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Original Research Article

Effect of miR-138 on migration and invasion of cervical cancer cells, and the underlying mechanism

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Abstract

Purpose: *To study the influence of microRNA-138 (miR-138) on the migration and invasion of cervical cancer cells, and the underlying mechanism.*

Methods: *Fifteen cervical carcinoma subjects were enrolled in the study. Control group comprised cervical epithelial cell line (End1/E6E7) while cervical cancer group was human cervical squamous cell carcinoma cell line c33a. Both were cultured routinely without any treatment. In miR-138 overexpression group, cells were cultured in progeny of human cervical squamous carcinoma cell line c33a infected with miR-138 gene overexpression lentivirus. Expression levels of miR-138 in excised cervical cancer tissues were determined using qPCR. Cell proliferation was determined with CCK8 assay. Immunoblotting was utilized to assay protein expression levels. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to determine mRNA expression levels, while cell migration and invasion were assessed by Transwell method.*

Results: *There was significant down-regulation of miR-138 expression in cervical cancer tissue, relative to nearby tissues ($p < 0.05$). In miR-138 overexpression group, cell proliferation, number of migrated and invaded cells were significantly reduced, relative to corresponding levels in cervical cancer cells. There were significantly higher expression levels of apoptosis-related proteins FAS, Bax and FasL in miR-138 overexpression group than in cervical cancer cells, while Bcl-2 was significantly down-regulated, relative to cervical cancer group ($p < 0.05$). In cervical cancer cells, mRNA and protein levels of SIRT1 and HIF-1α were significantly up-regulated, relative to corresponding control, but levels of HIF-1α and miR-138 were significantly reduced in overexpression group when compared to cervical cancer group ($p < 0.05$).*

Conclusion: *Up-regulating miR-138 in cervical cancer cells reduces HIF-1α through inhibition of SIRT1 signaling, resulting in suppression of multiplication, migration and invasion of cervical cancer cells, while enhancing apoptotic changes.*

Keywords: *MicroRNA-138, Cervical cancer, Migration, Invasion, Silent signal regulator 1*

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INTRODUCTION

Cancer of the cervix is a malignancy seen regularly in women in clinics, and it is the second most important factor linked to fatalities due to reproductive system neoplasms in women in China [1]. Lesions due to cancer of the cervix are prolonged processes that usually take 5 - 10

years to develop. Thus, it is important to diagnose and treat the disease in time, so as to improve the outcome in sufferers [2]. At present, there is no radical clinical treatment for patients with cervical cancer. The treatment involves mainly chemoradiotherapy and surgical resection. In recent years, with advancements in targeted therapy, the clinical treatment of malignant tumors has increasingly adopted targeted therapy. Thus, it is important to investigate the pathogenesis and etiology of cervical cancer, and to find new therapeutic targets for reducing the clinical symptoms, slowing down the progression of cancer, and enhancing the quality of existence for subjects [3]. MicroRNAs (miRNAs) are small and highly conserved non-coding RNA molecules which play important roles in the regulation of cellular biological functions. In particular, miR-138 has been confirmed to be abnormally expressed in cervical cancer patients, and it participates in the occurrence and development of cervical cancer [4,5]. However, there are limited reports on the effect of miR-138 on biological behaviors of cervical cancer cells such as proliferation, migration and invasion, and the associated mechanism(s). Based on this, the aim of this research was to study the influence of miR-138 on the migration and invasion of cervical carcinoma cells, and the possible mechanism involved, so as to identify potential therapeutic targets for the disease.

METHODS

General information on patients

Fifteen (15) cervical cancer patients who received hospital treatment from June 2021 to February 2023, were chosen and enrolled in this study. Cervical cancer tissues, adjacent tissues, and clinical data of the patients were collected. The average age of the patients was 46.63 ± 3.32 years, with ages ranging from 35 to 58 years. This study was reviewed and approved by the ethics committee of the First People's Hospital of Liangshan Yi Automotive Precision, China (approval no. FPJLYAP2020002). Patients submitted signed statements indicating a willingness to participate in the study. This research was conducted according to the principles of Declaration of Helsinki promulgated in 1964 as amended in 1996 [6].

Inclusion criteria

Subjects diagnosed with cervical cancer through pathological examination [7]; patients without a history of pelvic radiation, and those with complete clinical medical records, participated in the study.

Criteria for exclusion

Patients who had received drugs and surgery due to cervical problems; subjects who had other cancers; those with serious cardiac, hepatic and renal dysfunctions, and subjects who had history of uterine surgery, were excluded.

Materials and reagents

Human cervical squamous cell carcinoma cell line c33a and normal cervical epithelial cell line (End1/e6e7) were purchased from the cell bank of ATCC, while ethylene diamine tetraacetic acid, trypsin, penicillin, streptomycin, DMEM, double antibody, and FBS were products of Thermo Fisher Scientific, USA. β-Actin primer, MiR-138, and mRNA primers for HIF-1α and SIRT1 were bought from Sigma, USA. Qualitative real-time PCR kit, sheep anti-rabbit secondary immunoglobulin and CCK-8 assay kit were purchased from Shanghai Biyuntian Co.). Transwell chamber (Corning) and artificial reconstituted basement membrane adhesive (Matrigel) were obtained from BD Company (USA). Primary antibodies for Fas, Bax, FasL, Bcl-2, HIF-1α and SIRT1 were products of Abcam Biotechnology, UK. Cellular miR-138 gene overexpressed using lentivirus was purchased from Shanghai Jikai Gene Co. Limited.

Cell groups and culturing

Cell culture was done in a temperature-controlled T25 flask in DMEM in the presence of 10 % FBS and 5 % CO_2 at 37 ^oC. The cancer cells were digested, passaged, and frozen according to the cell growth. The cells were assigned to blank control, cervical cancer, and miR-138 overexpression groups. Cells in blank control group were normal cervical epithelial cell lines (End1/E6E7) without any treatment and were cultured routinely. Cells in cervical cancer group were human cervical squamous cell carcinoma cell line c33a which were cultured routinely without any treatment. Cells in the miR-138 overexpression group were cultured in the progeny of human cervical squamous cell carcinoma cell line c33a infected with miR-138 gene overexpression lentivirus. Each experiment was repeated 6 times.

Assay of protein expressions

In every group, cells inoculated in 6-well plates at a concentration of 1×10^6 cells per well were

maintained in a constant-temperature incubator at 37 ºC in a 5 % CO_2 atmosphere. After stable passage of miR-138 overexpression cells infected with miR-138 gene overexpression lentivirus, total cellular protein was extracted using RIPA buffer by making a 10 % homogenate at 4 ºC. After centrifugation, the protein concentration of each lysate was measured with the BCA procedure. Thereafter, protein resolution was done using SDS-PAGE, followed by electro-transfer to PVDF filaments subsequently sealed by incubation with skimmed milk. The membranes were successively incubated with primary and 2º immunoglobulins. Thereafter, the blots were subjected to ECL, followed by image analysis using Bio-Rad laboratory software.

Assay of mRNA expressions

Cell seeding was done as indicated above, followed by culturing at 37 ℃ in a 5 % CO_2 atmosphere in a constant-temperature incubator. After stable passage of miR-138 overexpression cells infected with miR-138 gene overexpression lentivirus, total RNA was extracted from the cervical cancer tissues and adjacent tissues using RNA extraction kit. Then, the miRNA was reverse-transcribed into cDNA. Thereafter, miRNA fluorescence quantitative PCR detection kit was used for RT-PCR, and the cycle was completed according to the kit instructions. The relative mRNA expression levels were calculated using $2^{-\Delta\Delta Ct}$ method.

Evaluation of cell proliferation potential

When the cells in miR-138 overexpression group were stably passaged by miR-138 gene overexpression lentivirus infection, CCK8 reagent (10 μL) was introduced. The cells were cultured at 37 ºC at a constant temperature in a 5 % CO_2 incubator for 4 h. The optical density of the cells in each group was read at 450 nm in a microplate reader, as an index of proliferative potential.

Transwell assay

After the cells in miR-138 overexpression group were stably passaged by miR-138 gene overexpression lentivirus infection, the density of each group was adjusted to 5 x 10^5 cells/well, and the cells were inoculated into Transwell top compartment, while the lower chamber had intact medium containing 10% FBS. Overnight incubation was done, after which they were subjected to fixation, staining and counting under light microscopy, and the migratory potential of the cells was calculated. For the determination of cell invasion potential, the upper chamber of Transwell was first coated with Matrigel in an ultra-clean workbench. The subsequent steps were the same as outlined in cell migration.

Statistical analysis

The SPSS 22.0 was employed for result processing. Data are presented as mean ± standard deviation (SD). Two-group comparison was done using *t*-test. Statistical significance was assumed at $p < 0.05$.

RESULTS

Expression levels of miR-138 in cervical cancer and adjacent tissues

The relative expression of miR-138 in cervical cancer tissues was significantly lower than that in adjacent tissues ($p < 0.05$), as shown in Table 1.

Table 1: Expression of miR-138 in cervical cancer tissues and adjacent tissues (n=15)

Group	MiR-138
Cervical cancer tissue	0.48±0.16
Para-cancerous tissue	1.02±0.35
t	-5.435
P-value	0

Effect of overexpressed miR-138 on proliferation, migratory potential and invasiveness

As presented in Table 2, the cell proliferation potential, number of migrated cells, and number of invasive cells were significantly higher in cervical cancers than in the blank control cells, but they were significantly lower in miR-138 overexpression cells than in cervical cancer cells.

Impact of miR-138 overexpression on expressions of apoptotic proteins

As shown in Table 3, the apoptosis protein levels in miR-138 overexpression group were significantly up-regulated, relative to those in cervical cancer cells, while Bcl-2 protein was higher in cervical cancer cells ($p < 0.05$).

Effect of overexpression of miR-138 on relative mRNA expressions of SIRT1 and HIF-1αin cervical cancer cells

The relative mRNA expressions of SIRT1 and HIF-1-α were significantly higher in cervical cancer cells than in the blank control cells but were significantly lower in miR-138 overexpression group than in cervical cancer group ($p < 0.05$; Table 4).

Table 2: Impact of overexpressed miR-138 on cell proliferation, migration and invasiveness (n=6)

Group	Cell proliferation potential	Number of migrated cells	Number of invaded cells
Blank control	0.10±0.01	73.25±15.70	51.72±10.31
Cervical cancer	0.22±0.04[a]	142.74±24.34[a]	121.05±20.26[a]
MiR-138 overexpression	0.18±0.03[b]	106.48±17.44[b]	93.12±16.35[b]
F	25.846	19.022	26.157
P-value	0	0	0

[a]*P* < 0.05, *vs* the blank control; [b]*p* < 0.05, vs. cervical cancer cells

Table 3: Effect of overexpression of miR-138 on the expression of apoptotic proteins in cervical cancer cells (n = 6)

Group	Fas	Bax	FasL	Bcl-2
Blank control	0.35±0.14	0.37±0.09	0.41±0.14	0.54±0.03
Cervical cancer	0.33±0.17	0.43±0.14	0.44±0.14	0.49±0.04
MiR-138 overexpression	0.84±0.18[b]	0.86±0.16[b]	0.78±0.12[b]	0.31±0.03[b]
F	13.446	20.294	18.641	72.177
P-value	0.001	0.000	0.000	0.000

[b]*P* < 0.05, *vs* cervical cancer group

Table 4: Effect of miR-138 overexpression on relative mRNA expressions of HIF-1α and SIRT1 in cervical cancer cells (n = 6)

Group	HIF-1 α mRNA	SIRT1 mRNA
Blank control	1.24±0.32	0.83±0.35
Cervical cancer	2.47±0.54[a]	2.59±0.67[a]
MiR-138 overexpression	2.05±0.40[b]	1.76±0.43[b]
F	12.701	18.451
P-value	0.001	0

[a]*P* < 0.05, vs. the blank control; [b]*p* < 0.05, vs. cervical cancer group

Table 5: Effect of overexpression of miR-138 on protein expression levels of HIF-1 α and SIRT1 in cervical cancer cells

Group	HIF-1α	SIRT1
Blank control	0.18±0.04	0.13±0.03
Cervical cancer	0.85±0.27[a]	0.83±0.25[a]
MiR-138 overexpression	0.44±0.11[b]	0.49±0.17[b]
F	23.716	23.896
P-value	0	0

[a]*P* < 0.05, compared with the blank control group; [b]*p* < 0.05, compared with cervical cancer group

Influence of overexpression of miR-138 on protein expressions of HIF-1α and SIRT1 in cervical cancer cells

Table 5 shows that in cervical cancer cells, there were significantly higher protein levels of HIF-1 α and SIRT1 than in the blank control group, but miR-138 overexpression group had lower levels of these proteins than the cervical cancer group.

DISCUSSION

In recent years, with changes in lifestyles, dietary habits and working environment, the incidence of cervical cancer is on the increase, so much so that the disease has become a common malignant tumor of the reproductive system [5]. The clinical manifestations in subjects with cancer of the cervix comprise light water discharge, leucorrhea, odor, irregular vaginal bleeding, anemia, and pain during sexual intercourse, all of which severely affect reproductive health and function [6]. The precancerous lesion stage of the disease is known as cervical intraepithelial neoplasia [7]. The pathogenesis of cervical cancer has not yet been fully elucidated. However, recent research findings suggest that age, genetic susceptibility, inflammatory reaction, immune disorder, physical and chemical radiation, and other factors may be related to the occurrence and development of cervical cancer [8]. At present, chemoradiotherapy and surgical resection are mainly used for clinical treatment of cervical cancer patients. Although these strategies result in cancer cure in some patients, late diagnosis makes some patients lose not only the opportunity for surgical resection but also sensitivity to chemoradiotherapy, resulting in limited clinical treatment effect [9]. Cervical cancer is characterized by high degrees of incidence, invasiveness, metastatic potential and recurrence. The radical treatment of cervical cancer patients with targeted cancer cells has great clinical significance [10]. Therefore, it is of immense clinical benefit to study the pathogenesis and etiology of cervical cancer and to determine the molecular mechanisms underlying the proliferation, invasion and migration of cervical cancer cells. Moreover, it is crucial to identify new therapeutic targets for cervical cancer so as to decrease the associated clinical symptoms, slow down its pathological

progression, and enhance standard of life of the sufferers. MicroRNAs (miRNAs) have become a research hotspot in malignant tumor research. The miRNAs are a group of small non-coding RNAs involved in regulating various biological processes such as cell proliferation, differentiation, migration and apoptosis, through interaction with specific genes [11]. Interestingly, miR-138, which is highly conserved in vertebrates, belongs to a class of miRNAs that participate in regulating cancer-related inflammation. However, the actual function of miR-138 in development of cancer is not yet completely fully understood [12]. Nonetheless, research has confirmed that it is present in low levels in cervical cancer specimens, with close and positive correlations between its level and the degree of cervical intraepithelial lesions [13]. Thus, miR-138 level is intimately associated with the occurrence, development and extent of cervical neoplasm [13]. This study has shown significantly lower relative expression level of miR-138 in cervical cancer tissues than in nearby healthy tissues. The cell multiplication potential, population of migrated cells and the population of invaded cells were significantly higher in cervical cancer cells than in the blank control cells but were significantly lower in miR-138 overexpression group than in cervical cancer group. In another study, it was shown that aberrant Fas route (extrinsic route) was crucial in inhibition of apoptotic changes. It is known that FasL and Fas belong to TNF group of cell surface receptors. The interplay between Fas and FasL leads to ligand-induced apoptosis. Thus, the downregulation of Fas and FasL, or attenuation of their interaction, is associated with tumor occurrence [14]. A typical representative pro-apoptosis factor is Bax, while bcl-2 blocks apoptosis in cancer cells. Thus, the Bcl-2/bax ratio is clinically used as an index of degree of apoptosis in cancer cells [15]. The results of this study revealed significant up-regulation of Bax, Fas and FasL in miR-138 overexpression cells, relative to those in cervical cancer cells, while Bcl-2 level was down-regulated, relative to that in cervical carcinoma cells. These data indicate that miR-138 up-regulation enhanced apoptosis of cervical cancer cells.

In human and mammalian tissues, HIF-1α, an important and dimeric regulator of aerobic metabolism, is widely expressed. It has been revealed that HIF-1α regulates tumorigenesis-linked genes such as those involved in remodeling of ECM, invasiveness, DNA lesions, apoptotic and autophagic changes, and cancer cell multiplication [16]. Another study found that patients with cervical cancer had abnormalities in chromosome 3p, which led to abnormality in the tumor suppressor gene VHL. This makes the binding of HIF-1α to E3 ligase difficult, which in turn leads to steady up-regulation of hif-1ct protein level, leading to dysregulation of the cell cycle and apoptosis, and ultimately tumorigenesis [17]. Some researchers have reported that miR-138 targeted the migration of human leukemia K562 cells through inhibition of HIF-1α [18]. In addition, SIRT1, a NAD-linked enzyme present in mammals, regulates apoptosis and autophagic processes through acetylation of histones as well as non-histones [19]. Research has demonstrated that miR-138 participates in apoptosis regulation in colon carcinoma by regulating the expression of its target molecule SIRT1 [20]. The present work has revealed significantly higher relative mRNA and protein expressions of HIF-1α and SIRT1 in cervical cancer cells than in the blank control group, but they were significantly lower in miR-138 overexpression cells than in cervical cancer group. These results suggest that up-regulation of the level of miR-138 inhibited the SIRTI pathway in cervical cancer cells by targeting and reducing the expression of HIF-1α.

CONCLUSION

Up-regulating the level of miR-138 reduces HIF-1α and inhibits SIRT1 signaling pathway, resulting in the suppression of proliferation, migration and invasiveness of cervical cancer cells, and enhancement of apoptosis. This finding provides a theoretical basis for the clinical treatment of tumor metastasis and invasion.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication. Yanxi Li conceived and designed the study; Jun Peng, Yong Huang, Yichun Man, Yaqi Li, Ping Chen, and Erqing Peng collected and analyzed the data, while Yanxi Li wrote the manuscript.

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