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Down-Regulation of miRNA-34a, -143 and -212 in the Serum of Patients with Ovarian Cancer

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Abstract

Introduction: Ovarian cancer is one of the most common gynecological malignancy, ranking sixth in frequency and seventh for mortality. Because of the late stage at diagnosis, 5-years survival of patients is remaining below 50% and almost 70% of women present at late stages of carcinogenesis. Expression profile of circulating miRNAs in serum have emerged as potential biomarkers for early detecting various types of diseases including cancer. Present project investigated the expression profile of miRNA-34a, miRNA-143 and miRNA-212 in the serum of 30 ovarian cancer patients and 30 healthy subjects.

Materials and methods: 5 cc of whole blood was collected from each participant and total RNA was extracted using acid guanidinium-phenol-chloroform methods. Expression of targeted miRNAs was evaluated after cDNA synthesis using Real-Time PCR methods.

Results: Our results showed expression levels of miRNA-34a (P<0.0001), miRNA-143 (P=0.028) and miRNA-212 (P<0.0001) were significantly decreased in patients with ovarian cancer compare to controls. Data from Receiver Operating Characteristic (ROC) curve analysis has shown that expression profile of these miRNAs could act as potential biomarker for diagnosis of ovarian cancer patients.

XRCC3 Thr241Met polymorphism has been associated with cancer susceptibility. Studies have shown a relationship between Thr241Met polymorphism and gastric cancer. The present study was aimed at examining the presence of XRCC3 Thr241Met polymorphism in patients diagnosed with gastric cancer in the city of Macapá. We analyzed 150 DNA samples, of which 100 comprised the control group and 50 were case patients. Our findings revealed that 76% of case samples had the Thr/Met genotype (OR (CI 95% 54.29 (18.84-156.38) p ≤ 0.0001) whereas in the control group, the same genotype represented 7%. Also, most gastric cancer patients with XRCC3 241 Met polymorphism were heterozygotes. Given the small sample size in this study, a larger number of patients will be analyzed.

Keywords: Ovarian cancer; Biomarkers; Gastric cancer; Carcinogenesis

Introduction

Among females worldwide, ovarian cancer is one of the most common gynecological malignancies, ranking sixth in frequency and seventh for mortality [1,2]. The incidence of the disease has been estimated at 9.4 per 100,000 in more developed country, and 3.9 per 100,000 in Iranian population [1,3]. Because of few early or specific symptoms shared with many more common gastrointestinal and gynecological conditions and lack of reliable screening methods, almost 70% of women present at late stages of carcinogenesis [2,4]. Many efforts have recently been made in order to identify new and better markers to aid the diagnosis of ovarian cancer.

MicroRNAs (miRNAs) are small, 19-25 nucleotide non-coding RNA molecules that negatively regulate gene expression by translation inhibition or mRNA degradation after targeting the 3′UTR [5-8]. Dysregulation of miRNAs have been demonstrated in many types of cancer [7,9,10]. Several studies have demonstrated that miRNA expression profiles could be used as prognostic biomarkers in cancer. Because serum and/or plasma are relatively easy to access, circulating miRNAs are one of the most promising candidates for the diagnosis of cancer [10,11]. Therefore, identifying a unique serum miRNA expression profile could potentially help early diagnosis and treatment of patients with ovarian cancer.

Low transcript levels of miRNA-34a has been detected and associated with tumor progression in ovarian cancer, and also reduced miRNA-34a expression in a variety of cell lines and mouse models have been reported [7,12-14]. Earlier studies have revealed that miRNA-34a is a transcriptional target of p53 which positively regulates its expression [15]. Tp53 have showed potential effect in progress of various cancers [16,17]. It has been shown that down-regulation of miRNA-34a has been associated with many proteins such as BCL-2, C-MYC, SNAIL, and SIRT1 that are involved in the cell cycle and cell survival pathways [15,18]. So, miRNA-34a could be an interesting target for diagnosis and treatment of many cancers.

miRNA-143 and miRNA-212 should be studied, because their expression has been deregulated in many types of cancer [19,20]. Down-regulation of miRNA-143 in colon, gastric, prostate and other cancers has been reported [21,22]. *In vitro* studies have demonstrated that miRNA-143 targets 3'-UTR of BCL-2 mRNA and causes BCL-2 protein down-regulation. These findings suggest that miR-143 acts as tumor suppressor and could be a potential target for cancer therapy [8,21]. In addition, miRNA-143 has been found to directly interferes

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multiple mRNAs such as KRAS, ELK1, MYO6, ERK5, and hexokinase 2 (HK2), which then are involved in the pathogenesis of cancers [19,23]. The miR-212 is highly conserved in vertebrates. Although, increased miRNA-212 expression has been reported in colorectal carcinoma but it's down-regulation has been associated with many types of cancer [24-26]. A study on lung cancer cell lines revealed that overexpression of miR-212 reduced proliferation and migration, and led to cell cycle arrest through modulating the expression of p21 and cyclin D1 [27].

The expression levels of miRNA-34a, miRNA-143, and miRNA-212 has not been measured in the serum of patients with ovarian cancer. To the best our knowledge this is the first study to evaluate the expression levels of these miRNAs in the serum of patients with ovarian cancer. The aim of this study is the expression levels of miRNA-34a, miRNA-143, and miRNA-212 in the serum of women with ovarian cancer in compare to controls.

Materials and Methods

Samples: Sample collection was done after histopathological diagnosis of ovarian cancer, and those who received treatment (i.e., chemotherapy and radiotherapy) were excluded from this study. Signed written informed consent was obtained from patients undergoing surgery for ovarian cancer at Shahid Sodoughi Hospital (Yazd, Iran). A total of 30 patients were with epithelial ovarian cancer. Control subjects were healthy women, who admitted to the hospital for check-ups, and none of them had been diagnosed with a malignancy nor have any viral infection. The median age of Control subjects was 50 years and ranged from 35 to 67 years. Table 1 summarizes the clinical characteristics of patients. Five milliliters of whole blood were collected from each patient (n = 30) and control (n=30), and serum was immediately separated and stored at -80°C.

RNA extraction and cDNA synthesis

Acid guanidinium-phenol-chloroform methods by Ambion™ TRIzol™ Reagent (Invitrogen, Waltham, Massachusetts, USA) was used to extract total RNA from serum samples. After treatment with DNase I (Thermoscientific, Canada) to eliminate DNA contamination, three micrograms of total RNA from each sample were subjected to reverse transcription using the NG dART RT kit (EURX, Poland) and specific stem-loop primers (Table 2) for each of the selected miRNAs, according to the manufacturer's instructions.

Real-time PCR

Quantitative real-time PCR was performed by Rotor-Gene Q (Qiagen, Hilden, Germany). The expression levels of selected miRNAs were evaluated using Forward specific primers for each miRNA and universal reverse primer that is complementary to a sequence within the RT stem-loop primers, 1 µl of RT product, and RealQ PCR 2x Master Mix Green (AMPLIQON, Odense, Denmark). The sequences of all primers used in this study are listed in Table 2. The thermal reaction condition was as follows: initial denaturation at 95°C for 15 min, followed by 40 cycles of denaturation at 95°C for 30 sec, annealing at 62°C for 30 sec, and extension at 72°C for 30 sec. Real-time PCR was carried out in final reaction volume of 20 µl. Melting curves were plotted at the end of each cycle series to verify the purity of the products The expression levels of miRNA-34a, miRNA-143, and miRNA-212 were normalized to the miRNA-103a as an internal control, and ΔCts were calculated by the difference between Ct of the target miRNAs and Ct of miRNA-130a. Relative expression was calculated by 2-ΔΔCt formula [28].

Characteristic	No (%)
Age	
30-39	5 (0.16)
40-49	6 (0.2)
50-59	15 (0.5)
60-69	4 (0.13)
Stage	
III	21 (0.7)
IV	9 (0.3)
Histologic subtypes	
Serous	25 (0.83)
Others	5 (0.16)

Table 1: Patient Characteristics (N=30).

Targets	cDNA synthesis primer (stem loop)
miRNA34a-3p	5′GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTG-CACTGGATACGACAGGGCA3′
miRNA143-3p	5′GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTG-CACTGGATACGACGAGCTA3′
miRNA212-3p	5′GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTG-CACTGGATACGACGGCCGT3′
miRNA103a-3p	5′GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTG-CACTGGATACGACTCATAG3′
Real time PCR primers (Forward)	
miRNA34a-3p	5′CACGCACAATCAGCAAGTATAC3′
miRNA143-3p	5′CACGCATGAGATGAAGCACTG3′
miRNA212-3p	5′CACGCATAACAGTCTCCAGTC3′
miRNA103a-3p	5′CACGCAAGCAGCATTGTACAGGG3′
Real time PCR primer (Reverse)	
Universal	5′-CCAGTGCAGGGTCCGAGGTA-3′

Table 2: List and sequence of all primers used in this study.

Statistical Analysis

Statistical tests were carried out using SPSS (SPSS, Chicago, IL, USA) and Graphpad Prism version 6.0 (Graphpad Prism Software, Inc., San Diego, CA). Shapiro–Wilk test was performed for analyzing normal distribution of data, and student t-test or Mann-Whitney U-test was used to analyze relative expression of each miRNA between patients and healthy controls. Data were expressed as the mean ± standard error of the mean (SEM), and P-value lower than 0.05 ($P<0.05$) was considered statistically significant.

Results

Expression of studied miRNAs in the serum of patients

Statistical analysis of ΔCt values revealed that the expression levels of miRNA-34a and miRNA-212 significantly decreased in the serum of patients with ovarian cancer compared to healthy controls. As shown in Figure 1, the expression level of miRNA-34a (Fold change= 0.059; P value<0.0001) and miRNA-212 (Fold change=0.024; P value<0.0001) has significant differences in patients compared to healthy controls. Also, the expression level of miRNA-143 (Fold change=0.15; P value=0.028) has decreased in patients with ovarian cancer compared to healthy controls (Figure 1). This data suggesting that the down-regulation of miRNA-43a, miRNA-143 and miRNA-212 might be involved in the pathogenesis of ovarian cancer.

Expression profile of miRNA-34a, miRNA-143 and miRNA-212 could be used as potential biomarkers for identifying patients with ovarian cancer.

To examine whether the expression profile of studied miRNAs

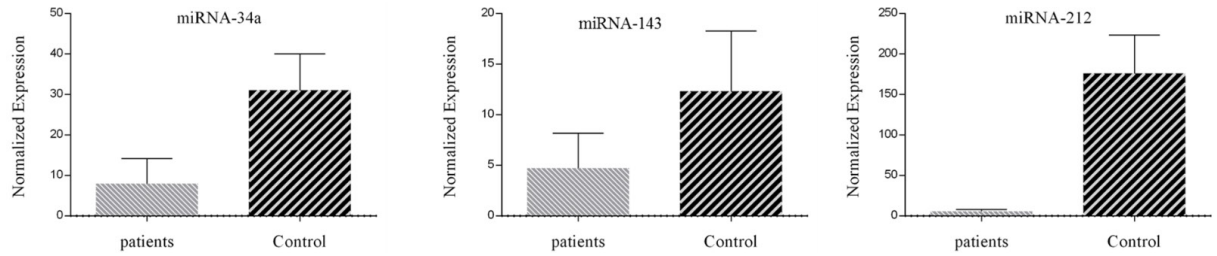

Figure 1: Expression level of miRNA-34a, miRNA-143 and miRNA-212 in the serum of patients with ovarian cancer (n=30) and healthy subjects (n=30). Expression levels of miRNA-34a (p<0.0001), miRNA-143 (p=0.028) and miRNA-212 (p<0.0001) were significantly down-regulated in ovarian cancer patients. miRNA-103 was used as an internal control for normalization. Error bars indicate means ± standard errors of the mean.

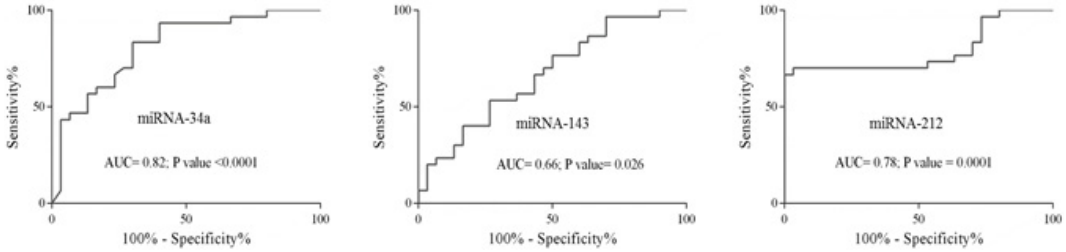

Figure 2: Result of ROC curve analysis for miRNA-34a, miRNA-143 and miRNA-212 expression as a potential biomarker.

Targets	Correlation with	Patients		Controls	
		r	P values	r	P values
miRNA-34a	miRNA-143	0.403	0.027	0.419	0.021
	miRNA-212	0.424	0.02	0.427	0.019
miRNA-143	miRNA-212	0.561**	0.001	0.287	0.125
** Significant P values (<0.01)					

Table 3: Correlation of the expression levels of studied miRNAs.

could act as potential biomarkers, receiver operating characteristic (ROC) curve analysis was performed and the area under the ROC curve (AUC) was calculated. Data from ROC curve analysis revealed that the expression profile of miRNA-34a (AUC=0.82; P value<0.0001), miRNA-143 (AUC= 0.66; P value=0.026) and miRNA-212 (AUC=0.78; P value=0.0001) could be used as potential biomarker for discriminating patients with ovarian cancer (Figure 2).

Spearman correlation test showed that the expression level of miRNA-143 and miRNA-212 has a significant positive correlation (rs=0.56; P value=0.001) with ovarian cancer (Table 3).

Discussion

Previous evidence indicate that dysregulation of miRNAs might play an important role in the pathogenesis of ovarian cancer. However, many of this study have been done on the expression of miRNAs in tumor tissues and cells [2,12]. miRNAs expression profile in tumor tissues could provide precise and accurate data for diagnosis of many types of cancer including ovarian cancer tissues. Recently, circulating miRNAs in blood serum have emerged as potential biomarkers for detecting various types of diseases including cancer [29-31]. Because of the late stage at diagnosis, 5-years survival of ovarian cancer patients is usually remain below 50% and almost 70% of women present at late stages of carcinogenesis [12,32]. Circulating miRNA profiling could improve early detection of ovarian cancer, and more successful treatment.

In this project, the expression profile of miRNA-34a, miRNA-143 and miRNA-212 in the serum of 30 ovarian cancer patients and 30 healthy subjects were evaluated. Our results revealed that the expression of these miRNAs significantly down-regulated in serum of patients compared to healthy subjects. down-regulation of miRNA-34a, miRNA-143 and miRNA-212 could be associated with pathogenesis of ovarian cancer and over-expression of these miRNAs could be a promising strategy for treating ovarian cancer.

Various studies revealed that dysregulation of miRNA-34a, miRNA-143 and miRNA-212 is involved in the pathogenesis of many types of cancer. Through suppressing of targeted genes including Bcl-2 Family, BRCA1, ERK5, and Snail1, these miRNAs regulate cellular processes such as cell growth, cell cycle, apoptosis, and MET that are important processes involved in the pathogenesis of many cancers [12,18,23,24,33,34]. A stud by Corney et al. have revealed that miRNA-34a expression is decreased in p53 mutant ovarian tumors. The transcription factor and tumor suppressor p53 is a direct trans-activator of gene that encoding miRNA-34a. However, their results have also demonstrated that the expression level of miRNA-34a was decreased in p53 wild-types tumors [12]. Their results suggesting that not only shared p53-dependent transactivation, also are controlling the expression of miRNA-34a in tumors with wild type p53. Study by Jin et al. has shown that decreased expression of miRNA-34a is associated with poor prognosis of gallbladder cancer. They indicated that miRNA-34 act as a tumor suppressor and overexpression of it resulted in reduced xenograft tumors [34]. These findings in accordance with our results indicate that miRNA-34a may serve as a tumor suppressor gene in ovarian cancer.

miRNA-143 significantly inhibits cell proliferation and promotes apoptosis, at least in part, through suppression of the expression of Bcl-2 [8,19,33]. Liu et al. have demonstrated that transfection of HeLa cells with pre-miRNA-143 could significantly decrease their proliferation and increased apoptosis. Also, they found that expression of miRNA-143 was decreased in cancerous cervical tissues compared to non-tumor tissues [8]. Wang et al. also showed that the expression of miRNA-143 was down-regulated in colon cancer but not in rectal

cancer [35]. It is believed that no previous studies have reported the expression profile of miRNA-143 in ovarian cancer, and this is the first study that revealed the down-regulation of miRNA-143 in the serum of ovarian cancer patients.

To date, many studies have indicated the down-regulation of miRNA-212 in many cancer and a few studies reported the overexpression of miRNA-212 in some cancers [24,25,27,36,37]. Incoronato et al. revealed that the miRNA-212 expression was decreased both *in vivo* and *in vitro* in lung cancer [36]. Also, Wei et al. found that the expression of miRNA-212 was significantly down-regulated in both tissue and serum of epithelial ovarian cancer patients. Their results have revealed that overexpression of miRNA-212 in ovarian cancer cells could inhibit cell proliferation, migration, and invasion [38].

Conclusion

Present results provided evidence for the association of expression profile of miRNA-34a, miRNA-143 and miRNA-212 with ovarian cancer. Expression profile of these miRNAs could serve as useful biomarkers for early identifying ovarian cancer.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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