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Original Article

The diagnostic value of miR-145 and miR-205 in patients with cervical cancer

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Abstract: Objective: To investigate the diagnostic value of miRNA-145 (miR-145) and miRNA-205 (miR-205) in cervical cancer patients. Methods: Cervical tissue samples were collected from 144 patients diagnosed with and suspected to have cervical cancer in our hospital. Confirmed by pathology, 84 samples were obtained from cervical cancer patients and 60 samples were from patients with cervical intraepithelial neoplasia. Meanwhile, 30 patients with cervicitis were also selected, and the expression levels of miR-145, miR-205 and human papillomavirus (HPV) were detected in cervical lesions and normal cervical tissue. Results: In comparison to normal cervical tissue, cervicitis and cervical intraepithelial neoplasia groups, the relative expression level of miR-145 was significantly lower, whereas the relative expression level of miR-205 was notably higher in the cervical cancer group, respectively ($P<0.001$). The area under the receiver operating characteristic (ROC) curve of miR-145 for diagnosis of cervical cancer in patients was 0.878, of which the sensitivity and the specificity were 0.905 and 0.822, respectively. The area under the ROC curve of miR-205 was 0.881, of which the sensitivity and the specificity was 0.869 and 0.889, respectively. Among all patients, the relative expression level of miR-145 was significantly lower while the relative expression level of miR-205 was considerably higher in HPV-positive patients than those of HPV-negative groups ($P<0.001$). Parauterine invasion, FIGO stage III-IV and lymphatic metastasis were considered as independent factors that affect the expression of miR-145. FIGO stage III-IV and lymphatic metastasis were independent factors affecting the expression of miR-205. Conclusion: The low expression level of miR-145 and the high expression level of miR-205 in patients with cervical cancer demonstrate a certain diagnostic value in cervical cancer. The expression level of miR-145 and miR-205 is correlated with HPV infection and cervical tumor malignancy.

Keywords: miRNA-145, miRNA-205, cervical cancer, human papillomavirus infection, diagnosis, pathological features

Introduction

Cervical cancer is a common gynecological malignancy, whose incidence ranks fourth among all female tumors worldwide [1, 2]. The incidence of cervical cancer has been found to be high in low- and middle-income countries, ranking second in gynecological tumors, and the diagnosis of this disease is often in the late stages in these countries [3, 4]. Studies have shown that a considerable number of patients with cervical cancer in China are already in advanced stages when diagnosed, they are then prone to relapse after surgery, leading to poor prognosis. Therefore, early diagnosis and early radical resection can be of great importance to the good prognosis of cervical cancer patients [5, 6]. Studies have revealed that more that 94% of cervical cancer patients are positive for human papillomavirus (HPV), but clinical studies have reported that less than 1% of HPV-positive patients will develop cervical cancer [7].

MicroRNA (miRNA) is widely studied in tumors, and over 50% of human malignant tumors are related to miRNAs [8, 9]. MiRNA-145 (miR-145) is highly expressed in ovarian, uterine, heart and other embryonic tissues and in the genitals [10]. However, some studies have demonstrated that miR-145 is not only downregulated and has anti-tumor effect in breast cancer, colon cancer, etc., but also has been proven to play an important role in the initiation and development of heart disease [11-14]. MiRNA-205 (miR-205) is a double-edged sword, which can either promote or suppress cancer development depending on tumor types. Previous stud-

Table 1. Q-PCR primer sequences

Primer	Forward primer 5'-3'	Reverse primer 5'-3'
miR-145	TGCGCGTCCAGTTTTCCCAGGAA	CCAGTGCAGGGTCCGAGGTATT
miR-205	TCCACCGGAGTCTGTCTCAT	GCTGTCAACGATACGCTACG
U6	CGGGTTTGTTTTGCATTTGT	AGTCCCAGCATGAACAGCTT

Note: miR-145, miRNA-145; miR-205, miRNA-205.

ies have reported that low expression level of miR-205 exerts a tumor suppressive effect in breast cancer, colorectal cancer, and ovarian cancer [15-17]. While in liver cancer, it functions as both tumor suppressor and promoter [18, 19]. However, studies on the expression and dynamic changes of these miRNAs in cervical cancer are very limited. This study investigated the expression levels of miR-145 and miR-205 in patients with cervical cancer, and leveraged the data to analyze their diagnostic value in cervical cancer. In addition, the correlation between miR-145, miR-205 and clinicopathological characteristics of cervical cancer or HPV infection were also studied.

Materials and methods

General information

One hundred and forty-four cervical tissue samples were collected from diagnosed and suspected patients in The First Affiliated Hospital of University of South China (March 2015 to August 2020). The patients were 25-71 years old, in which 84 patients were confirmed by pathology with cervical cancer, with an average age of 43.1±10.0 years, and 60 patients were diagnosed with cervical intraepithelial neoplasia, with an average age of 42.8±9.8 years. Thirty patients with cervicitis, with an average age of 43.6±9.7 years, were also selected for prospective research purposes. All participants signed an informed consent form. The study was approved by the Ethics Committee of The First Affiliated Hospital of University of South China.

Inclusion and exclusion criteria

Inclusion criteria: (1) Diagnosis of cervical cancer or cervical intraepithelial neoplasia or cervicitis; (2) Age between 18-75 years old; (3) All patients were underwent cervical biopsy or radical cervical cervix surgery in The First Affiliated Hospital of University of South China to obtain cervical tissues. The specimens were collected from pathological and normal tissues, respectively, which were stored in a -80°C freezer [20].

Exclusion criteria: (1) Patients with incomplete clinical data; (2) Patients with severe heart, liver, kidney and other diseases; (3) Patients with mental illness or cerebrovascular disease; (4) Patients with other cancers or who were without primary cervical cancer.

Clinical and pathological staging

The clinical staging and pathological staging of 84 cervical cancer samples were evaluated according to the diagnostic criteria in UICC/AJCC, 7th edition [21].

Methods

Detection of the relative expression levels of miR-145 and miR-205 in cervical tissues: Cervical tissue specimens, 2-3mm, were removed from the freezer. The expression levels of the miRNAs were measured via fluorescence real-time quantitative polymerase chain reaction (Q-PCR; ABI 7500, ABI Applied Biosystems, USA). Trizol kit (Molecular Research Center, USA) was applied to extract total RNA. Forward and reverse primers were designed and provided by Guangzhou Ruibo Biotechnology Company. Then, reverse transcription kit (Fernentas, Canada) was used to reverse transcribe miRNA into cDNA by reverse transcription PCR (RT-PCR), by which cDNA was used as a template for DNA amplification. Finally, the expression levels of miR-145 and miR-205 in cervical tissue samples were determined by fluorescence Q-PCR. The reaction system of reverse transcription kit (Fernentas, Canada) was 25 μL, including SYBR premix (2X) 12.5 μL, forward and reverse primers of target genes 0.5 μL each, cDNA template 2.0 μL, ddH_2O 9.5 μL. Reaction conditions were set up as pre-denaturation for 5 min at 95°C, 1 cycle, then denaturation for 10 s at 98°C, annealing for 10 s at 60°C, extension for 30 s at 68°C, with 40 cycles in total, finally 10 min at 72°C. PCR-amplified products were measured via fluorescence Q-PCR. The relative expression levels were quantified by the $2^{-\Delta\Delta CT}$ method using U6 miRNA as a reference. Primer sequences were shown in **Table 1**.

Table 2. Comparison of miR-145 and miR-205 expression levels in three groups of patients and the normal group ($\bar{x}$ ± sd)

Group	Case	miR-145 expression level	miR-205 expression level
Normal	174	1.956±0.792	0.564±0.205
Cervicitis	30	1.868±0.840	0.507±0.191
Cervical intraepithelial neoplasia	60	0.888±0.423***,###	0.814±0.318***,###
Cervical cancer	84	0.449±0.198***,###,@@@	1.245±0.349***,###,@@@
F	-	111.462	71.123
P	-	<0.001	<0.001

Note: Compared with the normal group, ***P<0.001; compared with the cervicitis group, ###P<0.001; compared with the cervical intraepithelial neoplasia group, @@@P<0.001. miR-145, miRNA-145; miR-205, miRNA-205.

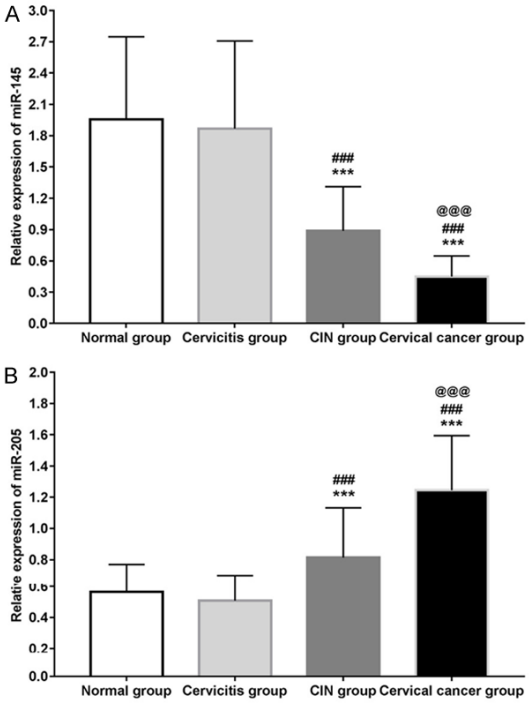

Figure 1. Comparison of miR-145 and miR-205 expression levels in three groups of patients and the normal group. A: The comparison of miR-145 expression levels in different groups; B: The comparison of miR-205 expression levels in different groups. Compared with the normal group, ***P<0.001; compared with the cervicitis group, ###P<0.001; compared with the cervical intraepithelial neoplasia group, @@@P<0.001. miR-145, miRNA-145; miR-205, miRNA-205.

HPV-DNA detection in cervical specimens: PCR was conducted on cervical specimens, and the second generation hybrid capture method was used to identify 14 high-risk types of HPV. DNA level was used to determine whether there was infection or not, by which DNA level was equal to or greater than 1 ng/L was regarded as positive, otherwise it was considered as negative.

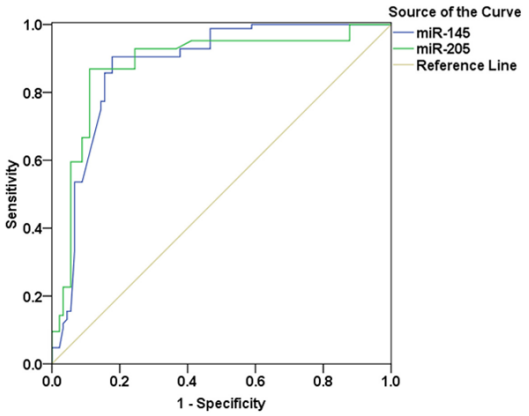

Figure 2. The ROC curve of miR-145 and miR-205 for the diagnosis of cervical cancer. ROC: receiver operating characteristic; miR-145, miRNA-145; miR-205, miRNA-205.

Outcome measures

Expression levels of miR-145, miR-205 and HPV-DNA were compared in the three groups of patients.

Receiver operating characteristic (ROC) curve was used to predict the diagnostic value of miR-145 and miR-205 for cervical cancer between the cervical cancer group and the combined group in relation to the other three.

Pathological characteristics and expression levels of miR-145 and miR-205 were investigated in 84 cervical cancer samples.

Statistical analysis

SPSS 17.0 software was applied for statistical analysis. The quantitative data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). The t test was used to analyze the data that was normally distributed with equal variance. If the

Table 3. Comparison of HPV infection among three groups of patients ($\bar{x} \pm sd$)

Group	HPV-positive rate
Cervicitis (n=30)	6 (20.00)
Cervical intraepithelial neoplasia (n=60)	29 (48.33)***
Cervical cancer (n=84)	83 (98.81)***,###
χ^2	78.831
P	<0.001

Note: Compared with the cervicitis group, ***P<0.001; compared with the cervical intraepithelial neoplasia group, ###P<0.001. miR-145, miRNA-145; miR-205, miRNA-205; HPV, human papillomavirus.

Table 4. Comparison of miR-145 and miR-205 expression levels in HPV-positive and -negative groups ($\bar{x} \pm sd$)

Group	miR-145 expression level	miR-205 expression level
HPV-positive (n=118)	0.619±0.467	1.107±0.411
HPV-negative (n=56)	1.311±0.794	0.708±0.328
t	7.029	6.363
P	<0.001	<0.001

Note: miR-145, miRNA-145; miR-205, miRNA-205; HPV, human papillomavirus.

data was not in a normal distribution or without equal variance, the rank sum test was carried out. Data among multiple groups was analyzed via one-way analysis of variance (ANOVA) and Tukey's post hoc test. ROC diagnostic curve was applied to evaluate the diagnostic value of miR-145 and miR-205 in cervical cancer. Figures were created with Medcalc software. AUC greater than 0.7 was considered as the better diagnostic value, and P<0.05 indicated a statistically significant difference.

Results

Comparison of miR-145 and miR-205 expression levels in three groups of patients and the normal group

The relative expression level of miR-145 in the cervical cancer group was significantly lower than that of the normal group, cervicitis group and cervical intraepithelial neoplasia group, while the relative expression level of miR-205 was considerably higher in the cervical cancer group than that of the normal group, cervicitis group and cervical intraepithelial neoplasia group (P<0.001). The relative expression level of miR-145 was notably lower, whereas the relative expression level of miR-205 was remarkably higher in the cervical intraepithelial neoplasia group, respectively, compared with the normal group and cervicitis group (P<0.001; **Table 2** and **Figure 1**).

The diagnostic value of miR-145 and miR-205 for cervical cancer

The area under the ROC curve of miR-145 for diagnosis of cervical cancer was 0.878 (95% CI: 0.724-0.933), P<0.001. When miR-145 was at the cut-off value of 0.675, the Youden index was 0.727, the specificity was 0.822, and the sensitivity was 0.905. The area under the ROC curve of miR-205 for diagnosis of cervical cancer was 0.881 (95% CI: 0.825-0.938), P<0.001. When miR-205 was at the cut-off value of 1.005, the Youden index was 0.758, specificity was 0.889 and the sensitivity was 0.869 (**Figure 2**).

Comparison of HPV infection among the three groups of patients

The HPV infection rates of the cervical cancer group and cervical intraepithelial neoplasia group were significantly higher compared with the cervicitis group (P<0.001), and the HPV infection rate of the cervical cancer group was considerably higher in comparison to cervical intraepithelial neoplasia group (P<0.001; **Table 3**).

Comparison of miR-145 and miR-205 expression levels in HPV-positive and -negative groups

The relative expression level of miR-145 was significantly lower, whereas the relative expression level of miR-205 was considerably higher in HPV-positive patients compared with the negative group (P<0.001), see **Table 4**.

Comparison of clinical and pathological features and miR-145 and miR-205 relative expression levels among 84 cervical cancer patients

In the scenarios of tumor volume equal to or greater than 5 cm, parauterine invasion, FIGO stage III-IV, and lymphatic metastasis, miR-145 expression was significantly downregulated whereas miR-205 expression was notably upregulated (P<0.05; **Table 5**).

Table 5. Comparison of clinical and pathological features and miR-145 and miR-205 relative expression levels among 84 cervical cancer patients ($\bar{x} \pm sd$)

Category	Case	miR-145	T	P	miR-205	t	P
Age			0.573	0.568		0.241	0.810
≥50 years	48	0.412±0.254			1.244±0.349		
<50 years	36	0.442±0.213			1.262±0.323		
Pathological type			0.099	0.921		0.250	0.803
Squamous cell carcinoma	75	0.425±0.259			1.238±0.342		
Adenocarcinoma	9	0.434±0.241			1.268±0.324		
Tumor volume			3.928	<0.001		3.937	<0.001
≥5 cm	49	0.325±0.178			1.426±0.398		
<5 cm	35	0.521±0.279			1.124±0.257		
Histological grade			0.691	0.492		1.642	0.105
Well-differentiated	18	0.439±0.264			1.196±0.287		
Moderately- and poorly-differentiated	66	0.399±0.204			1.352±0.374		
Parauterine invasion			2.567	0.012		2.570	0.012
Yes	15	0.315±0.186			1.389±0.373		
No	69	0.513±0.284			1.168±0.285		
FIGO staging			3.217	0.002		3.472	<0.001
I-II	68	0.547±0.297			1.154±0.269		
III-IV	16	0.307±0.178			1.439±0.371		
Lymphatic metastasis			3.439	<0.001		4.115	<0.001
Yes	64	0.529±0.257			1.162±0.254		
No	20	0.315±0.189			1.468±0.387		

Note: miR-145, miRNA-145; miR-205, miRNA-205.

Table 6. Multivariate logistic regression analysis of the expression of miR-145 and miR-205 and the clinical and pathological characteristics of cervical cancer

Factor	Independent variable	Outcome
Tumor volume	X1	≥5 cm=1, <5 cm=0
Parauterine invasion	X2	Yes=1, No=0
FIGO staging	X3	III-IV=1, I-III-II=0
Lymphatic metastasis	X4	No=1, Yes=0

Note: miR-145, miRNA-145; miR-205, miRNA-205.

Multivariate logistic regression analysis of the expression levels of miR-145 and miR-205 and the clinical and pathological characteristics of cervical cancer

If the expression level of miR-145 was greater than 0.449 (mean value) or miR-205 expression level was greater than 1.245 (mean value), it was considered as high expression, otherwise as low expression. The expression levels of miR-145 and miR-205 were used as dependent variables, and variables with differences in univariate analysis were selected as independent variables, including tumor size, parauterine invasion, FIGO staging, and lymphatic metastasis. After variable screening via the Ward method, multivariate logistic regression analysis was carried out, which found that parainvasion, FIGO stage III-IV and the presence of lymphatic metastasis were independent factors that affected the expression of miR-145, while FIGO stage III-IV and the presence of lymphatic metastasis were independent factors affecting the expression of miR-205 (**Tables 6**-**8**).

Discussion

The early diagnosis of malignant tumors has gained increasing attention in clinical practice. Reliable and accurate biomarkers in patients' serum that are applied in early diagnosis csn have a positive impact on the prognosis of patients. The diagnosis of cervical cancer patients using clinical signs, symptoms and commonly used tumor indicators can lead to a lack of specificity in the tumor diagnosis. As a

Table 7. Multivariate logistic regression analysis of miR-145

Factor	β	SE	Wald value	OR value (95% CI)	P
Tumor volume	0.706	0.854	0.156	0.065 (0.023-0.223)	0.417
Parauterine invasion	1.941	0.702	7.832	7.102 (1.726-27.369)	0.004
FIGO staging	1.125	0.312	3.214	3.954 (1.769-8.246)	0.016
Lymphatic metastasis	1.016	0.279	3.123	3.792 (1.742-7.693)	0.002

Note: miR-145, miRNA-145.

Table 8. Multivariate logistic regression analysis of miR-205

Factor	β	SE	Wald value	OR value (95% CI)	P
Tumor volume	0.763	0.821	0.169	0.079 (0.037-0.236)	0.427
Parauterine invasion	0.674	0.849	0.579	1.841 (0.379-10.268)	0.423
FIGO staging	1.243	0.436	3.436	3.469 (1.462-9.025)	0.027
Lymphatic metastasis	1.123	0.302	3.256	3.687 (1.982-9.743)	0.016

Note: miR-205, miRNA-205.

result, some patients miss the best time for the early diagnosis and treatment, causing the delay of the treatment [3, 4].

With the development of gene sequencing, it has been found that some non-coding RNAs (MicroRNAs, miRNAs) suppress or promote the process of tumor initiation, development, invasion and metastasis [22]. Studies have reported the abnormal expression of miRNAs in patients with cervical cancer as well, in which miRNAs can also inhibit or promote the proliferation of cervical cancer cells [23]. Research on the role of miR-145 in tumors has found that it mainly inhibits cancer cell development; however, miR-145 expression is downregulated in patients [24]. A study has demonstrated that the expression level of miR-145 is low in lung cancer tissues, and has further found that the lower the expression level of miR-145, the shorter the recurrence time, therefore, the low expression level of miR-145 is an indicator of poor prognosis [25]. Another study has also demonstrated that the expression level of miR-145 is low in colorectal cancer tissues. Restoration of miR-145 to the normal expression level has revealed a significant inhibitory effect on the proliferation of cancer cells [26]. Investigation of cervical cancer has found that miR-145 can downregulate myosin VI expression to inhibit the proliferation and migration of cervical cancer cells and reduce the invasion of cancer cells [27]. Previous studies on miR-205 have demonstrated the abnormal expression of miR-205 in endometrial cancer and non-small cell lung cancer, which promotes the proliferation and migration of cancer cells and can be used as a biomarker for early diagnosis [28]. Another study has reported that knockout of the suppressor of miR-205 results in the upregulation of its expression, which promotes the proliferation and malignant progression of cancer cells [29]. This study has also revealed the downregulation of miR-145 and upregulation of miR-205 in cervical cancer tissues. Further investigation has shown that miR-145 and miR-205 have a diagnostic value in cervical cancer and can serve as biomarkers in the early diagnosis of cervical cancer, which is consistent with the previous studies.

Research on HPV infection has reported that more than 94% of cervical cancer patients who are tested are HPV-positive [7]. Our study has also showed that HPV infection is positive in 98.81% of cervical cancer cases, which is consistent with previous investigations. Studies have demonstrated that HPV infection can inhibit the expression of miR-145, whose overexpression can inhibit the replication of HPV genes [30]. For HPV-positive cervical cancer patients, the expression level of miR-205 is significantly higher in cervical cancer tissues than that of normal tissues [31]. In this paper, we also reported that the expression level of miR-145 is low in HPV-positive patients, whereas the expression level of miR-205 is high, which is in accordance with previous results. Previous studies on the relationship between the clinical and pathological characteristics of cervical cancer and miR-145 have found that the low expression level of miR-145 is correlated with

clinical staging, lymphatic metastasis, and peripheral vascular infiltration [32]. High expression level of miR-205 can promote cervical cancer progression, and the expression of miR-205 is associated with tumor staging, lymphatic metastasis, and the depth of tissue invasion [33]. Our study has elucidated that tumors≥5 cm, parauterine invasion, FIGO stage III-IV, and lymphatic metastasis are correlated with the expression of miR-145 and miR-205, and multivariate logistic regression analysis demonstrates that parauterine invasion, FIGO stage III-IV and the lymphatic metastasis are independent factors that affect the expression of miR-145, while FIGO stage III-IV and the lymphatic metastasis are independent factors that influence the expression of miR-205.

There are some caveats in our study. For example, the sample size is small, our study is only done in a single-center, and the mechanism has not been studied. Thus, the molecular mechanism investigation and a multi-center randomized controlled research is warranted future studies.

In summary, the low expression level of miR-145 and abnormally high expression level of miR-205 in patients with cervical cancer have shown a clear diagnostic value in cervical cancer. The expression of miR-145 and miR-205 is correlated with HPV infection and tumor malignancy.

Disclosure of conflict of interest

None.

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