Current Problems in Cancer 43 (2019) 167–176

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

A six-microRNA signature predicts survival of patients with uterine corpus endometrial carcinoma

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ARTICLE INFO

Keywords:
Uterine corpus endometrial carcinoma
Biomarker
MicroRNA
Survival

ABSTRACT

Uterine corpus endometrial carcinoma (UCEC) is one of the most common female gynecological malignant tumors that threaten women health seriously. MicroRNAs (miRNAs) has been proved to play critical roles in tumor pathogenesis and malignant progression. In this study, we aimed to explore a novel signature of microRNA expression for predicting the overall survival (OS) of patients with UCEC. The genome-wide miRNA expression profiles and relevant clinical characteristics of 348 patients with UCEC were downloaded from the Cancer Genome Atlas (TCGA) data portal and analyzed comprehensively. A total of 144 miRNAs were confirmed to be expressed differentially in tumor tissues. Among them, 6 miRNAs (hsa-mir-15a.MIMAT0000068, hsa-mir-142.MIMAT0000433, hsa-mir-142.MIMAT0000434, hsa-mir-3170.MIMAT0015045, hsa-mir-1976.MIMAT0009451, and hsa-mir-146a.MIMAT0000449) were validated to be significantly correlated with the OS of patients with UCEC. The risk indictor established by the 6-microRNA signature was proved be an independent prognostic factor (Hazard ratio = 0.391; 95% CI: 0.195-0.783; $P = 0.008$). In conclusion, we identified

☆ Support for the study was provided by the National Natural Science Foundation of China (No. 31571443 to QY), the Jilin Provincial Science and Technology Department (No. 20150101121JC to QY), and the Health and Family Planning Commission of Jilin Province (No. 2014Z068 to QY).

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https://doi.org/10.1016/j.currproblcancer.2018.02.002

miRNAs that were correlated with the occurrence and progression of UCEC and established a 6-microRNA expression signature as a predictor for the OS of patients with UCEC.

Introduction

Uterine corpus endometrial carcinoma (UCEC) is one major malignant tumor of female reproductive system, which is derived from the inner lining cells of the uterus and pose a great threat to the health of women worldwide.[1,2] UCEC accounts for about 20%-30% of female reproductive system tumors second only to cervical cancer.[3] However, the prognosis of UCEC is poor especially in patients with recurrence or metastasis after surgery or radiotherapy. The etiological mechanism of UCEC has not been elucidated completely. As we know, the potential risk factors are as follows: (1) the unstable level estrogen after menopause; (2) a family history of endometrial carcinoma; and (3) obesity, infertility, diabetes, and hypertension, etc.[4-6] The early clinical symptoms of patients with UCEC include postmenopausal or perimenopausal vaginal irregular bleeding, pelvic cramping, and abdominal pain. Owing to the lack of early diagnosis, many patients with UCEC miss the best treatment strategy.[7,8] Thus it is imperative to identify a novel biomarker at molecular level to predict prognosis in a quick, sensitive, and accurate way for patients with UCEC.

MicroRNAs (miRNAs) are a unique class of endogenous and small noncoding RNAs, which are about 18 to 25 nucleotides in length. They mainly alter gene expression at posttranscriptional level by base-pairing with the 3′-untranslated region (3′UTR) of their target mRNAs completely or incompletely.[9] Translation inhibition and mRNA degradation are 2 main pathways of miRNA-guided gene regulation.[9,10] A lot of studies have indicated that multiple miRNAs expressed aberrantly in various tumors and were involved in tumor genesis and progression as oncogenes or tumor suppressor genes.[11,12] miRNAs play important roles in many biological processes such as cell cycle, proliferation, differentiation, and apoptosis to a certain extent.[13] Previous studies have demonstrated numerous miRNAs expressed abnormally in UCEC. MiR-205 was up-regulated in endometrial endometrioid carcinoma and the increased level of miR-205 may promoted cellular proliferation, migration, invasion, and inhibited apoptosis.[14,15] Ran reported that miR-218 was significantly down-expressed in Tax-resistant EC cells and overexpression of miR-218 reactivated the sensibility of paclitaxel resistant EC cells to paclitaxel through binding to the 3′UTR of HMGB1 and inhibiting HMGB1-mediated autophagy.[16]

Recently, substantial evidence also confirmed that miRNAs were detectable in serum or plasma stably and had potential to be noninvasive biomarkers for diagnosis and prognosis of various cancers. MiRNAs provided an innovative idea to screen and monitor cancer patients.[17-19] The Cancer Genome Atlas (TCGA) is a public dataset including comprehensive and coordinated genome changes in up to 33 types of cancer, which has been used to collect, select, and analyze genomic alterations in various cancers and has generated prognostic miRNA signature models in lung adenocarcinoma, cervical cancer, and glioblastoma multiforme, etc.[20-23] Although the miRNA expression data of patients with UCEC were provided in TCGA database, a similar model predicting the prognosis of patients with UCEC has not been constructed up to now. In our present study, we analyzed the genome-wide miRNAs expression data and clinical characteristics of 348 patients with UCEC from the latest UCEC data gathered in TCGA and screened out miRNAs expressed aberrantly in tumors tissues comparing to the paired adjacent tissues. Then a 6-microRNA signature model was generated and proved to be competent as an independent predictor for the overall survival (OS) of patients with UCEC.

Table 1
Univariate analysis of miRNAs associated with overall survival in patients with UCEC.

MiRNAs	HR	95% CI	*P* value[a]
hsa-mir-15a.MIMAT0000068	0.566	0.375-0.853	**0.007**
hsa-mir-142.MIMAT0000433	0.718	0.555-0.928	**0.011**
hsa-mir-142.MIMAT0000434	0.755	0.592-0.964	**0.024**
hsa-mir-3170.MIMAT0015045	0.774	0.616-0.973	**0.028**
hsa-mir-1976.MIMAT0009451	0.692	0.492-0.972	**0.034**
hsa-mir-146a.MIMAT0000449	0.799	0.642-0.995	**0.045**

[a] Statistical significant results (in bold).

Materials and methods

Data acquisition and selection

Level 3 data of 863 miRNAs expression profiles and clinical information of patients with UCEC were downloaded from TCGA data portal (http://cancergenome.nih.gov/) in May 2016. Both the miRNAs expression data and the clinical information data are open-access. Then a total of 348 patients were screened out in accordance with the following inclusion criteria: (1) miRNAs expression and clinical information (complete and evaluable) were both provided; (2) the patients with more than 30 days following-up days; and (3) the patients didn't die from other disease or accidence during the following-up days. Among the 348 patients (labeled as cohort T), 15 patients (labeled as cohort N) provided corresponding miRNAs expression of the paired adjacent tissues. We summarized the clinical characteristics of the 2 cohorts respectively in Table 1. TCGA dataset collected and processed patients' genome data complying with the data access policies which have been approved by its ethics committee, so our present study dispensed with further ethical approval.

Data processing and analysis

All miRNAs expression data were normalized through transforming them by log2. Student *t*-test was applied to compare the difference of continuous variable (age) and chi-square test was used to compare the distribution of binary variables (tumor clinical stage, tumor grade, tumor status, and vital status) between cohort N and cohort T to verify the homogeneity between them. The paired-sample *t* test was performed to find out the miRNAs expressed differently between tumor tissues and the paired adjacent tissues (setting significant *P* value as 0.001) for further analyses. The unpaired *t*-test was employed to analyze the difference of miRNAs expression levels between different clinical characteristics (setting significant *P* value as 0.01).

MiRNAs expression were transformed into binary variables—high expression group (expression level higher than the median) and low expression group (expression level lower than the median). Then the Kaplan-Meier method and the log-rank test were applied to identify miRNAs associated with the OS of patients with UCEC. The univariate cox proportional hazards regression models were used (significant *P* value was set as 0.001) to explore the relationship between the OS and factor providing clues for prognostic. Expression values of the miRNAs ($P < 0.05$ in the univariate Cox regression analysis) and survival status of the 348 patients were utilized to compute the risk score, and a miRNA expression signature was then generated by principal component model. Multivariate Cox regression analysis was applied to validate the independence of the miRNA expression signature as a factor affecting the OS. The results generated by Cox regression analysis were presented as hazard ratio (HR) and 95% CI. Unless specifically noted, all tests were 2-sides and regarded $P < 0.05$ as statistically significant difference. All the statistical analysis above was performed with Statistical Product and Service Solution 22.0 (SPSS 22.0, IBM) and BRB-Array Tools 4.5 which is developed by Dr Richard Simon and the BRBA-array Tools Development Team.[24,25]

Bioinformatic analyses

DIANA mirPath tools were applied to perform pathway enrichment analyses for miRNAs in the signature. The potential target genes were predicted by the microT-CDS (v5.0).[26] Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway enrichment and Gene ontology (GO) analysis of these target genes were carried out respectively by the mirPath v.3 with default settings.

Results

Differentially expressed miRNAs in tumor tissues comparing to the paired adjacent tissues

Based on the inclusion criteria, 348 patients (cohort T) were enrolled. Among them, 15 patients provided corresponding adjacent tissues (cohort N). All the patients were clinically diagnosed with UCEC. Their age was 64.21 ± 11.09 (mean ± SD). The median follow-up time was 22.86 ± 20.31 (mean ± SD) months. Other details of clinical characteristics of cohort T and cohort N were listed in Table S1. By a series of statistical analyses, there were no significant difference in distributions of age, median follow-up time, vital status, tumor status, and clinical stage between cohort T and cohort N.

Analysis of miRNAs expression profiles in patients of cohort N identified 144 miRNAs expressed differently ($P < 0.001$) between tumor tissues and the paired adjacent tissues, in which 129 miRNAs (89.6%) were up-expressed and 15 miRNAs (10.4%) were down-expressed in the tumor tissues (Table S2). Among the 144 differentially expressed miRNAs, 66 miRNAs exhibited a greater than 5-fold in the transformed values (Fig 1). Besides, the unsupervised hierarchical clustering discriminated the tumor and the normal class clearly with the 144 differentially expressed miRNAs (Fig 2). Class comparison analysis was conducted to explore the miRNAs related to cancer progression. Then analyses of gene differential expression identified 71, 2, and 5 miRNAs that were associated with tumor grade, tumor status, and tumor clinical stage, respectively (Table S3).

Construction of a 6-microRNA signature predicting the prognosis of patients with UCEC

Six miRNAs (hsa-mir-15a.MIMAT0000068, hsa-mir-142.MIMAT0000433, hsa-mir-142.MIMAT0000434, hsa-mir-3170.MIMAT0015045, hsa-mir-1976.MIMAT0009451, and hsa-mir-146a.MIMAT0000449) were validated to be correlated to the OS of patients with UCEC by

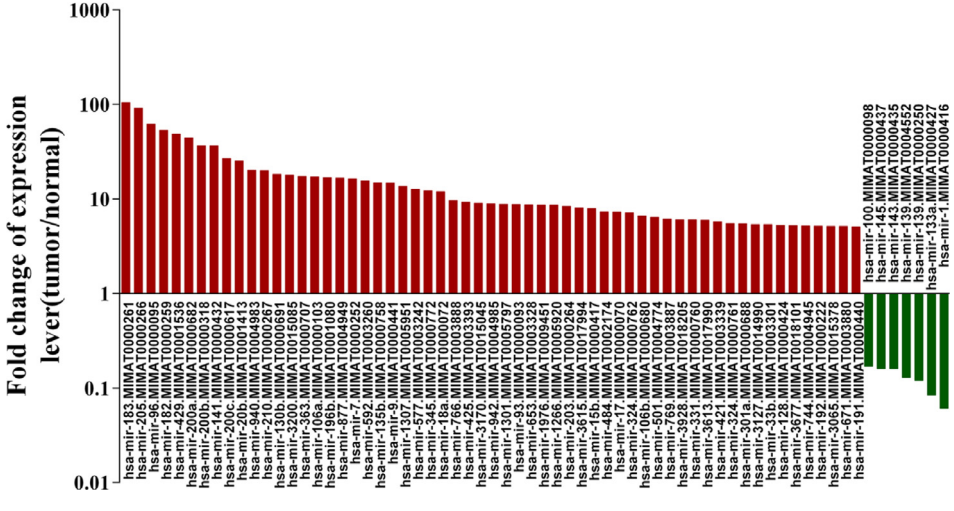

Fig. 1. Differentially expressed microRNAs between UCEC and adjacent tissues with fold-change ≥5. (Color version of figure is available online.)

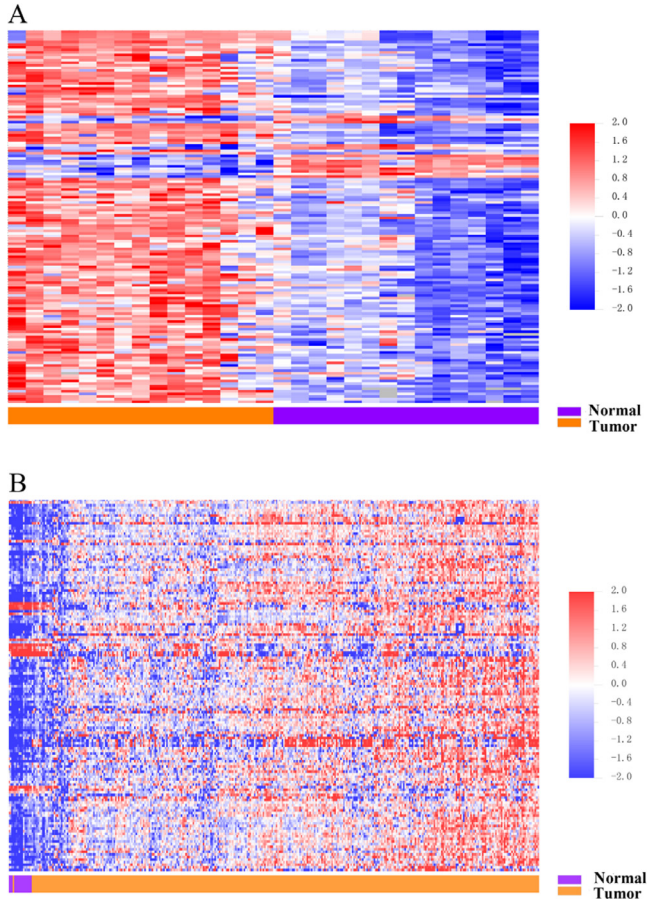

Fig. 2. Unsupervised hierarchical cluster analysis of 144 differentially expressed miRNAs. (A) Unsupervised hierarchical cluster analysis of 144 differentially expressed miRNAs in paired samples. (B) Unsupervised hierarchical cluster analysis of 144 differentially expressed miRNAs in unpaired samples. (Color version of figure is available online.).

the univariate cox regression analysis (Table 1). Kaplan-Meier survival curves indicated all of them were beneficial factors for patients with UCEC (Fig 3). Then, a 6-miRNA expression signature model was constructed by the principal component analysis with Cox proportional hazards regression. Risk score for each patient was computed by a math formula Σiwi xi +2.571281 where wi and xi are weight value and logged miRNA expression for the i-th miRNA (Risk score = (−0.038966 × logged expression of hsa-mir-15a.MIMAT0000068) + (−0.084357 × logged expression of hsa-mir-142.MIMAT0000433) + (−0.099515 × logged expression of hsa-mir-142.MIMAT0000434) + (−0.172778 × logged expression of hsa-mir-3170.MIMAT0015045) + (−0.070654 × logged expression of hsa-mir-1976.MIMAT0009451) + (−0.051031 × logged expression of hsa-mir-146a.MIMAT0000449) +2.571281). A patient would be deem as high (low) risk if his risk score was higher than (lower than) risk group.

Identification of the 6-microRNA signature as an independent predictor for the OS of patients with UCEC

The ability of the 6-microRNA signature to predict prognosis independently was examined with univariate Cox regression and multivariate Cox regression. The univariate Cox regression

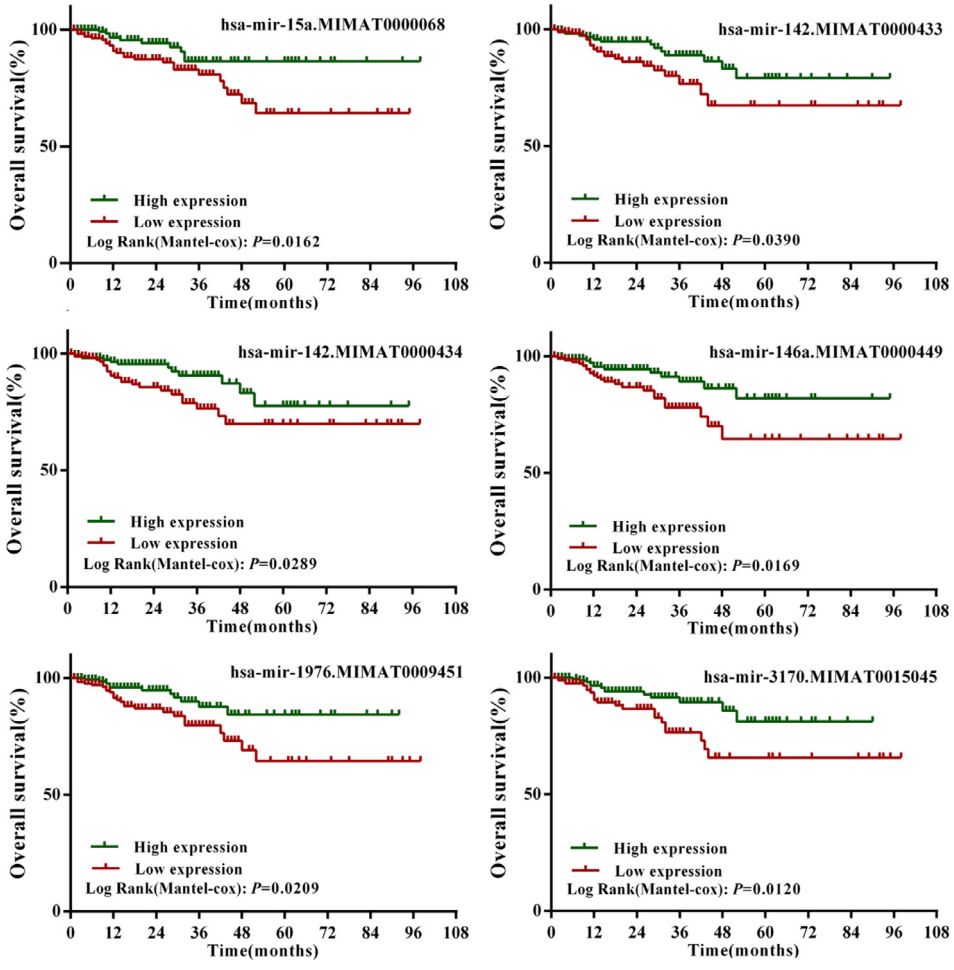

Fig. 3. Kaplan-Meier survival curves for 6 survival related miRNAs. All miRNAs (hsa-mir-15a.MIMAT0000068, hsa-mir-142.MIMAT0000433, hsa-mir-142.MIMAT0000434, hsa-mir-3170.MIMAT0015045, hsa-mir-1976.MIMAT0009451, and hsa-mir-146a.MIMAT0000449) were positively associated with overall survival. (horizontal axis: overall survival time; vertical axis: survival function). (Color version of figure is available online.)

analyses were conducted to evaluate the ability of clinical parameters (age, tumor status, tumor clinical stage, and tumor grade) and the 6-microRNA signature to predict the OS for patients with UCEC. The results showed that tumor status ($P < 0.001$), tumor clinical stage ($P < 0.001$), tumor grade ($P = 0.004$), and the 6-microRNA signature ($P = 0.008$) were significantly associated with the OS of patients with UCEC (Table 2). Next, Kaplan-Meier survival curves were applied and demonstrated the distribution of survival time in different states of significant variables above (Fig 4). Furthermore, the significant variables above were put into a multivariate cox regression model with conditional forward method and independent predictors for the OS of patients with UCEC including the 6-microRNA signature (HR = 0.446; 95% CI: 0.218-0.913), tumor status (HR = 0.148; 95% CI: 0.063-0.348), and tumor clinical stage (HR = 0.390; 95% CI: 0.175-0.870) were identified (Table 2).

Target gene prediction and functional enrichment of the 6-microRNA signature in UCEC

The presumptive target genes of the 6 integrated-signature miRNAs were predicted by microT-CDS (v5.0). The numbers of their target genes were 898, 1011, 283, 221, 645, and 413

Table 2
Univariate and multivariate analysis of parameters associated with overall survival.

		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value[a]
Six-microRNA signature	Low risk vs high risk	0.391 (0.195-0.783)	**0.008**	0.446 (0.218-0.913)	**0.027**
Tumor status	Tumor free vs with tumor	0.081 (0.039-0.168)	**<0.001**	0.148 (0.063-0.348)	**<0.01**
Clinical stage	III + IV vs I + II	0.151 (0.074-0.307)	**<0.001**	0.390 (0.175-0.870)	**0.021**
Tumor grade	G1 + G2 vs G3 + G4	0.253 (0.099-0.652)	**0.004**	0.718 (0.257-2.007)	0.528

[a] Statistical significant results (in bold).

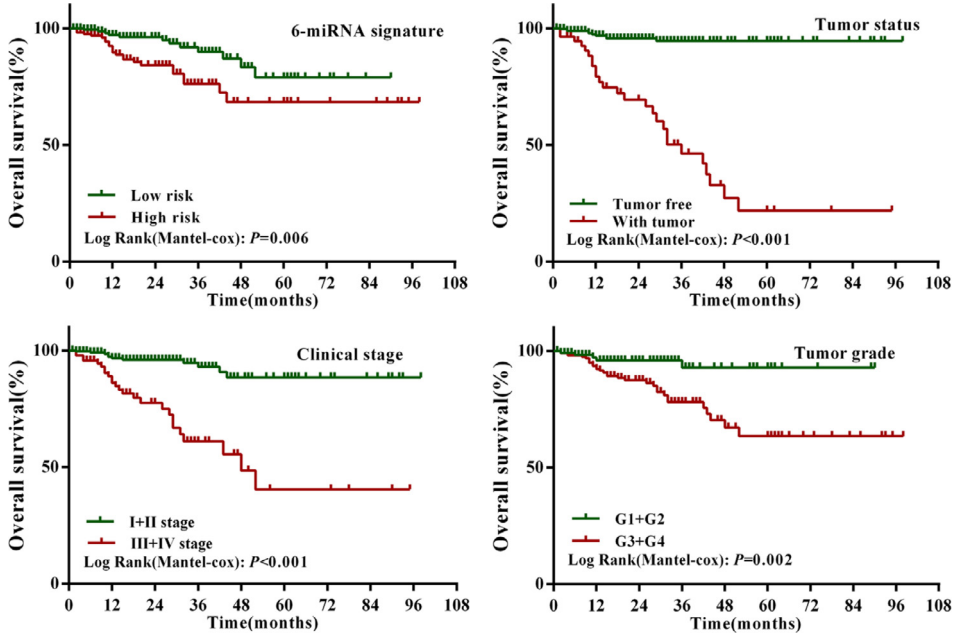

Fig. 4. Kaplan-Meier survival curves for patients with UCEC. A total of 348 patients with UCEC were compared in 2 groups according to: 6-microRNA signature (high risk vs low risk); tumor status (with tumor vs tumor free); clinical stage (III + IV stage vs I + II stage); tumor grade (G3 + G4 vs G1 + G2). (horizontal axis: overall survival time; vertical axis: survival function). (Color version of figure is available online.)

successively. In order to elucidate the biological function of these target genes, we performed a GO annotation and KEGG analyses by DIANA-mirPath v.3 with them. The GO annotation indicated these target genes were associated with cellular protein modification, biosynthetic process, neurotrophin TRK receptor signaling pathway and so on. Furthermore, the results of KEGG analyses revealed these target genes mainly function in cancer-related diseases including proteoglycans in cancer, mTOR signaling pathway, Hippo signaling pathway, FoxO signaling pathway. The top 15 GO annotation and KEGG analyses were listed respectively in Table S4.

Discussion

MiRNAs are a class of endogenous, noncoding small RNA that regulate gene expression negatively at the posttranscriptional level. They usually lead to translation inhibition or degradation

of mRNA by binding to the 3′UTR of their targeted genes.[27] In recent years, accumulating evidence have shown miRNAs play critical roles in occurrence and development of various tumors and may serve as molecular indicator for the prognosis and target for the therapy of tumors. With the appearance and abundance of TCGA data portal, miRNAs signatures as potential molecular biomarkers for diagnosis and prognosis were identified in more and more cancers such as breast cancer, hepatocellular carcinoma, colon adenocarcinoma, and esophageal cancer.[28-31] As to UCEC, several studies have demonstrated abnormal expression of miRNAs were detected and act as oncogenes or tumor suppressor genes. Chen reported that miR-10b was up-expressed in endometrium tissues and the silence of miR-10b promoted cell apoptosis and inhibited proliferation, migration, and invasion of endometrial cancer cells via regulating the expression of its target gene—HOCB3.[32] Zhao demonstrated that miR-126 was down-regulated in the EC tissues comparing to paired adjacent tissues. Upregulation of miR-126 resulted in the inhibition of migration and invasion of endometrial cancer cells by targeting IRS1.[33] However, existing studies only explored the roles of some specific miRNAs in the UCEC. A miRNA signature for the diagnosis and prognosis of the UCEC according to the analysis of aberrant expression of miRNAs in the UCEC has not been reported, to the best of our knowledge.

Here, we analyzed genome wide miRNA expression profiles of 348 patients with UCEC in TCGA data portal and found 144 miRNAs expressed differentially in tumor tissues comparing to paired adjacent tissues. The robustness of discriminative features of these 144 differentially expressed miRNAs were verified under unpaired conditions. Among them, 71 miRNAs were associated with tumor grade, 2 miRNAs with tumor status and 5 miRNAs with clinical stage when it comes to the clinical pathologic features. With univariate Cox regression analyses, 6 miRNAs (hsa-mir-15a.MIMAT0000068, hsa-mir-142.MIMAT0000433, hsa-mir-142.MIMAT0000434, hsa-mir-3170.MIMAT0015045, hsa-mir-1976.MIMAT0009451, and hsa-mir-146a.MIMAT0000449) were identified to be associated with the OS of the patients with UCEC. With Kaplan-Meier survival curves, the 6 miRNAs were all proved to be beneficial factors for the OS of patients with UCEC. Furthermore, with the stepwise Cox regression and a principal component analyses, a 6-microRNA signature was established and confirmed to be an independent predictor for the OS of UCEC. The KEGG analysis documented the 6 miRNAs in the signature above participated in regulating several important cancer-related pathways such as FoxO signaling pathway, TGF-β signaling pathway, Ras signaling pathway, and the pancreatic cancer signaling pathway. Some miRNAs in the signature serve crucial roles in the occurrence and progression of other cancers and their biological functions these cancers have been revealed before. Deng et al demonstrated that miR-142-3p was detected to be down-expressed in cervical cancer cells and overexpression of miR-142-3p inhibited proliferation and invasion of cervical cancer cells by targeting FZD7. It means that miR-142-3p serves as an inhibitor of cell proliferation and invasion in cervical cancer.[34] Chen et al reported that the expression of miR-1976 was down-regulated evidently in non–small cell lung cancer (NSCLC) tissues and the down-regulated miR-1976 usually indicated a higher TNM stage and poor prognosis. Overexpression of miR-1976 inhibited cell proliferation and metastasis in NSCLC tissues by targeting PLCE1 and may serve as a potential prognostic marker for NSCLC patients.[35] However, the exact roles of the 6 miRNAs in the signature played in the UCEC are still obscure.

Several limitation should be taken into account in the present study. Firstly, only 15 patients with UCEC provided miRNA expression data of paired adjacent tissues in TCGA data portal. Future studies with more samples would improve the accuracy of our results. Secondly, the distribution of G1 + G2 and G3 + G4 in tumor grade between cohort T and cohort N was statistically different, which would decrease the statistical power when applying the differentially expressed miRNAs in cohort N to survival analyses in cohort T. Thirdly, although the 6-microRNA signature was established through strict data screening and analyses, few studies have demonstrated the roles of the 6 miRNAs in the occurrence and progression of UCEC. We need further studies exploring specific biological functions of these 6 miRNAs respectively in the UCEC.

Conclusions

In conclusion, by analyzing the genome-wide miRNAs expression of UCEC tissues and their corresponding clinical characteristic from TCGA data portal, we validated a 6-microRNA signature that could serve as an independent predictor for the OS of patients with UCEC. However, future studies with more samples are required to validate the sensitivity and accuracy of the signature before it is applied to clinical practice.

Vitae

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Acknowledgments

The authors thank The Cancer Genome Atlas (TCGA) project for providing data and also Ye Kuang for help with preparation of the figures.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.currproblcancer.2018.02.002.

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