European Review for Medical and Pharmacological Sciences 2020; 24: 1697-1703

Diagnostic significance of serum miR-26b and miR-21 expressions in ovarian cancer and their associations with clinicopathological characteristics and prognosis of patients

K.-W. SONG[1], Q.-G. ZHANG[2], W.-B. TAN[2], Y.-N. FANG[1]

[1]Department of Obstetrics, The First People's Hospital of Jining, Jining, China
[2]Department of Basic Medicine, Jining Medical University, Jining, China

Abstract. – OBJECTIVE: The aim of this study was to detect the expressions of serum micro-ribonucleic acid (miR)-26b and miR-21 in ovarian cancer patients, and to explore their associations with the diagnosis, clinicopathological parameters and prognosis of ovarian cancer.

PATIENTS AND METHODS: A total of 86 patients diagnosed with ovarian cancer in our hospital from January 2014 to January 2015 were enrolled in the observation group. Meanwhile, another 86 subjects receiving physical examination in our hospital during the same period were enrolled in the control group. The expressions of serum miR-26b and miR-21 in both groups were detected *via* Real Time fluorescence-quantitative Polymerase Chain Reaction (RT-qPCR). Receiver operating characteristic (ROC) curves were plotted. Later, the clinical diagnostic value of combined detection of miR-26b and miR-21 in ovarian cancer was analyzed. Moreover, the associations of serum miR-26b and miR-21 expressions with clinicopathological characteristics and prognosis of ovarian cancer patients were explored.

RESULTS: The expression of serum miR-26b in ovarian cancer patients was significantly lower than that of healthy subjects, while miR-21 expression was markedly higher in ovarian cancer patients ($p<0.05$). The area under the ROC curve (AUC), the sensitivity and specificity of miR-26b detection, miR-21 detection and combined detection in the diagnosis of ovarian cancer were 0.753 *vs.* 0.826 *vs.* 0.916, 47.2 *vs.* 76.3 *vs.* 87.6 and 78.5 *vs.* 85.6 *vs.* 90.4, respectively. Therefore, it could be observed that both the sensitivity and specificity of combined detection were remarkably higher than those of single detection ($p<0.05$). In addition, the expressions of serum miR-26b and miR-21 were associated with clinical stage and lymph node metastasis of ovarian cancer patients, whereas it was not correlated with age and histological type. The 3-year survival rate of patients with high expression of serum miR-26b was significantly higher than that in those with low expression of serum miR-26b. However, the 3-year survival rate of patients with low expression of serum miR-21 was higher than that in those with high expression.

CONCLUSIONS: MiR-21 is highly expressed, while miR-26b is lowly expressed in the serum of ovarian cancer patients. Both of them may be involved in the incidence and development of ovarian cancer. Furthermore, combined monitoring of serum miR-26b and miR-21 has a certain value in the clinical diagnosis and treatment of ovarian cancer.

Key Words:
Ovarian cancer, MiR-26b, MiR-21.

Introduction

Currently, the morbidity rate of ovarian cancer ranks 3rd among common gynecological malignant tumors worldwide. However, its mortality rate[1] ranks 1st. The 5-year survival rate of ovarian cancer patients is approximately 30%, with un-optimistic survival outcomes. Around 50% of patients will relapse and/or die within 2 years, with an increasing morbidity rate year by year[2]. Researches have demonstrated that the serum levels of tumor markers often begin to rise in most tumors before the occurrence of imaging manifestations and clinical symptoms. Therefore, they are often used for early diagnosis and screening of tumors. In addition, searching for biomarkers with high sensitivity and specificity is the key to early diagnosis and treatment of ovarian cancer.

According to previous reports[3,4], the occurrence and development of tumors, including ovarian cancer, are closely related to micro-ribonucleic acids (miRNAs). MiRNAs can be stably expressed in the serum of tumor patients, and they may be a new type of potential tumor biomarkers[5,6]. It has been

Corresponding Author: Yanning Fang, MM; e-mail: gujuan567@163.com

found fthat miR-26b is lowly expressed in gastric cancer, liver cancer and breast cancer tissues and cells, inhibiting the proliferation of tumor cells[7,8]. However, miR-21 is highly expressed in a variety of tumors, indicating its cancer-promoting role[9,10]. However, the exact effects of miR-26b and miR-21 on ovarian cancer remain unclear.

Currently, no reports have explored the expressions of serum miR-26b and miR-21 in ovarian cancer patients. Their diagnostic significance and associations with pathological parameters and prognosis have not been fully elucidated so far. In the present study, the expressions of serum miR-26b and miR-21 in ovarian cancer patients were first detected. Their associations with the diagnosis, clinicopathological characteristics and prognosis of ovarian cancer were explored as well. Our findings might help to provide a theoretical basis for early clinical diagnosis and treatment of ovarian cancer.

Patients and Methods

Patients

This investigation was approved by the Ethics Committee of The first People's Hospital of Jining. Informed consents were obtained from all participants before the study. A total of 86 ovarian cancer patients treated in our hospital from January 2014 to January 2015 were enrolled in the observation group. Their average age was (46.1±2.8) years, with a mean body mass index (BMI) of (22.45±3.16) kg/m^2. All these patients were pathologically diagnosed with ovarian cancer after the operation. According to the International Federation of Gynecology and Obstetrics (2012 FIGO) staging and WHO grading criteria, these ovarian patients included 12 cases in stage I, 22 cases in stage II, 37 cases in stage III and 15 cases in stage IV. In terms of histological type, there were 38 cases of serous adenocarcinoma, 25 cases of mucinous adenocarcinoma, 17 cases of endometrioid adenocarcinoma and 6 cases of other types. In terms of the degree of differentiation, there were 28 cases of poor differentiation, 32 cases of moderate differentiation and 26 cases of high differentiation. Besides, lymph node metastasis, menopause and non-menopause occurred in 49, 65 and 21 cases, respectively. No patient in the observation group received radiotherapy, chemotherapy and immune or hormone therapy before the operation. Meanwhile, 86 subjects receiving physical examination in our hospital during the same period were enrolled in the control group. The average age of normal controls was (46.8±2.6) years, with a mean BMI of (22.37±2.95) kg/m^2. There were 63 cases of menopause and 23 cases of non-menopause. The age, BMI and pathological parameters were comparable between the two groups (p>0.05). All patients had complete clinicopathological data and signed informed consent.

Main Materials

Main instruments: Centrifuge (Johnson & Johnson Medical Equipment, Shanghai, China), S100 Polymerase Chain Reaction (PCR) amplifier (Bio-Rad, Hercules, CA, USA), water bath kettle (Changzhou Noki Instrument Co., Ltd., Changzhou, China), vertical electrophoresis apparatus (Bio-Rad, Hercules, CA, USA), and Tanon 1600 gel imaging system (Shanghai Tanon Technology Co., Ltd., Shanghai, China). Main reagents: lysis buffer (Qiagen, Hilden, Germany), TRIzol kit (Invitrogen, Carlsbad, CA, USA), Reverse Transcription kit (Toyobo, Osaka, Japan) and TaqMan microRNA probe (Applied Biosystems, Foster City, CA, USA). The primers were synthesized by TaKaRa (Dalian, China).

Detection Methods

Sample collection: 3 mL of fasting anterior cubital venous blood was collected from patients the next morning after admission. Later, collected samples were stored in a vacuum drying tube and centrifuged at 3000 rpm for 10 min. The supernatant was stored in a refrigerator at -80°C for use. 3 mL of venous blood was drawn from patients with recurrence within 2 years of follow-up. Meanwhile, 3 mL of fasting venous blood was drawn from subjects in the control group in the morning of physical examination as well.

Detection of serum expressions of miR-26b and miR-21: The samples were thawed, and total RNA was extracted (purity ratio: 1.8-2.0). Primers were designed based on target gene mRNA sequences using the Primer Express 3.0 software (Applied Biosystems, Foster City, CA, USA). The detection primers and probes for qPCR were synthesized. The first complementary deoxyribose nucleic acid (cDNA) strand was used as a template for PCR. Specific reaction conditions were as follows: 42°C for 20 min, 95°C for 5 min, 40 cycles of 95°C for 15 s, 60°C for 20 s, and 72°C for 15 s, 95°C for 1 min, 60°C for 30 s, and 95°C for 30 s. The experiment was repeated 3 times to reduce errors and bias. U6 was used

Table I. Primer sequences.

Gene	Primer (5 '→ 3')
MiR-26b	Forward: CCCAAGCTTAAAAACCTCCACCACGAAT Reverse: ACACTCCAGCTGGGTTCAAGTAATTCAGG
MiR-21	Forward: GCGGTAGCTTATCAGACTGA Reverse: TGCGTGTCGTGGAGTC
U6	Forward: GCTTCGGCAGCACATATACTAAAAT Reverse: CGCTTCACGAATTTGCGTGTCAT

as an internal reference. The relative expression levels of serum miR-26b and miR-21 were detected by the $2^{-\Delta\Delta Ct}$ method. The primer sequences were shown in Table I.

Diagnostic significance of serum miR-26b and miR-21: Receiver operating characteristic (ROC) curves were plotted and the critical values of serum miR-26b and miR-21 in the diagnosis of ovarian cancer were determined. Subsequently, the area under the curve (AUC) was calculated. Based on this, the diagnostic value of tumor markers was evaluated as follows: AUC≤0.5 (no diagnostic value), 0.5<AUC≤0.7 (lower diagnostic accuracy), 0.7<AUC≤0.9 (higher diagnostic accuracy) and AUC>0.9 (the highest diagnostic accuracy)[11].

Observation Indexes

All patients were followed up for 2 years by WeChat, telephone and outpatient clinic. There were 3 cases of shedding and 40 cases of recurrence. The associations of serum miR-26b and miR-21 expressions with clinicopathological characteristics and prognosis were analyzed.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA) software was used for all statistical analysis. Measurement data were expressed as ($\bar{\chi}$±s). Independent-sample *t*-test or analysis of variance (ANOVA) followed by Post-Hoc Test (Least Significant Difference) was adopted for intergroup comparison. Enumeration data were expressed as *n*, and the Chi-square test was adopted for intergroup comparison. $p<0.05$ was considered statistically significant.

Results

Expression Levels of Serum MiR-26b and MiR-21 in Patients of the Observation Group and Control Group Before the Operation

The expression level of serum miR-26b in the observation group (0.645±0.017) was significantly lower than that of the control group (1.002±0.023), and the difference was statistically significant ($p<0.05$). However, the expression level of serum miR-21 in the observation group (2.105±0.231) was markedly higher than that of the control group (1.214±0.156), and the difference was also statistically significant ($p<0.05$; Table II).

Diagnostic Value of MiR-26b and MiR-21 Levels in Ovarian Cancer

The AUC, critical value, sensitivity and specificity of miR-26b detection, miR-21 detection and combined detection in the diagnosis of ovarian cancer were 0.753 *vs.* 0.826 *vs.* 0.916, 0.854 μg/L *vs.* 1.027 μg/L *vs.* 0.890 μg/L, 47.2 *vs.* 76.3 *vs.* 87.6 and 78.5 *vs.* 85.6 *vs.* 90.4, respectively. Therefore, it could be observed that both the sensitivity and specificity of combined detection were significantly higher than those of single detection (Table III).

Associations of MiR-26b and MiR-21 with Pathological Features of Ovarian Cancer

The serum expressions of miR-26b and miR-21 were associated with clinical stage and lymph node metastasis in ovarian cancer patients ($p<0.05$), whereas were not correlated with age, menopausal status, tumor diameter, histological type and degree of differentiation ($p<0.05$; Table IV).

Table II. Expression levels of miR-26b and miR-21 in both groups.

Group	n	miR-26b	miR-21	*t*	*p*
Observation group	86	0.645±0.017	2.105±0.231	7.348	0.000
Control group	86	1.002±0.023	1.214±0.156	8.167	0.000

Table III. Diagnostic value of detection of miR-26b and miR-21 levels in ovarian cancer.

Gene	AUC	Critical value (μg/L)	Youden index	95% CI	Sensitivity	Specificity
miR-26b	0.753	0.854	0.702	0.708-0.825	47.2	78.5
miR-21	0.826	1.027	0.754	0.821-0.932	76.3	85.6
miR-26b + miR-21	0.905	0.890	0.818	0.817-0.953	87.6	90.4

Associations of Serum Expressions of MiR-26b and MiR-21 with Prognosis of Ovarian Cancer Patients

In miR-26b high-expression group and miR-26b low-expression group, the median survival time and accumulative survival rate were 24 months *vs.* 16 months and 55.68% *vs.* 19.56%, respectively. It could be seen that the accumulative survival rate in the miR-26b high-expression group was markedly higher than that of the miR-26b low-expression group, showing statistically significant differences (χ^2=6.547, p<0.05). Besides, in miR-21 high-expression group and miR-21 low-expression group, the median survival time and accumulative survival rate were 15 months *vs.* 26 months and 20.00% *vs.* 56.52%, respectively. The results demonstrated that the accumulative survival rate in the miR-21 low-expression group was significantly higher than that of the miR-21 high-expression group (χ^2=5.782, p<0.05; Figure 1).

Discussion

The onset of ovarian cancer is insidious, making it difficult for early detection and effective resection. Ovarian cancer cells are easy to tolerate radiotherapy and chemotherapy, ultimately leading to tumor recurrence and treatment failure. Currently, ovarian cancer seriously threatens the life health of patients. Previous scholars have demonstrated that the levels of serum tumor markers begin to rise in most tumors before the occurrence of imaging manifestations and clinical symptoms. Therefore, they are often used for early diagnosis and screening of tumors. Furthermore, searching for markers is of great significance in the diagnosis, treatment and prognosis of ovarian cancer[12,13].

MiRNAs are involved in the physiological processes of growth and differentiation of human cells. Meanwhile, they participate in pathological processes such as inflammation and cancer development.

Table IV. Associations of miR-26b and miR-21 with pathological features of ovarian cancer.

Pathological parameter	*n*	miR-26b	*t/F*	*p*	miR-21	*t/F*	*p*
Age (years old)	86						
≥60	49	0.642±0.015	0.312	0.817	2.109±0.224	0.228	0.921
<60	37	0.651±0.012			2.012±0.186		
Menopausal status							
Menopause	65	0.640±0.016	0.386	0.724	2.113±0.217	0.315	0.912
Non-menopause	21	0.654±0.011			2.010±0.188		
Tumor diameter (cm)							
≥3	51	0.638±0.014	0.423	0.645	2.120±0.189	0.514	0.583
<3	35	0.657±0.010			2.009±0.175		
Histological type							
Serous adenocarcinoma	38	0.653±0.017	0.512	0.573	2.004±0.173	0.645	0.515
Mucinous adenocarcinoma	25	0.648±0.015			2.012±0.178		
Endometrioid adenocarcinoma	17	0.633±0.014			2.110±0.186		
Other types	6	0.625±0.012			2.142±0.191		
Degree of differentiation			0.489	0.612		0.606	0.520
High	26	0.651±0.013			2.057±0.176		
Moderate	32	0.642±0.014			2.108±0.183		
Poor	28	0.627±0.012			2.139±0.187		
Lymph node metastasis			2.230	0.010		2.015	0.013
Yes	49	0.593±0.009			1.614±0.153		
No	37	0.725±0.021			2.786±0.302		
FIGO stage			1.024	0.041		1.425	0.032
I-II	34	0.602±0.013			1.623±0.156		
III-IV	52	0.714±0.019			2.657±0.285		

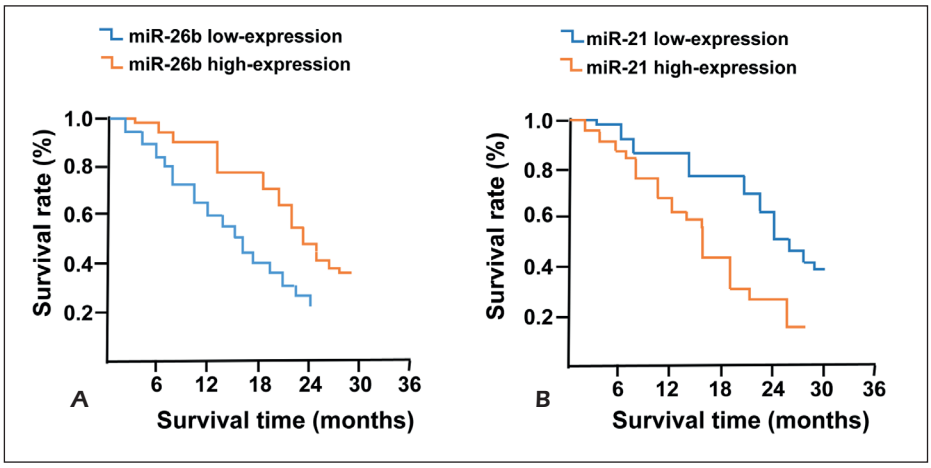

Figure 1. Associations of miR-26b **A**, and miR-21 **B**, expression levels with accumulative survival rate of ovarian cancer patients. The median survival time is prolonged in the miR-26b high-expression group compared with that in the miR-26b low-expression group ($p<0.05$). However, it is markedly longer in the miR-21 low-expression group compared with that in the miR-21 high-expression group ($p<0.05$).

The normal expression of miRNAs can regulate cell proliferation and differentiation. However, their abnormal expressions can lead to the increased incidence and development of tumors[14]. Moreover, the expressions of miRNAs are closely related to cell growth, differentiation, proliferation, metastasis and apoptosis[15,16]. Previous studies have demonstrated that miRNAs have close correlations with the occurrence and development of tumors. High-throughput chip detection technique has demonstrated that significant differences are observed in the expressions of miRNAs between normal tissues and tumor tissues, with tissue specificity. Fortunately, miRNAs can be detected in serum and plasma in the human body, bringing hope for the development of non-invasive diagnostic markers[17]. In addition, miRNAs exist stably in plasma and serum. Their expressions are consistent among different individuals in the same species, making miRNAs possible to be used as tumor markers. Although the mechanism of miRNAs in the blood of tumors is controversial, tumors do affect the levels of miRNAs in the blood[18].

MiR-26 is mainly enriched in the heart, with no cardiac specificity. Its family members include miR-26b, miR-26a-1 and miR-26a-2. Cancer is considered a genetic disease, during which these genes can act as either oncogenes or tumor suppressor genes. Among them, miR-26b is abnormally expressed in a variety of tumor tissues, which also plays the role of oncogene or tumor suppressor gene in different tumors[19,20]. This indicates that miR-26b has tumor specificity. Numerous reports have found that miR-26b is significantly down-regulated in various human cancers, acting as a tumor suppressor gene. MiR-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting USP9X[21]. Meanwhile, it suppresses the NF-κB signaling pathway and enhances the chemosensitivity of hepatocellular carcinoma cells *via* targeting TAK1 and TAB3[22]. In addition, miR-26b can inhibit the growth of a variety of human tumor cells, such as colon cancer, cervical cancer and breast cancer[23-25].

MiR-21 is highly expressed in malignant tumors, such as lung cancer, prostate cancer and liver cancer[26-28]. Therefore, most scholars believe that it plays an oncogenic role in many human cancers. However, there are controversies about the expression of miR-21 in ovarian cancer. It is mostly believed that miR-21 is highly expressed in ovarian cancer, acting as an oncogene. Our results showed that the expression of miR-21 was significantly up-regulated in ovarian cancer patients compared with healthy subjects ($p<0.05$). Meanwhile, its expression level was associated with clinicopathological stage and lymph node metastasis of ovarian cancer ($p<0.0.5$). These findings suggested that miR-21 might regulate the occurrence and development of ovarian cancer as an oncogene. However, its specific mechanism of action remains unclear, which requires further research with larger sample size.

In the present work, the serum expression of miR-26b in ovarian cancer patients was lower than that of healthy subjects, while miR-21 expression was higher in ovarian patients ($p<0.05$). The expressions of miR-26b and miR-21 were associated with clinical stage and lymph node metastasis in ovarian cancer patients, whereas were not correlated with age and histological type. In addition, the 3-year survival rate was significantly higher in patients with high expression of miR-26b than that in those with low expression. However, the 3-year survival rate was markedly higher in patients with low expression of miR-21 than that of those with high expression ($p<0.05$). The above results demonstrated that miR-21 was highly expressed while miR-26b was lowly expressed in the serum of ovarian cancer patients.

Both of them were associated with the occurrence, development and prognosis of ovarian cancer.

Currently, ovarian cancer is mainly diagnosed by means of imaging and pathological examination. However, there is inevitably missed diagnosis, and the diagnosis rate of early ovarian cancer is extremely low. Early detection depends on highly sensitive markers. The distinction between tumors and non-tumors depends on specific markers as well. Meanwhile, the localization of tumor relies on specific markers in tissues and organs. Moreover, the levels of tumor markers are related to the volume and stage of tumors, which is helpful to evaluate the prognosis. However, tumor markers are diverse and complicated at present. Neither sensitivity nor specificity is satisfactory, seriously limiting the screening and auxiliary diagnosis of tumors. Finally, this leads to a relatively low detection rate. MiRNAs can resist RNase degradation by forming the lipoprotein complex, which can stably exist in the blood. Meanwhile, they can be detected by repeated purification. Therefore, the invasive examination is reduced, making the detection convenient, simple and effective, and is suitable for early clinical screening for ovarian cancer. This study manifested that combined detection of miR-26b and miR-21 exhibited high sensitivity and specificity in the diagnosis of ovarian cancer, and the AUC was up to 0.916. All these findings indicated that serum miR-26b and miR-21 could be served as ideal diagnostic markers for ovarian cancer.

Conclusions

Our results show that combined monitoring of serum miR-26b and miR-21 has certain value in the clinical diagnosis and treatment of ovarian cancer, which is expected to raise the early detection rate of ovarian cancer.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

1) Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.
2) Li J, Feng L, Tian C, Tang YL, Tang Y, Hu FQ. Long noncoding RNA-JPX predicts the poor prognosis of ovarian cancer patients and promotes tumor cell proliferation, invasion and migration by the PI3K/Akt/mTOR signaling pathway. Eur Rev Med Pharmacol Sci 2018; 22: 8135-8144.
3) Guo TY, Xu HY, Chen WJ, Wu MX, Dai X. Downregulation of miR-1294 associates with prognosis and tumor progression in epithelial ovarian cancer. Eur Rev Med Pharmacol Sci 2018; 22: 7646-7652.
4) Jiang JH, Lv QY, Yi YX, Liao J, Wang XW, Zhang W. MicroRNA-200a promotes proliferation and invasion of ovarian cancer cells by targeting PTEN. Eur Rev Med Pharmacol Sci 2018; 22: 6260-6267.
5) Chin LJ, Slack FJ. A truth serum for cancer--microRNAs have major potential as cancer biomarkers. Cell Res 2008; 18: 983-984.
6) Zhao YN, Chen GS, Hong SJ. Circulating microRNAs in gynecological malignancies: from detection to prediction. Exp Hematol Oncol 2014; 3: 14.
7) Lu J, He ML, Wang L, Chen Y, Liu X, Dong Q, Chen YC, Peng Y, Yao KT, Kung HF, Li XP. MiR-26a inhibits cell growth and tumorigenesis of nasopharyngeal carcinoma through repression of EZH2. Cancer Res 2011; 71: 225-233.
8) Deng M, Tang HL, Lu XH, Liu MY, Lu XM, Gu YX, Liu JF, He ZM. miR-26a suppresses tumor growth and metastasis by targeting FGF9 in gastric cancer. PLoS One 2013; 8: e72662.
9) Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Menard S, Palazzo JP, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin GA, Querzoli P, Negrini M, Croce CM. MicroRNA gene expression deregulation in human breast cancer. Cancer Res 2005; 65: 7065-7070.
10) Moriyama T, Ohuchida K, Mizumoto K, Yu J, Sato N, Nabae T, Takahata S, Toma H, Nagai E, Tanaka M. MicroRNA-21 modulates biological functions of pancreatic cancer cells including their proliferation, invasion, and chemoresistance. Mol Cancer Ther 2009; 8: 1067-1074.
11) Fischer JE, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. Intensive Care Med 2003; 29: 1043-1051.
12) Yu Y, Zhang X, Tian H, Zhang Z, Tian Y. Knockdown of long non-coding RNA HOTAIR increases cisplatin sensitivity in ovarian cancer by inhibiting cisplatin-induced autophagy. J BUON 2018; 23: 1396-1401.
13) Suh DH, Kim HS, Chang SJ, Bristow RE. Surgical management of recurrent ovarian cancer. Gynecol Oncol 2016; 142: 357-367.
14) Blower PE, Chung JH, Verducci JS, Lin S, Park JK, Dai Z, Liu CG, Schmittgen TD, Reinhold WC, Croce CM, Weinstein JN, Sadee W. MicroRNAs modulate the chemosensitivity of tumor cells. Mol Cancer Ther 2008; 7: 1-9.
15) Wang S, Olson EN. AngiomiRs--key regulators of angiogenesis. Curr Opin Genet Dev 2009; 19: 205-211.
16) Gounaris-Shannon S, Chevassut T. The role of miRNA in haematological malignancy. Bone Marrow Res 2013; 2013: 269107.
17) Witwer KW. Circulating microRNA biomarker studies: pitfalls and potential solutions. Clin Chem 2015; 61: 56-63.
18) Nelson KM, Weiss GJ. MicroRNAs and cancer: past, present, and potential future. Mol Cancer Ther 2008; 7: 3655-3660.

19) Palumbo T, Faucz FR, Azevedo M, Xekouki P, Iliopoulos D, Stratakis CA. Functional screen analysis reveals miR-26b and miR-128 as central regulators of pituitary somatomammotrophic tumor growth through activation of the PTEN-AKT pathway. Oncogene 2013; 32: 1651-1659.
20) Liu XX, Li XJ, Zhang B, Liang YJ, Zhou CX, Cao DX, He M, Chen GQ, He JR, Zhao Q. MicroRNA-26b is underexpressed in human breast cancer and induces cell apoptosis by targeting SLC7A11. FEBS Lett 2011; 585: 1363-1367.
21) Shen G, Lin Y, Yang X, Zhang J, Xu Z, Jia H. MicroRNA-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting USP9X. BMC Cancer 2014; 14: 393.
22) Zhao N, Wang R, Zhou L, Zhu Y, Gong J, Zhuang SM. MicroRNA-26b suppresses the NF-kappaB signaling and enhances the chemosensitivity of hepatocellular carcinoma cells by targeting TAK1 and TAB3. Mol Cancer 2014; 13: 35.
23) Zhang Z, Kim K, Li X, Moreno M, Sharp T, Goodheart MJ, Safe S, Dupuy AJ, Amendt BA. MicroRNA-26b represses colon cancer cell proliferation by inhibiting lymphoid enhancer factor 1 expression. Mol Cancer Ther 2014; 13: 1942-1951.
24) Dong J, Sui L, Wang Q, Chen M, Sun H. MicroRNA-26a inhibits cell proliferation and invasion of cervical cancer cells by targeting protein tyrosine phosphatase type IVA 1. Mol Med Rep 2014; 10: 1426-1432.
25) Li J, Kong X, Zhang J, Luo Q, Li X, Fang L. Correction: MiRNA-26b inhibits proliferation by targeting PTGS2 in breast cancer. Cancer Cell Int 2013; 13: 17.
26) Liu XG, Zhu WY, Huang YY, Ma LN, Zhou SQ, Wang YK, Zeng F, Zhou JH, Zhang YK. High expression of serum miR-21 and tumor miR-200c associated with poor prognosis in patients with lung cancer. Med Oncol 2012; 29: 618-626.
27) Folini M, Gandellini P, Longoni N, Profumo V, Callari M, Pennati M, Colecchia M, Supino R, Veneroni S, Salvioni R, Valdagni R, Daidone MG, Zaffaroni N. miR-21: an oncomir on strike in prostate cancer. Mol Cancer 2010; 9: 12.
28) Zhang J, Jiao J, Cermelli S, Muir K, Jung KH, Zou R, Rashid A, Gagea M, Zabludoff S, Kalluri R, Beretta L. miR-21 inhibition reduces liver fibrosis and prevents tumor development by inducing apoptosis of CD24+ progenitor cells. Cancer Res 2015; 75: 1859-1867.