensive treatments (Koh et al., 2019)

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(Melamed et al.,2018). However, like other malignancies, poor prognosis and invasion and metastasis of advanced tumors still have great influence on the survival rate of patients (Paccez et al.,2019). Recently, many studies have suggested that dihydroartemisinin has a good anti-tumor effect on skin cancer, squamous cell carcinoma and other malignancies (Aalijahan et al.,2019), but the clinical research on its sensitization mechanism and CC is still few. Therefore, in-depth study of its development mechanism in CC is quite significant for exploring effective methods of diagnosis and treatment.

CC cell dysfunction may be caused by carcinogenic factors, such as human papillomavirus (HPV), some cytokines and growth factors through different mechanisms (Pardini et al.,2018). Clinically, it has been confirmed that the abnormal expression of miRNA as a post-transcriptional regulator is relevant to cancer development and progression (Zhou et al.,2020). For example, miR-150-5p was found as an oncogene in ovarian cancer (Just et al.,2019), and miRNA-21-5p was highly expressed in esophageal cancer, which could be used as a biological marker (Chen et al.,2018). We also found that miR-214 was called “pleiotropic hub” and was considered as the key regulatory gene for the development and progression of various tumors (Song et al.,2019). It is worth noting that the miR-214 expression is down-regulated in human CC (Wang et al.,2018). And up-regulating miR-214 expression dramatically reduced the growth of cancer cells (Lee et al.,2019). PTEN is a homologue of protein tyrosine phosphatase, which plays a vital role in many types of tumors (Chen et al.,2018). It has been reported that PTEN can interfere with the apoptosis, proliferation and migration of cells (Han et al.,2020), miR-214 can affect nasopharyngeal carcinoma cells by targeting PTEN protein expression (Han et al.,2020), and dihydroartemisinin inhibits PTEN/AKT pathway to induce apoptosis of acute myeloid leukemia cells (An et al.,2020). Thus, we speculate that dihydroartemisinin may have a certain effect on CC cell development through miR-214/PTEN. In order to verify the conjecture, we carried out the following research, aiming to provide new ideas and reference for future clinical diagnosis and treatment.

## Materials and methods

### Research objects

### Patient data

Sixty-nine CC patients who were admitted in our hospital from February 2018 to February 2020 and 78 health check-ups were selected as the research objects for prospective analysis. CC patients were included into the research group (RG), and healthy people were enrolled to the control group (CG). This experiment was approved by the Ethics Committee of our hospital, and all the above subjects signed the informed consent form.

### Inclusion and exclusion criteria

Inclusion criteria: patients were 30-70 years old; CC was diagnosed after biopsy in our hospital; the clinical stage was early; patients received radical resection of tumor. Exclusion criteria: patients who were complicated with other severe diseases; patients were treated with radiotherapy and chemotherapy, surgery and antibiotics within half a year before admission; patients who were complicated with autoimmune defects, or organ dysfunction; patients who were transferred from one hospital to another.

### Cell data

Human CC cell Hela and normal cervical epithelial cell HUCEC were purchased from ATCC. They were cultivated in a MEM medium consisting of 10% fetal bovine serum (FBS) (37℃, 5%$CO_2$). The fluid was changed every 2-3 days, and the cells were digested with trypsin and sub cultured when cell confluence reached 70%-80%. And those in logarithmic growth phase were used in experiments.

### Methods

### Cell transfection

PTEN over-expression lentiviral vector, PTEN inhibition-expression lentiviral vector and PTEN empty vector were constructed, and the above sequences, miR-214-mimics, miR-214-inhibition and miR-214 negative control (miR-NC) were transfected with LipofectaminTM 2000 reagent. The success rate of transfection was verified by 24hqRT-PCR.

### qRT-PCR detection

Total RNA was extracted by Trizol method, and the purity was verified by ultraviolet spectrophotometer. Then, it was reverse

transcribed into cDNA according to Trizol extraction reverse transcription kit. The reaction system was as follows: 10 μL SYBR, 2 ng cDNA, 20 μmol/L upstream primer and downstream primer, 0.8 μL each, distilled water added to 20 μL. Reaction conditions were as follows: 94℃for 1 min, 54℃for 1min, 72℃for 1 min, totaling 40 cycles. The primer sequence was synthesized by Shanghai GenePharma Co., Ltd (Table 1), and the expression of target gene was counted by $2^{-\Delta\Delta Ct}$ method.

**Western blot (WB) detection**

The cells were lysed by lysis solution, and the protein concentration was verified by BCA method. Then, diluent was added to adjust the protein concentration to 30 g/L. It was separated by 12% SDS-PAGE electrophoresis buffer and transferred to PVDF membrane. After that, it was sealed 4 h with 5% skimmed milk at room temperature, added with diluted PTEN, Bax and Bcl-2 primary antibodies, and incubated at 4℃all night. After the membrane was washed, secondary antibodies labeled with horseradish peroxidase were added, and the protein bands were developed using the enhanced chemiluminescence (ECL) reagent, and gray values of strips were measured by automatic gel image analysis system.

*Table 1:* **primer sequence**

| | R (5'-3') | F (5'-3') |
|---|---|---|
| miR-214 | CAGGACAGCAGGCACAGACA | TCAACTGGTGTCGTGGAGTC |
| U6 | CTCGCTTCGGCAGCACA | AACGCTTCACGAATTTGCGT |
| PETN | TTGAAGACCATAACCCACCACAG | CATTTACACCAGTTCGTCCCTTTC |
| β-actin | AAGATGACCCAGATCATGTTTGAGACC | GCCAGGTCCAGACGCAGGAT |

**MTT experiment**

Twenty-four hours after transfection, CC cells were inoculated into a 96-well plate ($5\times10^3$/mL), and 10 μL MTT reagent was supplemented to each well when cultured for 0, 24, 48 and 72 h respectively. Next, they were cultured for 4 h right along, the culture medium was discarded, and 100 μL DMSO was supplemented. The absorbance values were detected at 490 nm wavelength by microplate reader, and the cell growth curve was drawn.

**Cell scratch test**

Cells were digested by trypsin and inoculated in a 6-well plate, and the cell concentration was adjusted to $1\times10^6$ cells/mL. When cell confluence reached 90%, scratches were made from top to bottom with a 200 μL pipette tip, and cells were continuously cultivated for 24 h. It was observed with inverted microscope and the percentage of cell front moving distance was measured.

**Flow cytometry**

Cell concentration of trypsin digested cells was adjusted to $1\times10^6$ cells/mL and centrifuged for 5 min (500×g). Altogether 195 μL binding buffer and 5μl Annexin V-FITC were supplemented and cultivated 10 min under dark conditions, and then 55 μL PI was added and incubated 10 min under dark conditions, and finally 400 μL binding buffer was supplemented. The apoptosis rate was detected by flow cytometry.

**Dihydroartemisinin treatment**

Untransfected CC cells were inoculated in a 96-well plate and treated 24 h with 20 μmol/L dihydroartemisinin. MTT and cell scratch test were the same as above.

**Outcome measures**

**Main outcome measures**

The miR-214 and PTEN expression in CC, effects of miR-214 and PTEN on CC cells, and changes of miR-214, PTEN and biological behavior in those cells treated with dihydroartemisinin were included.

**Secondary outcome measures**

The predictive value of miR-214 and PTEN for CC, and the relationship between the two were taken into account.

**Statistical methods**

SPSS22.0 was employed for statistical analysis. The counting data were analyzed by Chi-square test, and the measurement data were assessed by independent-samples T test. The correlation was analyzed by Pearson correlation coefficient. The comparison among multiple groups was assessed by one-way analysis of variance (ANOVA) and LSD back testing. Multiple time points were compared by repeated measures ANOVA and bonferroni back testing. The predicted value was analyzed by ROC curve. The difference was statistically obvious when P<0.05.

**Results**

**miR-214 and PTEN expression in CC**

The miR-214 and PTEN expression in the two groups was detected by PCR. And the results showed that the levels in CC patients in the RG were obviously lower than those in the CG (p<0.05). (Figure 1)

**Predictive value of miR-214 and PTEN in CC**

ROC curve analysis manifested that miR-214 had a sensitivity of 80.77% and a specificity of 84.06% when cut-off value was 0.805, and PTEN had a sensitivity of 55.13% and a specificity of 94.20% when cut-off value was 0.715. (Figure 2, Table 2)

**Correlation between miR-214 and PTEN in RG**

Pearson correlation coefficient analysis manifested that miR-214 was positively correlated with PTEN expression (r=0.720, p<0.001). (Figure 3)

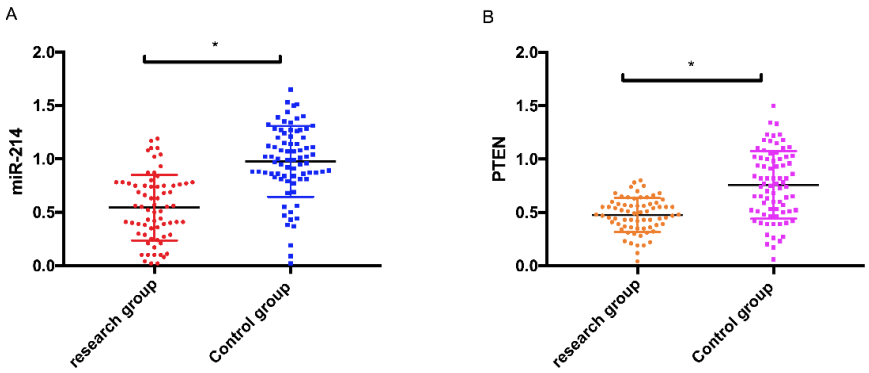


Figure 1. **miR-214 and PTEN expression in CC**

A) miR-214 expression in both groups; B) PTEN expression of both groups.

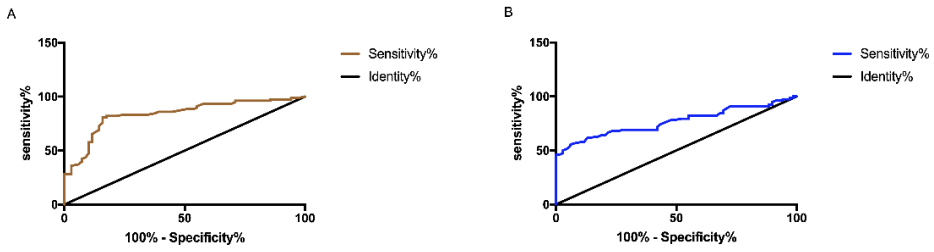


Figure 2. **Predictive value of miR-214 and PTEN for CC**

A) ROC curve of miR-214 in predicting CC; B) ROC curve of PTEN in predicting CC.

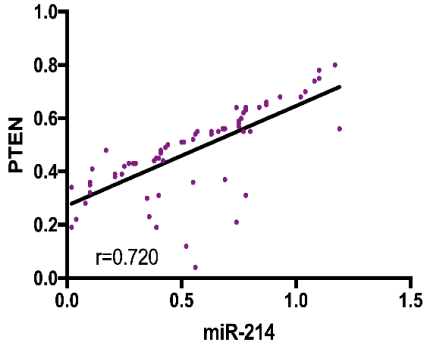


Figure 3 ***Correlation analysis between miR-214 and PTEN in RG***

*Table 2.* **Diagnostic effect of miR-214 and PTEN on CC**

| | miR-214 | PTEN |
|---|---|---|
| AUC | 0.838 | 0.768 |
| Std. Error | 0.034 | 0.040 |
| 95%CI | 0.772-0.904 | 0.691-0.846 |
| Cut-off | > 0.805 | > 0.715 |
| Sensitivity (%) | 80.77 | 55.13 |
| Specificity (%) | 84.06 | 94.20 |
| Youden index (%) | 64.83 | 49.33 |
| P | ＜ 0.001 | ＜ 0.001 |

**miR-214's effect on CC cells**

The miR-214 expression in Hela and HUCEC cells was tested. And the results manifested that the expression in Hela was markedly lower than that in HUCEC cells ($p<0.05$). After miR-214 was transfected, the biological behavior of Hela cells was detected. It was found that the proliferation of the miR-214 group was inhibited, the mobility was higher than that of the over-expressed miR-214 group and the miR-NC group ($p<0.05$), and the apoptosis rate was lower ($p<0.05$). The PTEN and Bax expression in the miR-214 group was lower than that in the other two groups ($p<0.05$), and Bcl-2 was higher ($p<0.05$). (Figure 4)

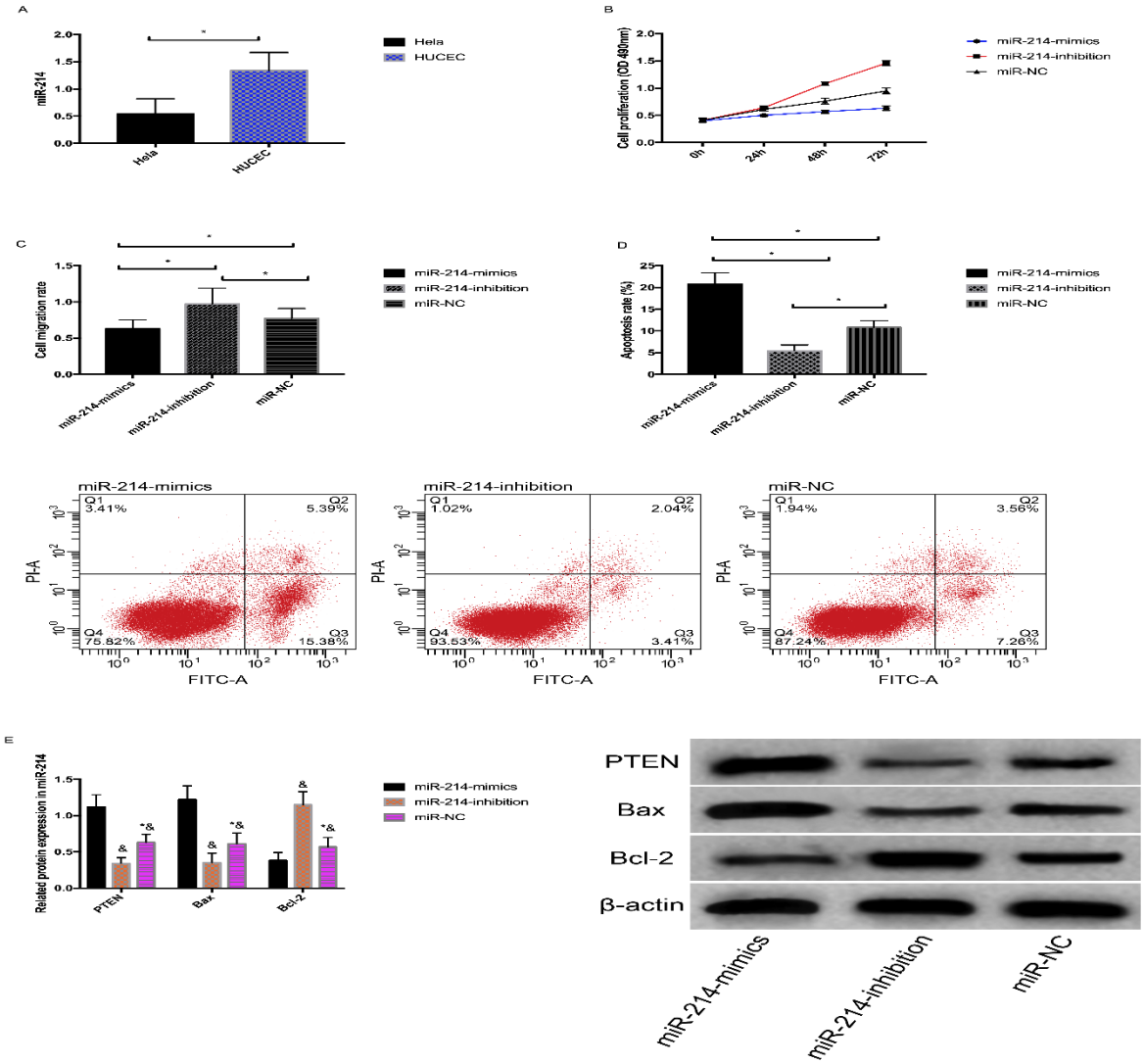


Figure 4. **Effects of miR-214 on CC cells**

A) miR-214 expression in HeLa and HUCEC cells; B) Cell proliferation; C) Cell migration; D) Apoptosis rate; E) Expression of cell-related protein. Note: & indicates the comparison with over-expression group, and * indicates the comparison with inhibition group.

**PTEN's effect on CC cells**

The PTEN expression in Hela and HUCEC cells showed that the expression in Hela was dramatically lower than that in HUCEC cells ($p<0.05$). After PTEN was transfected, the biological behavior of Hela cells was detected. It was found that the proliferation of the PTEN group was inhibited, the mobility was higher than that of the over-expression PTEN group and the NC group ($p<0.05$), and the apoptosis rate was lower ($p<0.05$). The PTEN and Bax expression in the miR-214 group was lower than that in the other two groups ($p<0.05$), and Bcl-2 was higher ($p<0.05$). (Figure 5)

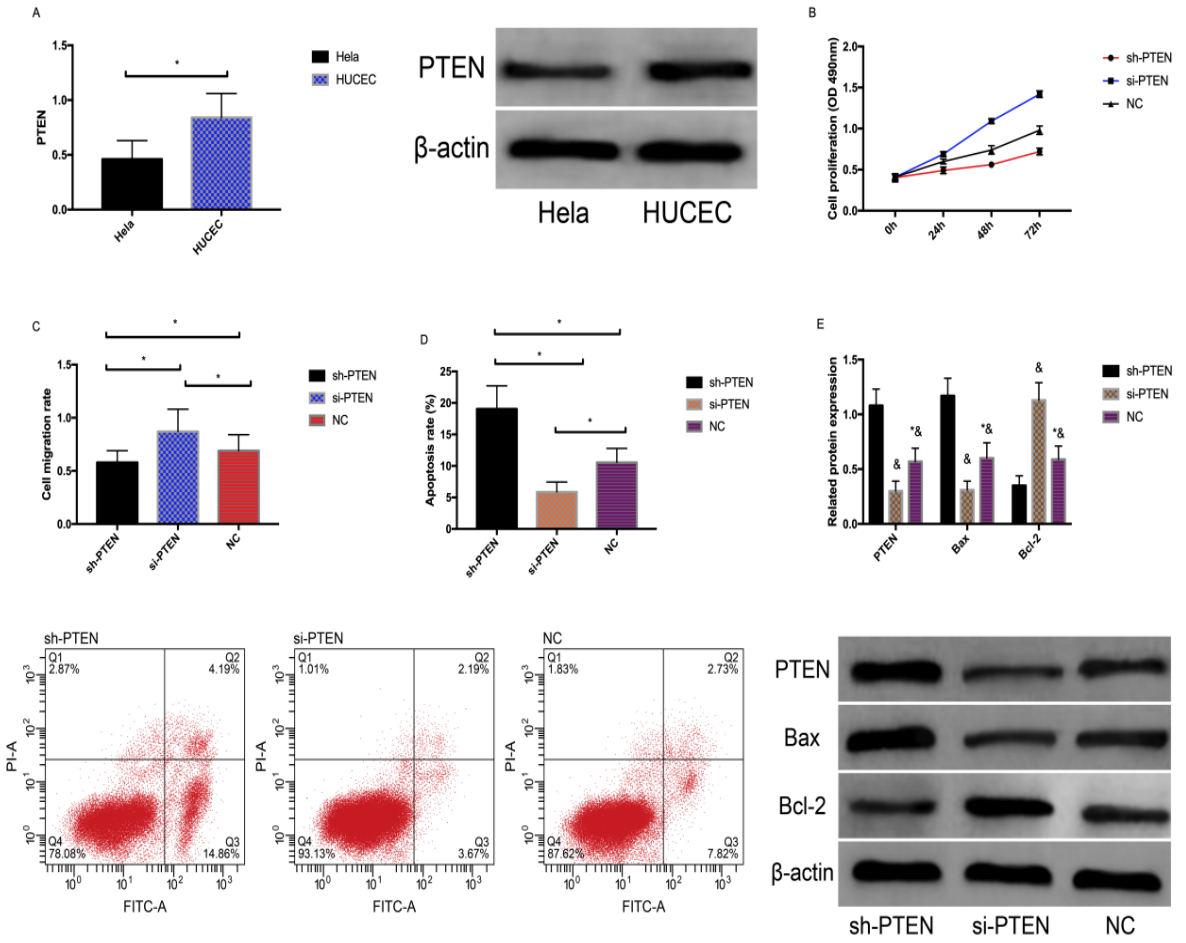


Figure 5. **Effects of PTEN on CC cells**

A) PTEN expression in HeLa and HUCEC cells; B) Cell proliferation; C) Cell migration; D) Apoptosis rate; E) Expression of cell-related protein. Note: & indicates the comparison with over-expression group, and * indicates the comparison with inhibition group.

**Changes of miR-214, PTEN and biological behavior in CC cells treated with dihydroartemisinin**

The miR-214 and PTEN expression in CC cells treated with dihydroartemisinin was detected. And the results showed that the expression increased ($p<0.05$), and the proliferation and mobility of those cells decreased ($p<0.05$). (Figure 6)

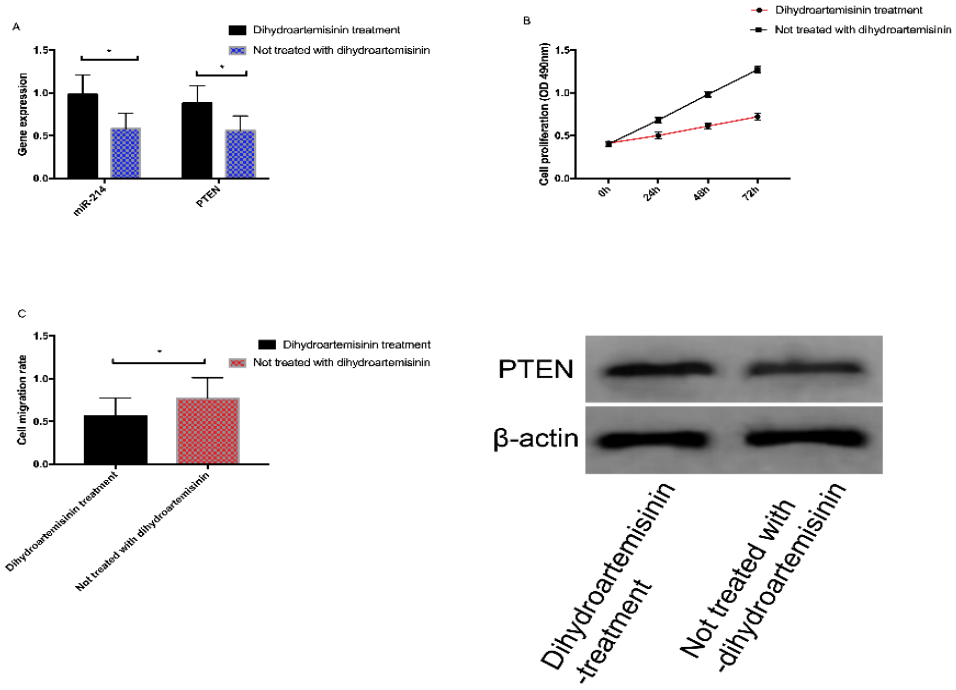


Figure 6. **Changes of miR-214, PTEN and biological behavior in CC cells after dihydroartemisinin treatment**

A) miR-214 and PTEN expression in CC cells treated with dihydroartemisinin; B) Cell proliferation; C) Cell migration.

**Discussion**

CC is a malignant epithelial tumor formed in the cervix, which can be observed in women infected with papillomavirus, regular oral contraceptives and multiple pregnancies (Arbyn et al.,2020). Early detection of CC is one of the most key aspects in the treatment, but CC diagnosis, treatment and prognosis are still not satisfactory, despite many efforts, so it is still necessary to find and develop new biomarkers for diagnosis (Song et al.,2019). Among various biomarkers of prognosis, diagnosis and treatment, miRNA has become a powerful biomarker for detecting, treating and monitoring the response to CC treatment (Liang et al., 2019). At present, it has been clinically proved that dihydroartemisinin has the activity of inhibiting various cancer cells (Yu et al., 2018). Therefore, this experiment combined them to observe the effect of dihydroartemisinin on CC cells depending on miR-214/PTEN signal axis, which is of great significance for future clinical diagnosis and treatment.

The experimental results showed that the miR-214 and PTEN levels in CC patients were obviously lower than those in normal people, which suggested that the two might be involved in CC development and progression. Chen Y et al (Jamaspishvili et al.,2018).and Jamaspishvili T et al. (Tricoli et al.,2019) studied the miR-214 and PTEN expression in ovarian cancer and prostate cancer, and the results were consistent with ours, which could support this experiment. Through ROC curve analysis, we discovered that miR-214 and PTEN had good diagnostic value for CC, suggesting that they could be used as serum markers to assist future clinical diagnosis. Pearson correlation coefficient analysis manifested that miR-214 was positively correlated with PTEN expression in the RG, which also preliminarily confirmed the relationship between them. At the moment, CEA and CA199 are commonly used as tumor markers clinically, and miR-214 and PTEN have good diagnostic specificity, which is more conducive to CC early screening. Early screening has a higher impact on the survival rate of CC. Tricoli L et al. (Haddadi et al.,2019) proposed that miR-214 could be used as a prognostic marker of liver cancer, and

also indicated its future clinical application prospect. PTEN protein is a kind of lipid phosphatase, which can inhibit tumor development and progression by antagonizing tyrosine kinase and inhibiting the activity of phosphatidylinositol 3-kinase (PI3K)/AKT pathway. Studies have shown that PTEN deletion is a common event in breast cancer [25]. However, its role and mechanism in CC still need to be further explored.

To further determine miR-214 and PTEN's effects on CC, we detected their biological behaviors by transfecting the two into CC cell Hela. The results showed that the migration rate of the miR-214 group was higher than that of the over-expressed miR-214 group and the miR-NC group, while the apoptosis rate was lower. The PTEN and Bax expression in the miR-214 group was lower than the other two groups, and Bcl-2 was higher. Apoptosis is the main mode of programmed cell death, and the proteins of Bcl-2 family are the key regulators of internal pathway, including BAX protein which promotes apoptosis and Bcl-2 protein which inhibits apoptosis (Warren et al., 2019). Combined with the above experimental results, it is suggested that miR-214 acts as a tumor suppressor gene in CC, which is also consistent with the previous research results (Peng et al., 2020) and can support ours. This also suggests that miR-214 may be a potential therapeutic target for CC, but this experiment has not carried out further analysis, which will be the focus of our future research. PTEN has been proved to interfere with apoptosis, proliferation and migration of cells. This study found that PTEN was abnormally expressed in CC. After PTEN was transfected into CC cells, its biological behavior showed that the PTEN group inhibited proliferation, and its mobility was higher than that of the over-expressed PTEN group and the NC group, but its apoptosis rate was lower. The PTEN and Bax expression in the miR-214 group was lower than the other two groups, and Bcl-2 was higher. The mechanism of PTEN on CC was confirmed. It is suggested that PTEN can significantly reduce the activity of cancer cells. Lu Q proposed that PTEN could inhibit the proliferation of bladder cancer cells (Lu et al., 2019), similar to our experimental results.

A large number of studies reveal that dihydroartemisinin has a good anti-tumor cell proliferation effect on various malignancies. Therefore, we treated transfected CC cells with dihydroartemisinin in this experiment, and detected the miR-214 and PTEN expression in those cells treated with dihydroartemisinin. The results manifested that the expression increased, suggesting that dihydroartemisinin could dramatically inhibit the miR-214 and PTEN expression in CC cells. Furthermore, the proliferation and mobility of CC cells decreased after treated with dihydroartemisinin, which further confirmed the anti-tumor effect of dihydroartemisinin, and also suggested that it could affect CC cells through miR-214 and PTEN.

However, due to the limited conditions, there are still some shortcomings. For example, we proposed that miR-214 might be a future therapeutic target for CC, but failed to carry out basic experiments and drug resistance analysis, which remains to be considered. However, due to the short experimental period, we could not judge the influence of miR-214 and PTEN on CC long-term prognosis. We will conduct a more comprehensive experimental analysis for the above shortcomings as soon as possible, and obtain more perfect experimental results for clinical reference.

To sum up, dihydroartemisinin relies on miR-214/PTEN signal axis to inhibit CC cell proliferation and migration, which will have great application prospects in future diagnosis and treatment.

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