

Original Article

miR-200a/miR-141 and miR-205 upregulation might be associated with hormone receptor status and prognosis in endometrial carcinomas

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Abstract: The aim of this study was to compare the clinicopathological significance of miR-200a/miR-141 and miR-205 expression in endometrioid carcinomas (ECs) versus nonendometrioid carcinomas (NECs) and to assess their correlation with hormone receptor status. miR-200a/miR-141 and miR-205 expression in 154 endometrial cancers was determined by qRT-PCR. The status of estrogen and progesterone receptor (ER/PR) was assessed using immunohistochemistry. miR-200a/miR-141 and miR-205 increased significantly in ECs and in NECs. The expression level of miR-200a was significantly higher in NECs than in ECs ($P = 0.025$). Furthermore, there was a trend that NECs with worse clinicopathological variables had a higher miR-200a expression, while an inverse trend existed in ECs. miR-205 upregulation occurred frequently in NECs without lymph node metastases ($P = 0.030$), whereas such association was not present in ECs. Interestingly, in ECs, miR-200a/miR-141 upregulation occurred frequently in the hormone receptor positive subgroups than the negative subgroups ($P < 0.05$). Similarly, the expression level of miR-205 was higher in the hormone receptor positive subgroups and the association between miR-205 and PR reached statistical significance ($P = 0.024$). In contrast, in NECs, a negative correlation was found between miR-200a/miR-141 and ER or PR status. Meanwhile, in ECs, miR-200a upregulation correlated with prolonged survival in the ER positive subgroup ($P = 0.046$), whereas an inverse trend existed in the ER negative subgroup. Our findings suggest that miR-200a/miR-141 and miR-205 increased significantly in ECs and in NECs. However, they might behave differently in ECs versus NECs. miR-200a/miR-141 and miR-205 might be associated with hormone receptor status in endometrial cancer and may possess prognostic impacts.

Keywords: Endometrial carcinoma, miR-200a/miR-141, miR-205, ER, PR

Introduction

Endometrial carcinoma is the most common malignancy of the female genital tract. On the basis of clinical behavior and etiology, endometrial cancers have long been categorized into 2 major subtypes [1]. Type I tumors (approximately 80%) are endometrioid carcinomas (ECs), express estrogen and progesterone receptors (ER, PR), and usually follow a favorable course. In contrast, type II (10%-20%) tumors are non-endometrioid carcinomas (NECs) with poor prognosis and are not associated with estrogen excess. Although ECs has a relatively low mortality rate, some tumors are aggressive and insensitive to surgery, chemotherapy or radiation therapy. In fact, little knowledge of the biological differences is available to predict endo-

metrial cancer outcomes besides their pathological distinctions.

MicroRNAs (miRNAs) are small non-coding RNA elements that control cellular function by modulating the stability and translation of multiple target messenger RNAs (mRNAs) at the post-transcriptional level [2]. To date, among the differentially expressed miRNAs, miR-200 family (miR-200a/miR-141, miR-200b/miR200c/miR-429) and miR-205 are most upregulated in endometrioid samples compared to benign tissues [3, 4]. However, the difference of these miRNA expression and their implied roles in ECs versus NECs have not been extensively evaluated. Previously, based on limited number of patient samples including 15 NECs, we found that the expression levels of miR-200a/miR-

miR-200a/miR-141 and miR-205 alterations in endometrial carcinomas

Table 1. Clinicopathological features of 154 endometrial carcinomas

Variable	No. of cases	
	ECs	NECs
Total	102	52
Age	median 53.5 years, range 33-77	median 58 years, range 39-80
Grade (ECs)		
Low	73 (71.6%)	/
High	29 (28.4%)	/
Myometrial invasion ^a		
< 1/2	70 (78.7%)	29 (61.7%)
≥ 1/2	19 (21.3%)	18 (38.3%)
Lymph node metastases ^b		
No	44 (84.6%)	30 (85.7%)
Yes	8 (15.4%)	5 (14.3%)
Vessel invasion ^a		
No	75 (84.3%)	35 (74.5%)
Yes	14 (15.7%)	12 (25.5%)
Stage ^a		
I and II	79 (88.8%)	34 (72.3%)
III and IV	10 (11.2%)	13 (27.7%)
ER		
Negative	23 (22.5%)	34 (65.4%)
Positive	79 (77.5%)	18 (34.6%)
PR		
Negative	22 (21.6%)	38 (73.1%)
Positive	80 (78.4%)	14 (26.9%)

^a89 ECs patients and 47 NECs patients received hysterectomy; ^b52 ECs patients and 35 NECs patients received lymphadenectomy.

141 and miR-205 significantly increased in ECs compared with normal controls, but did not in NECs. However, this finding was not consistent with several previous studies [5-8]. On the other hand, recent studies have suggested that there maybe a link between deregulated miRNAs and steroid hormones in malignancies. Limited studies have been published on the miR-200 family in connection with breast cancer and hormone receptor status, but few focused on endometrial cancer [9]. Interestingly, in the present study, sequence analyses demonstrated estrogen and progesterone receptor binding elements in the promoter region of miR-200a/miR-141 and miR-205. In addition, the complementary sites of miR-200a/miR-141 and miR-205 were identified in the 3'UTR or CDS of ER and PR mRNA. As both hormone receptor (HR) and miRNAs have the ability to regulate genes, their interaction within cancer may take on many forms. In some cases, HR can influence expression of various miRNAs. Conversely the miRNA can regulate expression

of an HR directly or regulate HR signaling by targeting the mRNAs of HR co-regulators and target genes [10, 11].

Together, these uncertainties promote us to further characterize the expression pattern of miR-200a/miR-141 and miR-205 in a larger cohort of endometrial cancers. We hypothesized that miR-200a/miR-141 and miR-205 alterations may be associated with hormone receptor status and may possess prognostic utility.

Materials and methods

Patients and samples

Formalin-fixed, paraffin-embedded (FFPE) tissue samples of 154 endometrial carcinomas (102 endometrioid carcinomas, 52 serous carcinomas) collected between 2001 and 2014 were obtained from the Surgical Pathology files of the First Hospital, Peking University, China.

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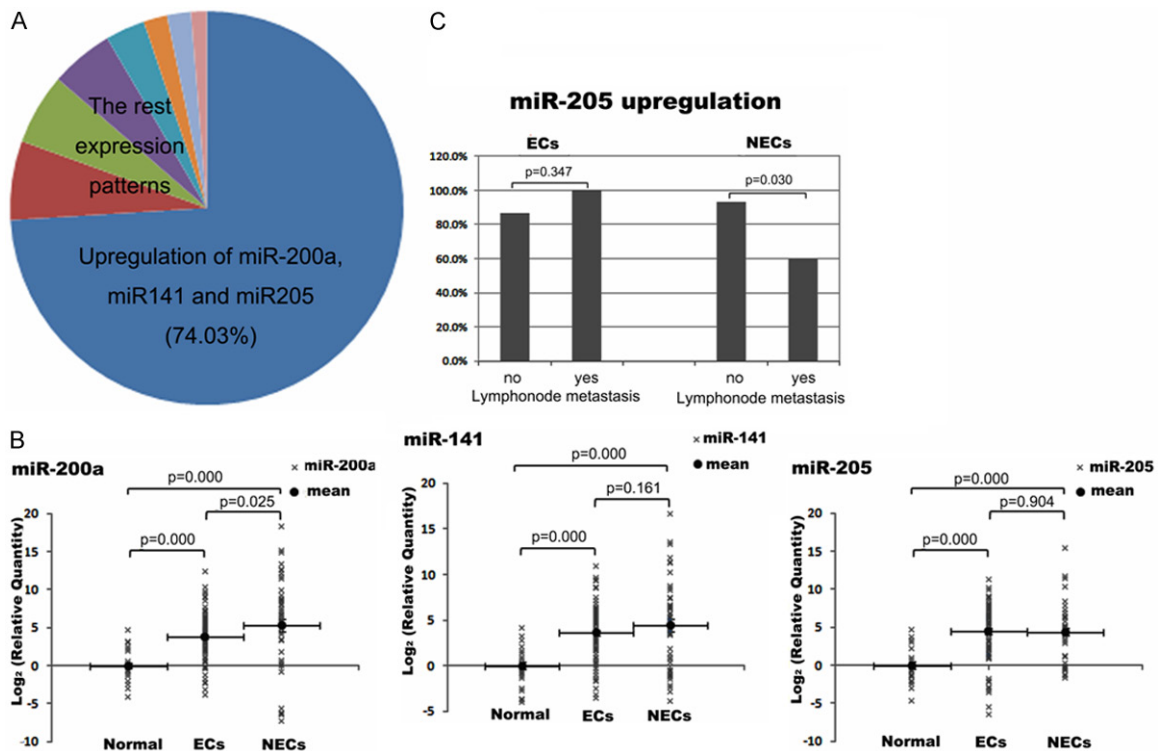


Figure 1. miR-200a/miR-141 and miR-205 alterations in endometrial cancers. A. The upregulation of miR-200a, miR-141 and miR-205 coexisted in majority of endometrial cancers. B. The expression levels of miR-200a, miR-141 and miR-205 were significantly increased in ECs as well as in NECs. In particular, miR-200a was significantly upregulated in NECs than in ECs. C. In NECs, miR-205 expression was significantly associated with the absence of lymph node metastases and the phenomenon was not present in ECs.

The clinicopathological features of all the patients are shown in **Table 1**. Twenty-six unmatched endometrial samples served as normal controls. Some endometrial carcinomas (58 ECs and 15 NECs) have been the subject of our earlier investigation [12]. The endometrial carcinoma cases were reviewed and classified using the 2014 World Health Organization criteria [13]. Tumors were staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) guidelines [14]. Additionally, inclusion criteria for all cases included the absence of any treatment prior to surgery. In the 154 cases, follow-up information was obtained for 79 patients. 72 (91.1%) Patients were alive without clinical evidence of tumor at a median interval of 25 months (range, 2-117 months). The study was approved by the institutional ethics committee.

RNA preparation and quantitative real-time PCR

Tumor samples from corresponding FFPE blocks were cut into 20- μ m fragments and total

RNA samples were extracted from the FFPE tissue using RNeasy FFPE kit (Qiagen, Crawley, UK) according to the manufacturer's instructions. The quality of the total RNA was measured using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Wilmington DE, USA). Reverse transcription and qRT-PCR amplification were performed in two steps. In the first reverse transcription step, 10 ng of RNA was used in reactions with specific stem-loop RT primer for miR-200a (ABI#000502), miR-141 (ABI#000463), miR-205 (ABI#000509), and endogenous control primer for small nuclear RNA U6 (ABI#001973). Reaction was performed with TaqMan MicroRNA Reverse Transcription Kit, according to the manufacturer's protocol (Applied Biosystems, Foster City, CA). In the second step, cDNA samples were amplified in Real Time PCR instrument 7500 (Applied Biosystems) with the specific TaqMan miR-200a, miR-141, and miR-205 assay and small nuclear RNA U6 as endogenous control. All reactions were run in triplicate, and the average threshold cycle and SD values were calculated. The relative quantity (RQ) of each miRNA

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Table 2. Comparison of clinicopathological features and expression levels of miR-200a, miR-141 and miR-205 in ECs and in NECs

Variable	Log ₂ (Relative Quantity) Mean ± SE					
	ECs			NECs		
	miR-200a	miR-141	miR-205	miR-200a	miR-141	miR-205
Grade (ECs)						
Low	3.96 ± 0.35	3.74 ± 0.33	4.29 ± 0.44	/	/	/
High	3.44 ± 0.61	3.17 ± 0.58	4.93 ± 0.53	/	/	/
<i>p</i>	0.447	0.369	0.415	/	/	/
Myometrial invasion						
< 1/2	3.57 ± 0.36	3.27 ± 0.35	4.29 ± 0.41	4.86 ± 1.13	4.16 ± 0.90	4.05 ± 0.66
≥ 1/2	3.50 ± 0.72	3.63 ± 0.49	4.26 ± 1.04	5.65 ± 1.43	4.39 ± 1.09	4.35 ± 0.88
<i>p</i>	0.921	0.622	0.975	0.663	0.876	0.787
Lymph node metastases						
No	4.32 ± 0.46	3.72 ± 0.45	4.06 ± 0.62	5.37 ± 1.00	4.71 ± 0.83	4.45 ± 0.60
Yes	3.82 ± 1.20	3.45 ± 1.03	4.00 ± 0.90	5.74 ± 1.22	4.85 ± 0.78	2.52 ± 1.38
<i>p</i>	0.679	0.818	0.971	0.884	0.947	0.233
Vessel invasion						
No	3.63 ± 0.34	3.38 ± 0.33	4.27 ± 0.44	4.93 ± 1.08	4.18 ± 0.85	4.24 ± 0.64
Yes	3.16 ± 1.01	3.15 ± 0.73	4.38 ± 0.70	5.83 ± 1.40	4.45 ± 1.07	3.93 ± 0.87
<i>p</i>	0.599	0.780	0.916	0.660	0.869	0.798
Stage						
I and II	3.62 ± 0.33	3.32 ± 0.32	4.26 ± 0.42	4.31 ± 1.08	3.81 ± 0.82	4.06 ± 0.55
III and IV	3.09 ± 1.22	3.49 ± 0.82	4.44 ± 0.76	7.38 ± 1.28	5.38 ± 1.25	4.44 ± 1.27
<i>p</i>	0.609	0.865	0.887	0.119	0.312	0.746
ER						
Negative	3.99 ± 0.72	3.00 ± 0.78	3.41 ± 0.91	6.09 ± 0.83	4.44 ± 0.76	4.40 ± 0.59
Positive	3.77 ± 0.34	3.75 ± 0.29	4.79 ± 0.36	4.01 ± 1.80	4.35 ± 1.27	4.41 ± 0.92
<i>p</i>	0.763	0.277	0.103	0.235	0.950	0.994
PR						
Negative	3.54 ± 0.75	3.04 ± 0.79	3.01 ± 0.91	6.01 ± 0.76	4.83 ± 0.70	4.26 ± 0.57
Positive	3.89 ± 0.33	3.73 ± 0.29	4.88 ± 0.36	3.64 ± 2.26	3.26 ± 1.51	4.81 ± 1.02
<i>p</i>	0.644	0.326	0.028	0.206	0.291	0.624

was calculated by the comparative CT ($2^{-\Delta\Delta CT}$) method, in which $\Delta\Delta CT$ was calculated as follows: $\Delta\Delta CT = (CT_{miR-of-interest} - CT_{U6}^{cancer}) - (CT_{miR-of-interest} - CT_{U6}^{control})$.

Immunohistochemistry

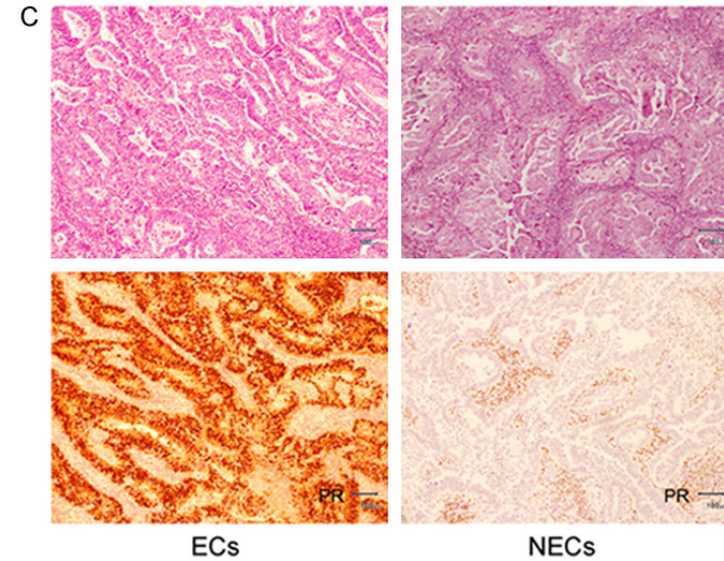
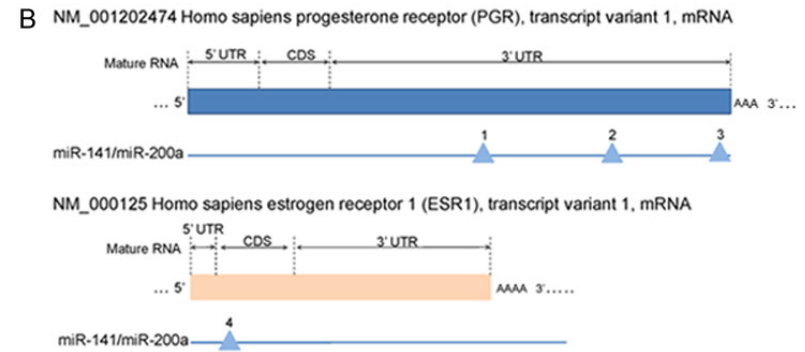
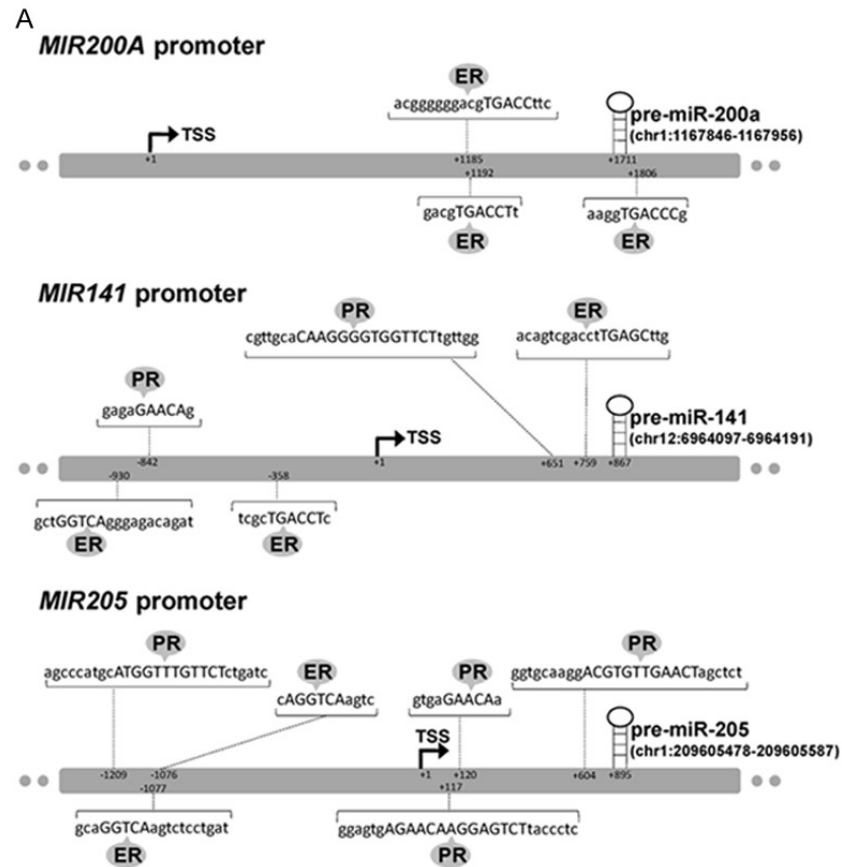
IHC Staining was performed using the Dako EnVision system on 4- μ m sections of FFPE tissue with primary antibodies against ER (1D5, Dako, Glostrup, Denmark) and PR (PgR636, Carpinteria, CA, USA). Base on our experiences and other studies, ER or PR nuclear staining in more than 10% of tumor cells was defined as ER or PR positive [15]. Normal endometrial glands and stromal cells exhibiting strong ER

and PR staining were used as positive controls. The negative control was run without the addition of the primary antibodies.

Statistical analyses

The associations between miRNA alterations and clinicopathological features were statistically analyzed with the Student's T-test and Chi-Square Test methods. Survival analysis was performed using Kaplan-Meier curves with log-rank tests. The Cox model was used to analyze the independent prognostic factors. Disease-free survival was considered as the length of time after surgery treatment until relapse, death from an unrelated disease, or the final

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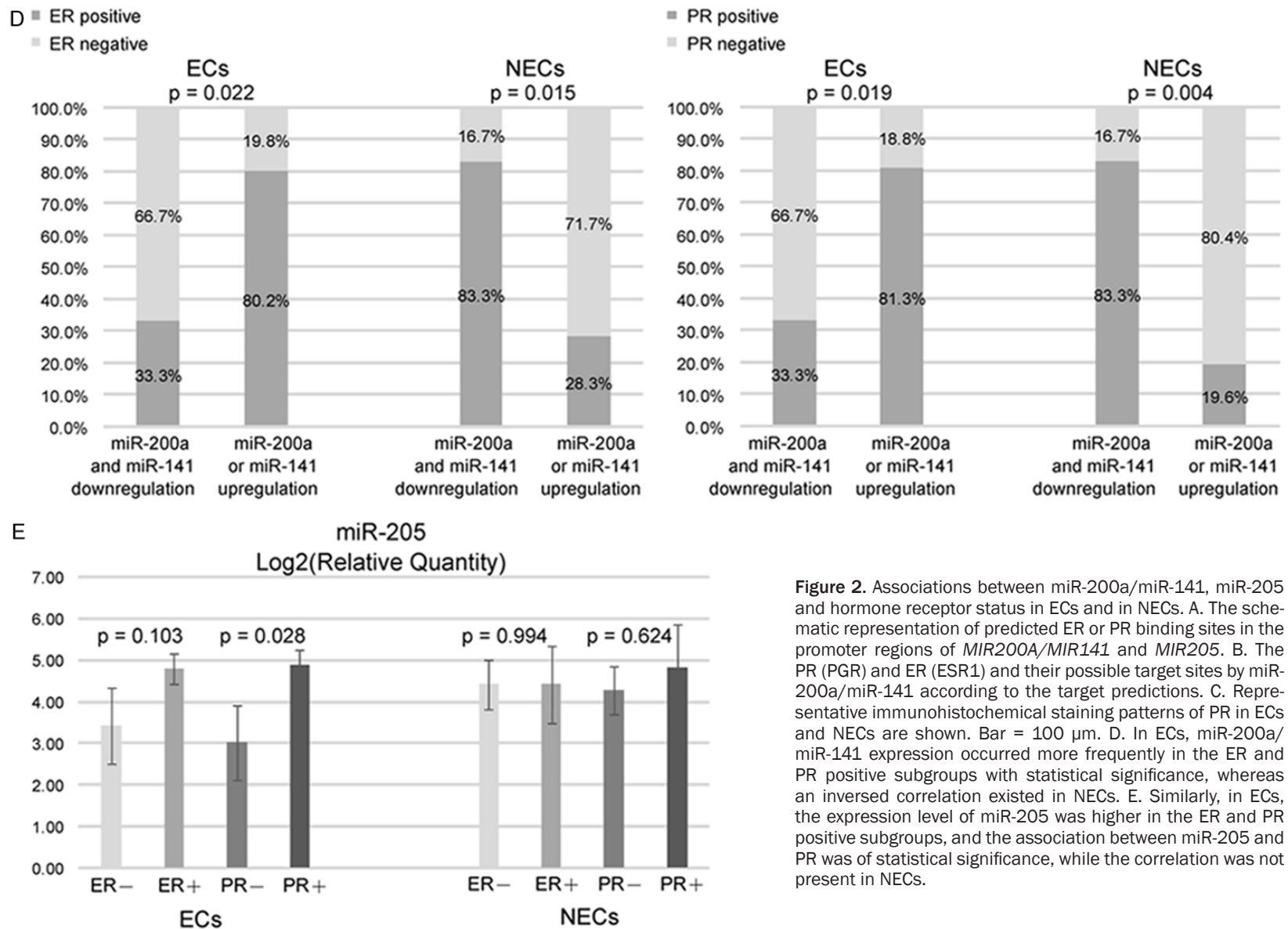


Figure 2. Associations between miR-200a/miR-141, miR-205 and hormone receptor status in ECs and in NECs. A. The schematic representation of predicted ER or PR binding sites in the promoter regions of *MIR200A/MIR141* and *MIR205*. B. The PR (PGR) and ER (ESR1) and their possible target sites by miR-200a/miR-141 according to the target predictions. C. Representative immunohistochemical staining patterns of PR in ECs and NECs are shown. Bar = 100 μ m. D. In ECs, miR-200a/miR-141 expression occurred more frequently in the ER and PR positive subgroups with statistical significance, whereas an inversed correlation existed in NECs. E. Similarly, in ECs, the expression level of miR-205 was higher in the ER and PR positive subgroups, and the association between miR-205 and PR was of statistical significance, while the correlation was not present in NECs.

day of the follow-up period with no disease found. A P value < 0.05 was considered to be statistically significant. Statistical analyses were performed using the SPSS (Chicago, IL) 13.0.

Results

Expression of miR-200a/141 and miR-205 in ECs and in NECs and their relationship with clinicopathological variables

In this cohort, upregulation of miR-200a, miR-141 and miR-205 frequently occurred in ECs (88.2%, 90.2%, 90.2%) as well as in NECs (86.5%, 75.0%, 84.6%), they coexisted in majority of endometrial cancer samples (74.03%, 114/154) (**Figure 1A**). The expression levels of these miRNAs were significantly increased in ECs as well as in NECs compared with normal controls ($P < 0.05$). Furthermore, the expression levels of miR-200a and miR-141 were higher in NECs than in ECs, and miR-200a showed the statistical significance ($P = 0.025$) (**Figure 1B**). In addition, there was a trend that NECs exhibiting worse clinicopathological factors, including deep myometrial invasion, lymph node metastases, vessel invasion, and late clinical stage, exhibited a higher miR-200a/miR-141 expression levels. By contrary, ECs with favorable clinicopathological variables had a higher miR-200a expression level, although all the associations did not reach statistical significance ($P > 0.05$) (**Table 2**).

miR-205 upregulation occurred significantly frequently in NECs without lymph node metastases ($P = 0.030$) and the expression level was also higher in this subgroup, although the association did not reach statistical significance (**Figure 1C**). However, the phenomenon was not present in ECs. miR-205 expression was not associated with other clinicopathological factors either in ECs or in NECs (**Table 2**).

ER and PR binding sites scanning

The miR-200a family has five members, belonging to two clusters according to the location in the genome. The first cluster, *MIR200A*, *MIR200B*, and *MIR429*, is located on human chromosome 1. The second cluster, *MIR200C* and *MIR141*, is located on chromosome 12.

Using the transcription factor prediction algorithm, rVista 2.0 (<http://rvista.dcode.org>), we

identified multiple ER/PR binding sites in the upstream of *MIR200A* (12/6), *MIR141* (18/10) and *MIR205* (12/16) respectively. In **Figure 2A**, we show a schematic representation of the 2 kb region upstream of the genes, highlighting the ER and PR binding sites in each case. We analyzed the 10 kb region upstream of the miRNA genes respectively. This was chosen as a conservative distance over which a transcription factor may exert its influence, as previously microRNAs within 50 kb of each other have been shown to be transcriptionally co-regulated [16, 17].

miRNA target prediction

The five members of miR-200 family are also classified into two groups according to their seed sequences. The seed sequence of miR-200a and miR-141 is AACACU, and the sequence of miR-200b/miR200c and miR-429 is AAUACU.

miR-200a/miR-141 binding sites were identified in the 3'UTR or CDS of ER and PR respectively using the target gene prediction algorithms including TargetScan (www.targetscan.org/) and Diana (<http://diana.cslab.ece.ntua.gr/tarbase>). ER contains 1 miR-200a/miR-141 binding site in its CDS region (7mer-1A, poorly conserved). PR contains 3 miR-200a/miR-141 binding sites in its 3'UTR (7mer-m8, 7mer-1A, poorly conserved) (**Figure 2B**).

Correlation between miR-200a/miR-141, miR-205 and hormone receptor status in ECs and in NECs

As expected, the ER, PR expressed more frequently in ECs (77.5%, 78.4%) than in NECs (34.6%, 26.9%) with statistical significance ($P < 0.05$) (**Table 1; Figure 2C**). And the ER or PR positivity was associated with favorable clinicopathological variables with statistical significance ($P < 0.05$) or borderline level significance ($P = 0.080$, $P = 0.061$). Patients with ER or PR positive expression also had a prolonged survival, although no statistical significance existed (data not shown).

Because miR-200a and miR-141 have the same seed sequence, in next analyses, we combined the status of miR-200a and miR-141. miR-200a/miR-141 upregulation was defined as miR-200a upregulation and/or miR-141 upregulation. In ECs, miR-200a/miR-141 upregulation

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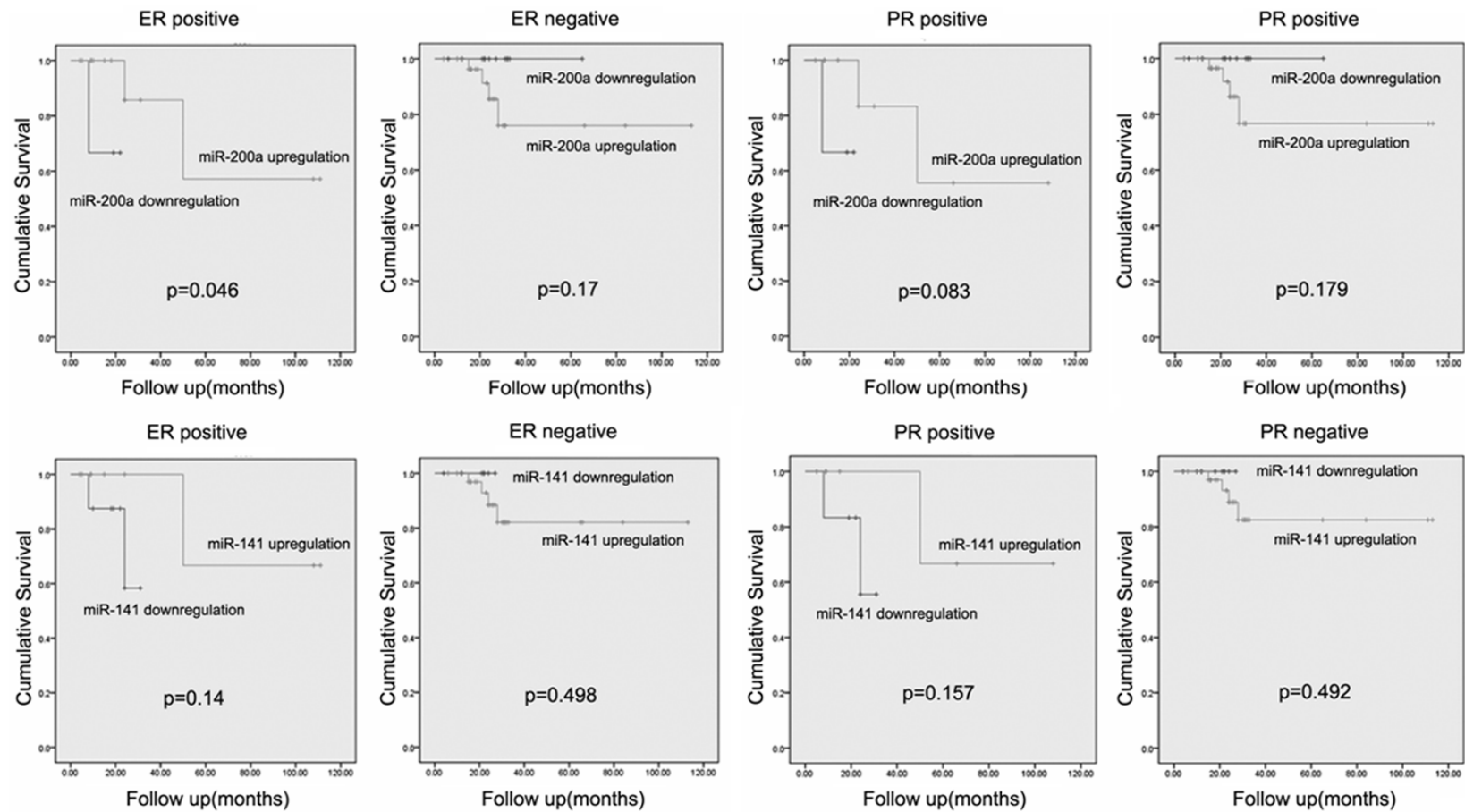


Figure 3. The predictive roles of miR-200a and miR-141 in ECs were associated with hormone receptor status. And the combined miR-200a upregulation and ER positive expression significantly correlated with favorable prognosis.

ulation occurred more often in the ER or PR positive subgroups than in the negative subgroups, and the correlations were of statistical significance ($P = 0.022$, $P = 0.019$). While in NECs, the correlations became inversed. miR-200a/miR-141 upregulation occurred frequently in the ER or PR negative subgroups ($P = 0.015$, $P = 0.004$) (**Figure 2D**).

Similarly, the expression level of miR-205 in ECs was higher in the ER+ and PR+ subgroups, and the association between miR-205 with PR status was of statistical significance ($P = 0.028$) (**Table 2; Figure 2E**). However, such association was not present in NECs ($P > 0.05$).

Association of miR-200a/miR-141 upregulation with patient survival in different hormone receptor expression subgroups

Because we have found miR-200a/miR-141, miR-205 expression correlated with ER or PR status, next we performed extended analyses based on hormone receptor status to assess whether hormone receptor status interferes with miR-200a/miR-141, miR-205 function.

The miR-200a, miR-141, miR-205, and ER, PR status alone was not significantly related to patient survival. However, when we classified the patients based on ER or PR status, we found that the predictive roles of miR-200a and miR-141 were associated with hormone receptor status. In ECs, miR-200a upregulation was significantly correlated with prolonged patient survival in the ER+ subgroup ($P = 0.046$), whereas the association became inversed in the ER- subgroup, although without statistical significance (**Figure 3**). However, the association of miR-200a upregulation with longer survival in the ER positive subgroup did not persist in multivariate analysis ($P > 0.05$). For miR-205 expression, the Kaplan-Meier curve did not demonstrate significant changes in hormone receptor positive versus negative status (data not shown). In NECs, the follow-up data was not sufficient to do survival analysis.

Discussion

Our data set represents the largest series of endometrial cancers assessed for miR-200a, miR-141 and miR-205 alterations. We found that the expression levels of miR-200a, miR-141 and miR-205 significantly increased in ECs

as well as in NECs. However, they might behave differently in ECs versus NECs.

To our knowledge, upregulation of miR-200 family member and miR-205 is observed consistently in ECs compared to normal controls. However, their roles in NECs have not been studied extensively. Only several studies demonstrated that these miRNAs were significantly increased in endometrioid carcinomas as well as in serous carcinomas and were not specific for histologic type [5-8]. We reconfirmed such observation in the present study. However, in an earlier study, based on small sample size (58 ECs and 15 NECs), we believed that expression of miR-200a, miR-141 and miR-205 was more often associated with ECs than NECs, the expression levels of these miRNAs increased significantly in ECs but did not in NECs. Thus, the result of our earlier investigation was not consistent with the findings of this cohort. However, due to the large number of patient samples, the findings of the present study were significant and may represent real expression pattern of miRNA-200a/miR-141 and miR-205 in endometrial cancer subtypes. The other reason of the different findings between this study and our earlier investigation may be because the earlier one included more old tissue blocks, and the higher extent of RNA degradation in older tissue blocks probably reduces the real-time PCR efficiency in miRNA analysis.

Altered expressions of miR-200 family and miR-205 have been linked with outcome of endometrial cancer patients. Based on tissue and plasma of 77 EC patients, Torres et al indicated that all miR-200 family members were significantly upregulated in ECs and most pronounced in early clinical stages and a systematic decrease of their expression was noted in higher stages and in poorly differentiated tumors [18]. miR-205 upregulation were associated poor survival and promote cell proliferation and invasion by targeting PTEN and ESRRG respectively in endometrial cancer [19, 20].

In this cohort, there was a trend that NECs with worse clinicopathological variables had a higher miR-200a expression, while an inverse trend existed in ECs. Thus, our findings of miR-200a/miR-141 expression in ECs are in line with others. For miR-205 expression, our findings seem not consistent with others. We did not found miR-205 expression correlated with clinico-

pathological factors or patient survival except that miR-205 upregulation occurred frequently in NECs without lymph node metastases with statistical significance; however, such association was not present in ECs. Together, our data may also imply that miR-200a/miR-141 and miR-205 behave differently in ECs versus in NECs.

Furthermore, our findings differ from other studies in terms of the roles of miR-200a/miR-141 and miR-205 as tumor suppressors, especially in terms of the epithelial to mesenchymal transition induced by loss of these miRNAs. Recently, study indicated that members of miR-200a family and miR-205 are responsible for repressing ZEB1 and ZEB2 as well as other mesenchymal genes. These miRNAs are considered as “guardians of the epithelial phenotype”, and loss of these miRNAs is a marker for aggressiveness and metastasis in endometrial, breast and ovarian cancer based on cell line models [21, 22]. However, it has to be taken into account that our material consisted of tumor samples that are more heterogeneous than cancer cell lines. In addition, one study postulated that miR-200 family member were downregulated only in malignant myoepitheliomas, but not in basal-like breast cancers and suggested that high expression of miR-200c and miR-429 stabilized the epithelial phenotype and prevented invasive cell growth [23]. Our tumor samples included both malignant and non-malignant stromal cells that may differ in miRNAs and ZEB protein expression. Thus, our results may present expression of miR-200a/miR-141 and miR-205 in the microenvironment of the tumors rather than only in malignant epithelial cells, in particular, with regard to the miR-200a/miR-141 alterations in NECs.

More interestingly, our data indicated that a vital link between miRNA-200/miR-141, miR-205 and hormone receptors, key elements in endometrial carcinogenesis, might exist. Recently, mounting evidence indicates that miRNAs are intimately involved with hormone receptor status [24, 25]. Studies leave no doubt that some miRNAs are regulated by steroid hormone in an ER or PR-dependent manner. A study from Panda et al indicated that endometrial miR-200c expression undergoes dynamic changes during transition from normal into cancerous states, possibly influenced by hormonal

milieu. miR-200c expression was elevated in normal endometrium from mid- and late-luteal phase, and in endometrial tumors. And Treatment of Ishikawa cells with 17 β -estradiol, progesterone, and medroxy progesterone acetate had modest effects on miR-200c expression [26]. Another study using microRNA microarray identified 17 and 14 ER-upregulated miRNAs in Ishikawa and EEC-1 cell lines upon E2 treatment, respectively. However, miR-200 family members and miR-205 were not included [27].

In this study, first, sequence analyses demonstrated multiply estrogen and progesterone receptor-binding elements in the upstream of *MIR200A/MIR141* and *MIR205*. Meanwhile, ER and PR were identified as potential targets of miR-200a/miR-141 by target prediction algorithms. Second, we found that, in ECs, miR-200a/miR-141 upregulation occurred more often in the ER or PR positive subgroups than in their negative subgroups. Similarly, the expression level of miR-205 in ECs was significantly higher in the PR positive subgroup. In contrast, in NECs, a negative correlation was found between miR-200a/miR-141 and ER or PR status. Third, miR-200a/miR-141 upregulation might possess different prognostic impact on ECs in hormone receptor positive and negative context. In the ER positive subgroup, miR-200a upregulation correlated well with prolonged survival, whereas an inverse trend existed in the ER negative subgroup. Thus, in ECs, as transcription factor, the hormone receptor might modulate expression of miR-200/miR-141 and miR-205 by activating their promoters. In NECs, a high miR-200a/miR-141 expression might offer a mechanism for the reduced hormone receptor expression through targeting their mRNAs.

In conclusion, our findings suggest that upregulation of miR-200a/miR-141 and miR-205 is the common molecular alterations in ECs and in NECs. However, they might play different roles in endometrial cancer subtypes. Furthermore, miR-200a/miR-141 and miR-205 might be associated with hormone receptor status through different mechanisms in ECs versus NECs and may possess prognostic impacts.

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Disclosure of conflict of interest

None.

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