MicroRNA-1297 inhibits metastasis and epithelial-mesenchymal transition by targeting AEG-1 in cervical cancer

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Abstract. Accumulating evidence has demonstrated that aberrant miRNAs contribute to cervical cancer (CC) development and progression. However, the roles of various miRNAs in CC remain to be determined. In the present study, we confirmed that a decreased miR-1297 expression was present in CC tissues and cell lines. Our clinical analysis revealed that the downregulated miR-1297 expression was significantly correlated with poor prognostic features including lymph node metastasis and lymphovascular space invasion. Moreover, we confirmed that miR-1297 was a novel independent prognostic marker for predicting the 5-year survival of CC patients. The ectopic overexpression of miR-1297 inhibited cell migration, invasion and EMT progression, while downregulated miR-1297 reversed these effects. In addition, miR-1297 regulated AEG-1 by directly binding to its 3'-UTR. In clinical samples of CC, miR-1297 was inversely correlated with AEG-1, which was upregulated in CC. Alteration of AEG-1 expression at least partially abolished the migration, invasion and EMT progression effects of miR-1297 on CC cells. In conclusion, our results indicated that miR-1297 functioned as a tumor suppressor gene in regulating the EMT and metastasis of CC via targeting of AEG-1, and may represent a novel potential therapeutic target and prognostic marker for CC.

Introduction

Cervical cancer (CC) is one of the most common cancers and the third leading cause of cancer-related deaths in women worldwide (1,2). Despite notable advances in the diagnosis and treatment of CC that have been achieved, the long-term prognosis of CC patients particularly for those at an advanced stage remains poor due to the high rates of tumor recurrence and distal metastasis (3,4). However, the detailed molecular mechanisms involved in the initiation and progression of CC remain largely unknown (5,6). Therefore, it is crucial to identify the molecular etiology and molecular mechanisms underlying the progression and metastasis in CC, and thus improve the therapeutic strategies and prognosis.

MicroRNAs (miRNAs) are a class of small, non-coding RNAs that negatively regulate protein expression by binding to the 3'-untranslated region (3'-UTR) of target mRNAs and function as post-transcriptional regulators of gene expression (7,8). Previous studies revealed that the initiation and progression of CC was a complex process in which numerous proteins and non-coding RNAs were involved in (9,10). Various miRNAs have been regarded as the biomarkers and therapeutic targets for CC patients (11). miR-1297, a novel cancer-related microRNA, has been found to play vital role in the pathogenesis of human cancer (12,13). miR-1297 promoted cell proliferation via downregulation of the tumor suppressor gene retinoblastoma (RB) 1 in liver cancer (14), while Liu et al reported that miR-1297 played a crucial role in promoting cell apoptosis and inhibiting proliferation by targeting EZH2 in hepatocellular carcinoma (15). Moreover, miR-1297 was overexpressed and contributed to cell proliferation, migration and tumor genesis in laryngeal squamous cell carcinoma by targeting PTEN (16). miR-1297 regulated the growth of testicular germ cell tumors through the PTEN/PI3K/AKT pathway (17). These studies identified miR-1297 as an oncogene. However, miR-1297 inhibited prostate cancer cell proliferation and invasion by targeting the AEG-1/Wnt signaling pathway (18). miR-1297 inhibited the growth, migration and invasion of colorectal cancer cells by targeting cyclo-oxygenase-2 (19). These studies revealed that miR-1297 was a tumor suppressor. Therefore, the functional roles of miR-1297 in human cancer are cancer-type specific. Nevertheless, the functional importance of miR-1297 and the molecular mechanisms in CC are still unclear.

In the present study, we investigated the effects of miR-1297 on CC cells by targeting AEG-1. Our data revealed that miR-1297 was downregulated in CC and that decreased miR-1297 was associated with poor prognostic features and a poor 5-year survival of CC patients. We also confirmed that miR-1297 regulated the migration, invasion and EMT
phenotype of CC by targeting AEG in vitro. These data revealed the underlying mechanism by which miR-1297 inhibited the migration and invasion of CC and regard miR-1297 as a novel prognostic biomarker for CC patients.

Materials and methods

Clinical samples and cell culture. CC and corresponding adjacent normal tissues were obtained from 117 patients who received routine surgery at The First Affiliated Hospital of Sun Yat-Sen University during January 2008 to December 2011. None of them had received any therapy before surgery. All tissues were stored at -80°C until RNA extraction. Informed consent was obtained from all the patients and the present study was approved by the Ethics Committee of the Sun Yat-sen University in accordance with the Declaration of Helsinki. Four CC cell lines (C33A, HeLa, CaSki and SiHa) and a normal human cervical epithelial cell line (H8) were obtained from the Institute of Biochemistry and Cell Biology (Chinese Academy of Sciences, Shanghai, China) and were cultured in Dulbecco's modified Eagle's medium (DMEM; HyClone, Academy of Sciences, Shanghai, China) and were cultured containing 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA) at 37°C with 5% CO₂.

Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). The RNA in CC tissues and cell lines was isolated with TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Reverse transcription of miRNA and mRNA were performed with MicroScript II RT kit (Qiagen, Hilden, Germany) and QuantScript RT kit (Tiangen, Beijing, China), respectively. SYBR-Green PCR kit (Qiagen) was used for RT-PCR quantification. The gene expression levels were calculated using the ΔΔCt method with U6 or GAPDH as an internal control. The hsa-miR-1297 primer was synthesized by Sangon (Shanghai, China), and the snRNA U6 qPCR Primer (HmiRQP9001), AEG-1 (HQPO016089) and GAPDH (HQPO006940) were purchased from GeneCopoeia (Guangzhou, China).

Cell transfection. miRNA vectors, including miR-1297 expression and control vector, and miR-1297 inhibitor and the negative control were obtained from GeneCopoeia. The AEG-1 overexpression plasmid and specific siRNA against AEG-1 and a scramble siRNA were synthesized by Sangon Biotech Co., Ltd. (Shanghai, China). The cells were transfected with the aforementioned vectors using Lipofectamine 2000 reagent (Invitrogen Life Technologies) in accordance with the manufacturer's protocol.

Western blot analysis. Cellular proteins from CC cells were extracted using RIPA buffer (Beyotime, Shanghai, China). Isolated proteins were subjected to electrophoresis on 4-20% SDS-PAGE and transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After being blocked with 5% non-fat milk/Tris-buffered saline Tween-20 (TBST) the membranes were incubated with the primary antibody (1:1,000; Cell Signaling Technology, Inc., Danvers, MA, USA) at 4°C overnight and incubated with an HRP-conjugated secondary antibody (1:5,000; ZSGB-BIO, Beijing, China) at room temperature for 2 h. The protein bands were detected and visualized with an enhanced chemiluminescence (ECL) reagent (Amersham, Little Chalfont, UK).

Immunohistochemical staining (IHC). Briefly, 4-μm sections were deparaffinized in xylene, rehydrated by graded ethanol, followed by blocking of endogenous peroxidase activity in 4% hydrogen peroxide for 10 min at room temperature. The corresponding antibody (1:300; Cell Signaling Technology, Inc.) was applied as the primary antibody using a streptavidin peroxidase-conjugated (SP-IHC) method. The staining results were semi-quantitatively evaluated by multiplying the staining intensity and the percentage of positive-stained cells. The percentage of positive cells was scored as follows: 0 for <5%; 1 for 6-25%; 2 for 26-50%; 3 for 51-75%; and 4 for >75%. The staining intensity was assessed as follows: 0, negative; 1, weak; 2, moderate; and 3, strong. Each section was assayed for 10 independent high magnifications (x400) fields to obtain the average scores.

Cell migration and invasion analyses. Matrigel-uncoated and -coated Transwell inserts (8-μm pore size; Millipore) were used to evaluate cell migration and invasion. Briefly, 2x10⁴ transfected cells were suspended in 150 μl serum-free RPMI-1640 medium into the upper chamber, and 700 μl RPMI-1640 medium containing 20% FBS was placed in the lower chamber. After 24 h of incubation, the cells were fixed in 4% paraformaldehyde for 20 min and stained with 0.1% crystal violet dye for 15 min. The cells on the inner layer were gently removed with a cotton swab and 5 randomly selected views were counted. Subsequently, the average number of cells per view was calculated.

Luciferase reporter assay. CC cells seeded into 24-well plates were transfected with 200 ng of miR-1297 mimic or inhibitor or the corresponding control vector along with 50 ng of wild-type (wt) or mutant (mt) 3’-UTR of AEG-1 mRNA. Forty-eight hours after transfection, these cells were collected and the luciferase activity was detected with a Dual-Luciferase Reporter Assay System following the manufacturer's instructions (Promega, Madison, WI, USA).

Statistical analysis. Data are presented as the mean ± SD of at least 3 independent replications. SPSS software 16.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA) were used for a two-tailed Student's t-test, Pearson's correlation analysis, Kaplan-Meier method and the log-rank test to evaluate the statistical significance. Differences were defined as P<0.05.

Results

miR-1297 is significantly downregulated in CC tissues and cell lines. We initially investigated the expression level of miR-1297 in 117 pairs of CC and their matched non-tumor tissues. We found that the expression of miR-1297 was significantly lower in CC tissues than those in corresponding non-tumor tissues (P<0.05; Fig. 1A). Moreover, we analyzed the expression of miR-1297 in a panel of CC cell lines and a normal human cervical epithelial cell line (H8). The data
revealed that the relative miR-1297 expression was obviously decreased in the CC cell lines compared with the H8 cells (P<0.05; Fig. 1B). These results indicated that decreased miR-1297 expression is potentially correlated with the development and progression of CC.

**Correlations between the expression of miR-1297 and the clinical features in CC tissues.** To explore its clinical relevance in CC tissues, we defined the different miR-1297 groups based on the median expression level. As shown in Table I, low miR-1297 expression was significantly associated with lymph node metastasis (LNM; P=0.008) and lymphovascular space invasion (LVSI; P=0.005). Therefore, these results indicated that decreased miR-1297 was involved in the development and progression of CC. Moreover, survival analysis revealed that the downregulation of miR-1297 was obviously correlated with shorter overall survival (P=0.0002; Fig. 2) in CC patients. Furthermore, the expression of miR-1297 was an independent prognostic factor for predicting the overall survival in CC patients (P=0.003, 0.007, respectively; Table II). These results revealed that miR-1297 could serve as a potential prognostic biomarker in CC patients.

**miR-1297 inhibits CC cell migration and invasion in vitro.** To explore the biological significance of miR-1297 in CC, we transduced CC cell lines with miR-1297 expression or anti-miR-1297 vector which contained different endogenous miR-1297 levels. As determined by qRT-PCR, we confirmed that miR-1297 effectively upregulated miR-1297 in C33A cells (P<0.05; Fig. 3A) or downregulated miR-1297 in CaSki cells (P<0.05; Fig. 3C). As examined by Matrigel-coated (for invasion) and -uncoated (for migration) Transwell assays, miR-1297 overexpression significantly inhibited the migration and invasion of C33A cells (P<0.05; Fig. 3B), whereas miR-1297 knockdown markedly increased the number of migrated and invaded CaSki cells (P<0.05; Fig. 3D). In conclusion, these data revealed that miR-1297 regulated CC cell migration and invasion and may exert an antimetastatic effect on CC.

**miR-1297 suppresses epithelial-mesenchymal transition in CC cells.** EMT has been proposed to have a critical role in the initiation of metastasis progression of cancer (20,21). To gain a mechanistic illustration of the potential role of miR-1297 in modulating CC metastasis, EMT markers were assessed. We found that miR-1297 overexpression facilitated the epithelial marker E-cadherin and suppressed N-cadherin and vimentin expression (P<0.05; Fig. 4A). In contrast, miR-1297 knockdown decreased E-cadherin expression and increased N-cadherin and vimentin expression (P<0.05; Fig. 4B). In addition, we further explored the correlation between miR-1297 expression and EMT markers in CC tissues. We found that the expression of E-cadherin in the high-expressing miR-1297 group was higher than that in the low-expressing miR-1297 group. Conversely, the expression level of vimentin in the high-expressing miR-1297 group was markedly lower than that in the low-expressing miR-1297 group (P<0.05; Fig. 4C). Collectively, these results revealed that miR-1297 functioned as a suppressor of EMT in CC cells.

**AEG-1 is a direct downstream target of miR-1297 in CC cells.** To elucidate the molecular mechanisms responsible for the functional influence of miR-1297 in CC cells, we searched the publicly available database TargetScan to explore the candidate target genes. Among them, AEG-1 was known to play an important role in CC invasion and metastasis. As shown in Fig. 5A, the sequence complementary to the binding sites of miR-1297 was revealed in the 3'-UTR of AEG-1. To confirm this, we performed a luciferase reporter assay to ascertain that miR-1297 could bind to the 3'-UTR of AEG-1. The results revealed that miR-1297 overexpression significantly decreased the luciferase activity of the wild-type (wt) AEG-1 3'-UTR while it had no influence on that of the mutant (mt) AEG-1 3'-UTR (P<0.05; Fig. 5B). On the contrary, miR-1297
miR-1297 knockdown increased the luciferase activity of the wt AEG-1 3’-UTR (P<0.05; Fig. 5B), but it did not affect the luciferase activity of the mt AEG-1 3’-UTR constructs. In addition, miR-1297 overexpression markedly decreased the mRNA and protein levels of AEG-1 in C33A cells (P<0.05, respectively; Fig. 5C and D). By contrast, the expression of AEG-1 mRNA and protein were significantly increased by the downregulation of miR-1297 in CaSki cells (P<0.05, respectively; Fig. 5C and D). miR-1297 is negatively correlated with the expression of AEG-1 in CC samples. To further evaluate the relationship between miR-1297 and AEG-1 in CC tissues, we assessed the AEG-1 mRNA and protein expression in two groups of miR-1297. As expected, our data revealed that both the AEG-1 mRNA and protein expression level in the high-expressing miR-1297 group were significantly lower than those in the low-expressing miR-1297 group in CC (P<0.05; Fig. 6A and B).

### Table II. Univariate and multivariate analysis of the 5-year overall survival of 117 CC patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<td>miR-1297 expression</td>
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<td>LNM</td>
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<td>1.237-6.568</td>
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<tr>
<td>LVSI</td>
<td>3.423</td>
<td>1.358-7.649</td>
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CC, cervical cancer; HR, hazard ratio; CI, confidence interval. *Statistically significant.

### Table I. Clinical correlation of miR-1297 expression in CC (n=117).

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Cases (n)</th>
<th>miR-1297＜high (n=55)</th>
<th>miR-1297＜low (n=62)</th>
<th>P-value</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>&lt;45</td>
<td>21</td>
<td>9</td>
<td>12</td>
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<tr>
<td>≥45</td>
<td>96</td>
<td>46</td>
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<tr>
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<td>94</td>
<td>44</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>11</td>
<td>12</td>
<td></td>
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<tr>
<td>Tumor size (cm)</td>
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<td>54</td>
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<td>≥4</td>
<td>15</td>
<td>7</td>
<td>8</td>
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<td></td>
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<td>Positive</td>
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<td>1</td>
<td>10</td>
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<tr>
<td>LVSI</td>
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<td>0.005a</td>
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<tr>
<td>Negative</td>
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<td>Positive</td>
<td>12</td>
<td>1</td>
<td>11</td>
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<td>Vaginal invasion</td>
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<tr>
<td>Positive</td>
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<td>7</td>
<td>11</td>
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<tr>
<td>Histology</td>
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<tr>
<td>Squamous</td>
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<td>Adenocarcinoma</td>
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<tr>
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<tr>
<td>Negative</td>
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<tr>
<td>Positive</td>
<td>14</td>
<td>6</td>
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CC, cervical cancer; FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis; LVSI, lymphovascular space invasion. *P<0.05.
Figure 3. miR-1297 inhibits CC cell migration and invasion in vitro. (A) C33A cells that were transfected with the corresponding miRNA vectors were subjected to qRT-PCR to assess the expression of miR-1297. (B) Cell migration and invasion as assessed by Transwell assays were inhibited by overexpression of miR-1297 in C33A cells. (C) CaSki cells that were transfected with miR-1297 inhibitors (anti-miR-1297) and negative control were subjected to qRT-PCR to assess the expression of miR-1297. (D) Cell migration and invasion as assessed by Transwell assays were increased by knockdown of miR-1297 in CaSki cells. n=6 independent experiments; *P<0.05, **P<0.01. CC, cervical cancer.

Figure 4. miR-1297 suppresses epithelial-mesenchymal transition in CC cells. (A) The overexpression of miR-1297 in C33A cells increased the expression of the epithelial cell marker E-cadherin and decreased the expression of the mesenchymal cell marker N-cadherin and vimentin. (B) In contrast, the expression of the antagomiR to miR-1297 decreased the expression of E-cadherin and increased the expression of N-cadherin and vimentin. (C) Immunohistochemical analysis of E-cadherin and vimentin in CC samples. In cases of high miR-1297 expression, there was strong E-cadherin (left, upper image) and no detectable vimentin protein (left, lower image) expression in the same tissue section. In contrast, in the case of low miR-1297 expression, there was no detectable E-cadherin (right, upper image) and strong vimentin protein (right, lower image) expression. n=117. Values are depicted as the mean ± SEM; *P<0.05 by t-test. CC, cervical cancer.
Moreover, we demonstrated that the mRNA level of AEG-1 in the CC tissues was inversely correlated with miR-1297 expression ($R^2=0.6845$, $P<0.0001$, Fig. 6C). Consistently, as assessed by IHC assay, the AEG-1 protein expression in the miR-1297 high-expressing tumors was obviously lower than that in the miR-1297 low-expressing tumors ($P<0.05$, Fig. 6D), which
was similar with previous studies (18). In conclusion, these data revealed that AEG-1 was a direct downstream target of miR-1297 in CC.

Alteration of AEG-1 abolishes the effects of miR-1297 on CC cells. To confirm that AEG-1 is a functional target of miR-1297, AEG-1 was overexpressed by a plasmid vector in miR-1297-overexpressing C33A cells (P<0.05; Fig. 7A). Furthermore, AEG-1 overexpression abrogated the inhibitory effect induced by miR-1297 on cell migration and invasion (P<0.05, respectively; Fig. 7B) and promoted EMT progression (P<0.05; Fig. 7E). Similarly, AEG-1 knockdown by a specific siRNA in the miR-1297-suppressive CaSki cells (P<0.05; Fig. 7C) significantly reversed the promotive function induced by miR-1297 knockdown on cell migration and invasion (P<0.05, respectively; Fig. 7D) and EMT progression (P<0.05; Fig. 7F). These data demonstrated that AEG-1 is not only a downstream target of miR-1297, but also a functional mediator of miR-1297 in CC.

Discussion

Numerous studies have demonstrated that aberrant miRNAs are involved in cancer initiation, development and progression (22,23), including cervical cancer (CC). miRNAs have been identified as novel prognostic biomarkers and effective therapeutic targets of CC. Therefore, finding novel cancer-related miRNAs and elucidating their molecular mechanisms in the modulating biological effects of cancers are still warranted. In previous studies, Wang et al demonstrated that miR-1297 regulated cell proliferation, cell colony formation and apoptosis by targeting HMGA1 in glioma cells (24). Moreover, miR-1297 promoted apoptosis and inhibited the proliferation and invasion of hepatocellular carcinoma cells by targeting HMGA2 (25). However, miR-1297 induced cell proliferation by targeting phosphatase and tensin homolog in testicular germ cell tumor cells (26). These data indicated that the expression level and biological effects were dependent on the type of cancer.
Local and systemic metastasis is a major cause leading to a dismal prognosis of CC. Increasing evidence has confirmed miRNAs as key regulators in the metastasis of various types of cancer, including CC (27). In the present study, we found that miR-1297 was significantly downregulated in CC tissues compared with the corresponding non-cancerous tissues. Similarly, the expression level of miR-1297 in CC cell lines was significantly decreased. Decreased miR-1297 expression was evidently correlated with malignant clinicopathological characteristics of CC patients, including lymph node metastasis and lymphovascular space invasion. Moreover, we found that the low-expressing miR-1297 group had a significant worse 5-year OS for CC patients. Multivariate Cox regression analysis indicated that miR-1297 was an independent prognostic factor in the prediction of the survival of CC patients. Collectively, these results revealed that miR-1297 was critical for the prognosis outcome of CC patients. Importantly, gain- and loss-of-function experiments demonstrated that miR-1297 inhibited cell migration, invasion and EMT, at least partially by targeting AEG-1. Furthermore, miR-1297 was inversely correlated with AEG-1 expression, which was increased in CC tissues. In addition, miR-1297 negatively modulated AEG-1 accumulation in CC cells. Collectively, these results demonstrated that miR-1297 functions as a tumor suppressor in the migration, invasion and EMT of CC by directly inhibiting AEG-1.

AEG-1, which is also called astrocyte elevated gene-1, has been recognized as a key regulator in cancer initiation, development and progression in different types of cancer (28). AEG-1 promoted cell proliferation through the FOXO1/PI3K/AKT signaling pathway in breast cancer (29). AEG-1 induced epithelial-mesenchymal transition through the activation of Wnt/β-catenin signaling in lung cancer and cervical squamous cell carcinoma (30,31). In CC, AEG-1 knockdown decreased its invasiveness, EMT and chemoresistance (32). Our results revealed that AEG-1 alteration abolished the inhibitory or stimulatory effect of miR-1297 on CC cells. Collectively, these data demonstrated that the suppressive effect of miR-1297 was mediated by targeting AEG-1 in CC.

In summary, we demonstrated that miR-1297 was downregulated in CC tissues and cell lines, and its decreased expression was correlated with malignant clinicopathological features. Furthermore, we confirmed that miR-1297 inhibited cell migration, invasion and EMT by inhibiting AEG-1. These results revealed that miR-1297 is a potential metastasis-associated tumor suppressor in CC. Collectively, the dysregulation of miR-1297 may play an important role in tumor metastasis and may be a novel prognostic factor and potential therapeutic target for CC.

Acknowledgements

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References


