Histol Histopathol (2015) 30: 539-548
DOI: 10.14670/HH-30.539

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

*Review*

# Role of miRNAs in endometrial cancer

**Shuangdi Li[1], Jiarong Zhang[1] and Xiaoping Wan[2]**

[1]Department of Obstetrics and Gynecology, Shanghai First People's Hospital Affiliated to Shanghai Jiao Tong University and [2]Department of Obstetrics and Gynecology, Shanghai First Maternity and Infant Hospital Affiliated to Shanghai Tong Ji University, Shanghai, China

**Summary.** Endometrial cancer (EC) is the most common gynecologic malignancy. MicroRNAs (miRNAs) were recently associated with carcinogenesis and progression of EC. In this review, we discuss recent advances and the emerging role of miRNAs in EC and their clinical implications, with special emphasis on the differences between deregulated miRNAs in type I and type II EC, as well as the impact of this dysregulation on EC initiation and progression.

**Key words:** Endometrial cancer, microRNA, Estrogen receptor, p53, Metastasis

## Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy, with an estimated 49,560 diagnosed cases and 8,190 deaths in 2013 in the United States (Siegel et al., 2013). The incidence of EC in China is also on the rise (Wang et al., 2012). From a clinical viewpoint, two different clinicopathological types can be broadly distinguished (Di Cristofano and Ellenson, 2007). Type I endometrioid endometrial cancers (EECs) account for 70-80% of cases and are generally positive for the estrogen receptor (ER; especially ERα) and progesterone receptor. Type II tumors (serous or clear cell tumors), which represent 20% of cases, are ER-negative and unrelated to estrogen stimulation. Commonly mutated genes in type I tumors include PTEN, ARID1A, CTNNB1, PIK3CA and KRAS (Cheung et al., 2011; McConechy et al., 2012). Microsatellite instability (MSI) is found in approximately one-third of type I tumors, but it is infrequent in type II tumors (Zighelboim et al., 2007). TP53, PIK3CA and PPP2R1A mutations are frequent in type II tumors (Kuhn et al., 2012; Le Gallo et al., 2012). However, in daily practice, tumors showing combined or hybrid morphological and molecular characteristics are not uncommon (Yeramian et al., 2013). This observation reflects, at least to some extent, an incomplete understanding of the molecular genetics of endometrial carcinogenesis.

MicroRNAs (miRNAs) are small noncoding RNAs that silence their cognate target genes by either degrading mRNAs or inhibiting their translation (Bartel, 2004). Therefore, they are implicated in the regulation of a variety of cellular processes, including stemness and metastasis. Additionally, miRNAs can function as either oncogenes or tumor suppressors (Calin et al., 2005; He et al., 2005; Ma et al., 2007). Deregulated expression of miRNAs has been associated recently with carcinogenesis in EC. For example, miR-185, miR-106a, miR-181a, miR210, miR-423, miR-103, miR-107, let-7c, miR-205, miR-449 and miR-429 were shown to have enhanced expression in EC tissues compared with normal tissues, whereas let-7e, miR-221, miR-30c, miR-152, miR-193, miR204, miR-99b and miR-193b had decreased expression in cancer tissues (Banno et al., 2013). In this review, the role of miRNAs in the

*Offprint requests to:* Jiaron Zhang, Department of Obstetrics and Gunecology, Shanghai First People's Hospital Affiliated to Shanghai Jiao Tong University, 100 Haining Road, Shanghai, China. e-mai: maggie1974@126.com and Xiaoping Wan, Department of Obstetrics and Gynecology, Shanghai First Maternity and Infant Hospital Affiliated to Shanghai Tong Ji University, 874 Changle Road, Shanghai, China. e-mail: Wanxiaoping61@126.com

carcinogenesis and development of EC is discussed, focusing on the tumor subtypes and clinical implications.

## Aberrant expression of miRNAs in type I and II ECs

Several studies have been conducted to identify miRNAs that are differentially expressed in type I and II ECs. Analysis of miRNAs in 57 EECs, 27 serous ECs and 6 endometrial carcinosarcomas led to the identification of distinct miRNA signatures in either tumor subtype. Eight miRNAs were significantly lower in EECs compared to serous tumors, with the most downregulated miRNAs being miR-19a and miR-19b (Ratner et al., 2010). In another study, miRNA expression levels were compared in 20 EECs, 21 serous ECs and 7 normal endometrial tissues. Six miRNAs were identified as being aberrantly and specifically downregulated in serous cancers, with miR-34b being the most pronounced (Hiroki et al., 2012). A similar study which analyzed the comparative expression levels of miRNAs in 14 EECs, 9 serous ECs and 4 normal endometrial tissues revealed 20 significantly dysregulated miRNAs in both EEC and serous cancer, including miR-133b, miR-205 and miR-200 family. In addition, 17 miRNAs were found to discriminate between EEC and serous cancer (Devor et al., 2011).

Although these preliminary studies highlighted the significance of a serous cancer-specific miRNA signature, it should be noted that consensus miRNAs were not found in these studies. In contrast, a large-scale study of "the Cancer Genome Atlas" (TCGA), which recruited 307 EEC patients, 53 serous cancer patients and 13 mixed histology EC patients, failed to find a characteristic miRNA expression profile distinguishing EECs and serous cancers (Network C.G.A.R., 2013). This result is not surprising given that some EECs may share the same phenotype with serous EC (Network C.G.A.R., 2013). Although some miRNAs may specifically deregulate in serous cancer, whether a miRNA signature capable of discriminating between type I and type II EC exists remains unclear. Further studies with more cancer samples and extensive tumor stratification (i.e., low-grade EEC, high-grade EEC, serous cancer) may help to clarify this issue.

## MiRNAs, estrogen action and EC

A major characteristic of type I EC is estrogen dependence. Estrogen interacts with miRNAs in multiple ways. E2 and ERα regulate miRNA processing directly or indirectly by interaction with Drosha, Dicer and Ago2, which are key enzymes in the miRNA processing pathway. Estrogen can regulate miRNA expression by either genomic (transcriptional) or "nongenomic" mechanisms of action (e.g., plasma membrane ERα or GPR30-asscoated signaling cascades) (Klinge, 2012). MiRNAs are also capable of regulating ER activity by either directly targeting the receptor or repressing coregulator expression (Klinge, 2012). In endometrial epithelial cells, estrogen has been shown to repress miR-21 and miR-20a expression (Pan et al., 2007). Moreover, miRNAs were found to be differentially expressed during the physiological phases of the menstrual cycle, suggesting that they are hormonally regulated in the human endometrial epithelium (Kuokkanen et al., 2010). These results highlight the possible relationship between estrogen action, miRNAs and EC.

### *MiRNA regulation of ERα in EC*

Ten miRNAs have been identified as *bona fide* ERα regulators: miR-22, miR-206; miR-221, 222; miR-18a, miR-18b, miR-193b and miR-302c (Klinge, 2012). In EC, miR-222-3p was found by our laboratory to be overexpressed in ERα-negative EC tumors and was associated with high grade, late stage and nodal metastasis (Liu et al., 2014). The ERα inhibitory effect of miR-222-3p was confirmed using a luciferase assay. Unlike that in breast cancer, miR-222-3p inhibition of ERα expression was seen at both the protein and mRNA level in EC (Liu et al., 2014). We have also verified the ERα targeting potential of miR-206 in EC. An inverse relationship between miR-206 and ERα in EEC was found, and the suppressive effect of miR-206 on ERα was demonstrated in EEC cell lines using a dual-luciferase reporter assay (Chen et al., 2012). In contrast to miR-222-3p, miR-206 acts as a tumor suppressor in EC. Ectopic expression of miR-206 inhibits cell growth, impairs cell invasion and induces cell cycle arrest in ERα-positive EEC cells. This result seems counterintuitive given that miR-206 expression is elevated in more aggressive ERα-positive EECs. We hypothesized that increased levels of miR-206 may inhibit ERα and together with other oncogenic signaling pathways allows the cell to undergo a proliferative switch from estrogen-dependent mode to a more transformed estrogen-independent status (Chen et al., 2012).

In addition to miR-222-3p and miR-206, Zhou (2010) found that miR-100 was significantly downregulated in ERα-positive EC and predicted that it targets ERα using miRanda and TargetScan prediction programs (Zhou et al., 2010). However, their results were not verified experimentally by a luciferase reporter assay. MiR-22 has been reported to directly target ERα in breast cancer cell lines (Pandey and Picard, 2009). In EEC, miR-22 has an inhibitory effect on ERα expression and is able to reverse 17β-estradiol (E2) induced cell proliferation, cell cycle progression and invasion of ERα-positive RL95-2 and Ishikawa cells. These results imply a tumor suppressive effect of miR-22 in EEC (Li et al., 2014).

Besides miRNAs directly targeting ERα, our laboratory has also investigated the relationship between miRNA and estrogen-related receptor gamma (ESRRG) in EC (Su et al., 2013). ESRRG can compete with ERs to bind to estrogen response elements (ERE) and may be a modulator of the ERα signal pathway. ESRRG

expression predicts a good clinical course in EC (Gao et al., 2006), and we identified the *ESRRG* gene to be a novel target of miR-205. MiR-205 was shown to be significantly upregulated in EEC. Furthermore, its inhibition increased the protein expression of ESRRG and suppressed cell proliferation, migration and invasion (Su et al., 2013). These observations have helped to better understand the mechanisms underlying the interaction between ER, estrogen-related receptor (ESRR) and miRNAs in EC.

### *Estrogen regulation of miRNA expression in EC*

Most of the studies concerning regulation of miRNAs by E2 were performed in breast cancer MCF-7 cell lines, which have been recently systematically reviewed (Klinge, 2012). In EC, Zhang (2012) identified let-7a family members and miR-27a as being upregulated by E2 (Zhang et al., 2012). These upregulated miRNAs can reduce Bcl2-associated X protein gene (BAX) expression at the post-transcriptional level, thereby promoting an increased BCL2/BAX ratio as well as enhanced survival and proliferation in Ishikawa and ECC-1 cell lines. Another research group found that estrogen can decrease miR-30c expression through ER-dependent and -independent pathways (Kong et al., 2014). The metastasis-associated gene 1 (*MTA1*) targeted by miR-30c is upregulated in EC cells and promotes cell proliferation, migration and invasion (Zhou et al., 2012; Kong et al., 2014). In addition, our laboratory has found that miR-206 levels decrease after E2 or ERα agonist treatment, indicating a feed-back loop between E2-ER and miR-206 (Chen et al., 2012).

Although nearly 20 studies have verified miRNA regulation by E2 in human cell lines, the lack of consistency of these results even with the well-studied MCF-7 cell line remains a problem (Klinge, 2012). This phenomenon may be due to the different treatment conditions, assay method used to measure miRNA expression and/or differences in cell lines. Further study on estrogen regulation of miRNA expression is needed. Overall, the interaction between miRNA and estrogen indicates miRNA may play a significant role in the progression of estrogen-related EC and may be a novel candidate for endocrine therapy.

## MiRNAs, PTEN expression and EC

The tumor suppressor gene PTEN is frequently abnormal in type I EC. LOH at chromosome 10q23 occurs in 40% of EC. Somatic PTEN mutations are almost exclusively restricted to EEC, occurring in 37-61% of these tumors, and lead to activation of the phosphoinositol-3-kinase (PI3K)/AKT pathway (Yeramian et al., 2013). In addition to mutations/deletions of PTEN, epigenetic mechanisms, such as promoter methylation, and regulation through miRNAs are also important explanations for the reduced PTEN expression (Zhang and Yu, 2010). Moreover, the activities of Forkhead box class O (FOXO) protein and mammalian target of rapamycin (mTOR) protein, functioning downstream of the PI3K/AKT signaling pathway, are enhanced by PTEN. MiRNAs targeting these genes will also be discussed below.

## MiRNAs directly targeting PTEN in EC

MiR-21 has been found to target PTEN in a variety of malignancies (Meng et al., 2006; Frankel et al., 2008; Ma et al., 2011), including EC (Qin et al., 2012). MiR-21 was observed to be overexpressed in EEC and thought to modulate EC cell proliferation through the downregulation of PTEN (Qin et al., 2012). However, another study revealed that although miR-21 was moderately elevated in EC compared with endometrial complex atypical hyperplasia, expression of miR-21 did not show a significant correlation with PTEN expression patterns (Lee et al., 2012). Therefore, the role of miR-21 in EC remains controversial.

Another miRNA which can directly target PTEN is miR-205, although this function has not been verified by a luciferase reporter assay in EC. MiR-205 was shown to target PTEN in non-small cell lung cancer (Cai et al., 2013) and nasopharyngeal carcinoma (Qu et al., 2012), and its overexpression in cancer cells can activate the PI3K/AKT pathway and promote cell proliferation (Qu et al., 2012; Cai et al., 2013). MiR-205 is overexpressed in both EEC (Karaayvaz et al., 2012; Lee et al., 2012, 2013; Torres et al., 2013) and endometrial serous adenocarcinomas (Hiroki et al., 2010). High levels of miR-205 have been associated with a malignant tumor phenotype (Su et al., 2013) and poor patient overall survival (Karaayvaz et al., 2012). MiR-205 was found to negatively correlate with the expression of PTEN protein but not mRNA, indicating that it may regulate PTEN expression through a post-transcriptional mechanism in EC (Karaayvaz et al., 2012). Additionally, miR-205 can target ESRRG in EC (Su et al., 2013) and act as a potent inhibitor of the epithelial mesenchymal transition (EMT) in endometrial carcinosarcoma (Diaz-Martin et al., 2014). Thus, miR-205 may act as a multi-faceted regulator in EC progression.

### *MiRNAs acting on PI3K/Akt-FOXO axis in EC*

FOXO proteins are central to diverse cellular functions, including cell proliferation, apoptosis, differentiation and resistance to oxidative stress and DNA damage (Lam et al., 2012). These proteins are particularly relevant for cell fate decisions in hormone-responsive reproductive tissues, including the endometrium. The most prominent and best characterized member of this protein family in human endometrium, FOXO1, is a major player in decidualization and menstruation, which helps to maintain normal reproductive function (Lam et al., 2012). In EC, FOXO1 expression correlates with the

responsiveness to progestin treatment (Ward et al., 2008).

FOXO proteins function downstream of the PI3K/AKT oncogenic signaling pathway. PTEN antagonizes PI3K activity, inhibits AKT and thus enhances FOXO activity. As mentioned above, deregulated miRNAs may target PTEN, thereby decreasing FOXO expression in EC. Moreover, an inverse correlation between FOXO1 expression and the abundance of several of the *in silico*-predicted miRNAs (i.e., miR-9, miR-27, miR-96, miR-153, miR-182, miR-183 and miR-186) that potentially bind the 3'-UTR of FOXO1 transcripts has been identified in both EEC cells and tissues. Induction of FOXO1 in Ishikawa cells by miRNA inhibitors was shown to be accompanied by G1 cell cycle arrest and cell death and attenuated by the small interfering RNA-mediated downregulation of FOXO1 expression. These findings suggest that a group of miRNAs act coordinately to repress FOXO1 expression, which in turn deregulates cell cycle control and apoptotic responses in EC (Myatt et al., 2010).

### *MiRNAs acting on PI3K/Akt-mTOR axis in EC*

MTOR is regulated by the excessive activation of the PI3K/Akt/mTOR signaling pathway to induce tumor cell proliferation, metastasis and other biological activities in many tumors (Slomovitz and Coleman, 2012). Elevated expression levels of mTOR and its activation products have been reported in EEC tissues and cell lines, which are particularly evident in Ishikawa, a PTEN-defective EC cell line (Choi et al., 2010). The increased expression of mTOR kinase in EEC coexists with downregulation of its in-silico targeting miRNAs, miR-99a, miR-100 and miR-199b (Torres et al., 2012), and the miRNA signatures consisting of these three miRNAs are strongly associated with the diagnosis of EEC. Another study has also shown that miR-199a-3p can inhibit the protein expression of mTOR by binding to the mTOR 3'-untranslated region, and the upregulation of miR-199a-3p can inhibit tumor cell proliferation through negative regulation of mTOR expression (Wu et al., 2013). These results suggest a new mechanism of miRNA-regulated mTOR pathway alterations in EEC.

## MiRNAs, MSI and EC

MSI is seen in 75% of EC associated with the hereditary non-polyposis colorectal carcinoma (HNPCC) and also in 25–30% of sporadic EC (Duggan et al., 1994). MSI occurs more frequently in EEC (30%) than in non-EEC. In sporadic tumors, the MSI-associated mismatch repair (MMR) deficiency leads to the accumulation of mutations in coding and non-coding DNA sequences (Yeramian et al., 2013). MiRNAs can target core MMR proteins and induce MSI. For example, miR-155 overexpression in colorectal cancer was reported to significantly downregulate hMSH2, hMSH6 and hMLH1, leading to a mutator phenotype and MSI (Valeri et al., 2010). However, in EC, the direct effect of miRNAs targeting MMR proteins has not been investigated thus far. In contrast, several miRNAs have shown an indirect effect on MMR protein expression. MiR-143 and miR-145 play a role in hMLH1 loss in EEC through their influence on DNA methyltransferase 3B (DNMT3B) expression (Zhang et al., 2013). Hypermethylation of two miRNAs, miR-203 (Huang et al., 2014) and miR-129-2 (Huang et al., 2009), have also been strongly associated with MSI and MLH1 methylation status in EEC.

## P53/miRNA network in EC

As the most prominent molecular feature of type II EC, p53 mutations occur in 90% of such tumors, while they are only present in 10-20% of EEC, which are mostly grade 3 tumors (Yeramian et al., 2013). The p53 pathway is heavily interconnected with miRNAs by regulating their expression and processing, and p53 itself represents a downstream target of miRNAs (Hunten et al., 2013). The connections between p53 and miRNAs in the development and progression of EC, especially type II EC, are discussed below.

### *P53-miR34 pathway in EC*

The miR-34 genes, *miR-34a* and *miR-34b/c*, were reported to be directly regulated by p53 by a number of studies since 2007 (Hunten et al., 2013). P53 activation can upregulate miR-34 expression, which displays tumor suppressive activities by causing induction of apoptosis and senescence and inhibition of cell cycle progression. In endometrial serous adenocarcinoma, miR-34b was found to be the most downregulated miRNA compared with EEC and normal endometria (Hiroki et al., 2012). The downregulation of miR-34b expression may result from p53 dysfunction and miR-34b promoter methylation. MiR-34b targets mesenchymal-epithelial transition factor (MET) to inhibit cell growth, migration and invasion. The association of miR-34b downregulation and increased metastatic proficiency suggests that the p53/miR-34b/MET pathway is involved in the aggressive behavior of endometrial serous adenocarcinoma (Hiroki et al., 2012).

Similar results can also be found with miR-34a. In ECC1 EC cells with wild-type p53, the activation of p53 was shown to cause miR-34a upregulation and loss of the expression of its target, L1CAM (Schirmer et al., 2014). L1CAM is an adhesion molecule which plays a role in EMT. L1CAM positivity in carcinomas has been associated with poor prognosis, and type II ECs, representing the most aggressive of serous and clear-cell ECs, are positive for L1CAM (Huszar et al., 2010). Overall, the p53-miR34 axis may be linked to the metastatic phenotype of type II EC by targeting multiple

downstream genes involved in EMT.

### *TP53 gain-of-function (GOF) and miR-130b-ZEB1 axis in EC*

P53 mutations may result in oncogenic features, such as GOF, which actively drive cells toward invasion and metastasis through transactivation or transrepression of a large set of genes (Dong et al., 2013). In EC, the GOF p53 mutant has been found to bind directly and transrepress the promoter of miR-130b, which is a specific inhibitor of ZEB1, leading to the upregulation of ZEB1 and subsequent activation of the E-cadherin suppressor BMI-1. Thus, p53 GOF mutations can accelerate tumor progression and metastasis through modulation of the miR-130b–ZEB1 axis in EC (Dong et al., 2013).

MiR-200c has been identified as a potent EMT regulator by targeting ZEB1 and ZEB2. MiR-200c expression was shown to be upregulated by p53 activation (Chang et al., 2011). However, the low expression of miR-200c in EC may be due not only to the loss of wild-type p53 but also the overexpression of GOF p53 mutants R175H and C135Y (Dong et al., 2013). Therefore, the downregulation of miR-200c is also involved in mutant p53 GOF induced EC cell invasion.

### *Regulation of p53 expression by miRNAs in EC*

Several miRNAs contribute to the tight control under which p53 is placed in the cell by directly interacting with the 3'-UTR of p53 mRNA. Among these miRNAs, we had focused on miR-125b (Nishida et al., 2011), which was significantly overexpressed in type II EC cells compared with type I EC cells (Jiang et al., 2011). The overexpression of miR-125b can increase proliferation and migration of EC cells partly through the inhibitory effect on its target gene, tumor protein p53 inducible nuclear protein 1 (TP53INP1) (Jiang et al., 2011). A second target of miR-125b, V-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (ERBB2), is associated with enhanced invasion in EC cells (Shang et al., 2012). Thus, miR-125b overexpression may contribute to the malignancy of EC. However, the negative regulation of p53 by miR-125b in EC has not been clarified, although the miRNA has been shown to directly regulate p53 protein in human neuroblastoma cells, lung fibroblast cells (Le et al., 2009) and colorectal cancer (Nishida et al., 2011).

## MiRNAs regulating invasion and metastasis of EC

Although EC is generally considered to be a cancer with good prognosis, the clinical outcome of type II EC is much poorer compared with that of type I EC. Type II EC is commonly diagnosed in advanced stages with deep myometrial invasion, extra-uterine metastasis and lymphatic dissemination (Colas et al., 2012). EMT has recently been recognized as an important mechanism in invasion and metastasis, and inactivation of E-cadherin (80–90%) has been shown to be more prevalent in type II EC than in type I EC (Yeramian et al., 2013). Several miRNAs, such as those of the miR-200 family, and the p53-miR-34-SNAIL feedback loop have been identified as potent EMT regulators. The role of miRNAs in the metastasis process with special emphasis on EMT of EC cells will be discussed below.

### *Role of miR-200 family in EC*

The miR-200 family has been demonstrated to be a powerful marker and determining factor of the epithelial phenotype of cancer cells by targeting two double zinc finger and homeodomain (ZEB1 and ZEB2) factors. MiR-200 is a consensus miRNA upregulated in EEC tissues relative to normal controls (Boren et al., 2008; Chung et al., 2009; Wu et al., 2009; Cohn et al., 2010; Ratner et al., 2010; Snowdon et al., 2011; Panda et al., 2012). Accordingly, miR-200 is overexpressed in Ishikawa cells (which represent type I EC), while its expression is extremely low in HEC50 and AN3CA cells (which represent the highly aggressive type II EC) (Cochrane et al., 2009). Low miR-200c expression strongly correlates with lack of E-cadherin expression and gain of mesenchymal markers in EC cells (Cochrane et al., 2009). Moreover, the expression of several other genes besides ZEBs, which have key regulatory functions in cellular transformation, inflammation, angiogenesis (Panda et al., 2012), cell motility and anoikis resistance (Howe et al., 2011), are also targeted by miR-200c in EC. In addition, miR-200 can target class III beta tubulin to induce tumor sensitivity to paclitaxel (Leskela et al., 2011). Thus, loss of miR-200 is considered to be a marker of aggressiveness and chemoresistance in EC (Cochrane et al., 2010). However, it is also argued that miR-200 family members may act as oncomiRNAs in EEC as miR-200 is specifically upregulated in EEC tissues, while inhibition of the miR-200 family decreases EC cell growth (Lee et al., 2011). MiR-200 decreases the expression of a potential tumor suppressor gene, BRD7, and subsequently regulates β-catenin translocation in the cytoplasm, resulting in activation of cyclin D1 and c-myc (Park et al., 2012). This discrepancy may be partly explained by the pluripotency of the miR-200 family, which can act both as onco-miRNAs and tumor suppressive miRNAs. Overall, these observations may suggest a distinct role of the miR-200 family in type I and type II EC.

### *Tyrosine kinase B (TrkB)-STAT3-miR-204 signaling axis in EC*

We recently identified a novel TrkB-STAT3-miR-204-5p signaling axis that plays an important role in EC metastasis (Bao et al., 2013b). The neurotrophic receptor TrkB serves in promoting EMT and resistance to anoikis

in EC (Bao et al., 2013a). In normal cells, TrkB induces the activation of STAT3 to regulate the expression of miR-204-5p, which in turn, directly modulates TrkB expression. This TrkB-STAT3-miR-204-5p regulatory circuit is disrupted in EC, which leads to the absence of miR-204 expression and the overexpression of TrkB, and subsequently to the promotion of the growth, migration and invasion of EC cells (Bao et al., 2013b). In addition, decreased expression of miR-204 causes dysfunctional regulation of FOXC1, which results in enhanced metastasis and invasion of tumor cells (Chung et al., 2012). Consistently, we found an association of a lower miR-204-5p expression with advanced FIGO stages, lymph node metastasis and potentially a lower chance for survival of EC patients (Bao et al., 2013b). The results of our study and others have highlighted the importance of miR-204 as a critical metastatic regulator in EC.

### *MiRNA signature of EMT in EC*

In the carcinosarcoma histology of type II EC, a specific miRNA signature that distinguishes epithelial from mesenchymal areas has been identified (Castilla et al., 2011). The most strongly upregulated miRNA was miR-155, whose role in EMT was suggested in association with TGFβ. Another key finding of this study was the marked downregulation of the miR-200 family (Castilla et al., 2011), which acts as a multifunctional potent inhibitor of the EMT process in EC, as mentioned above. Several other miRNAs have also been found to regulate the EMT process in EC, including miR-106b that targets TWIST1 (Dong et al., 2014) and miR-194 targeting the oncogene BMI-1 (Dong et al., 2011), as well as the above-mentioned miR-130b, which targets ZEB1 and inhibits EMT (Dong et al., 2013). Therefore it is suggested that miRNA expression profile could be valuable for inferring EMT in EC.

## Clinical implications of miRNAs in EC

Although the early detection of EC is relatively easy compared with ovarian cancer, highly sensitive and specific molecular biomarkers that can better predict the diagnosis and outcome of EC are not currently available. Unlike ovarian cancer, the sensitivity and positive predictive value of CA125 measurements are relatively low in detecting this malignancy (Sebastianelli et al., 2010). As mentioned above, miRNA expression profile studies have revealed a panel of miRNAs that can be used to distinguish EC from the normal endometrium. Thus, EC-associated miRNAs have the potential to be developed as novel diagnostic and therapeutic molecules. Until now, only three studies, all of which are confined to the most common EEC, have investigated

**Table 1.** Prognostic value of miRNAs in EC.

| miRNA(s) | Patients | Survival outcome | Comments | Reference |
|---|---|---|---|---|
| miR-205 | 48 ECs, including 24EECs, 13NEECs,11 other ECs | OS | High levels of miR-205 expression associated with poor patient OS | Karaayvaz et al., 2012 |
| miR-130b | 32 ECs, including 15EECs, 8NEECs, 9 other ECs | OS | High levels of miR-130b expression was associated with good patient OS. | Dong et al., 2013 |
| miR-1228/miR-200c/ miR-429 | 77 EECs | OS | MiRNA signature miR-1228/miR-200c/miR-429 overexpression predicted poor patient OS. | Torres et al., 2013 |
| miR-1228/miR-429 | 77 EECs | PFS | MiRNA signature miR-1228/miR-429 overexpression predicted poor patient PFS. | Torres et al., 2013 |
| miR-143/miR-145 | 107 ECs, including 85ECs, 22NECs | OS | Combination of DNMT3B overexpression and miR-145 or miR-143 downregulation was predictive of poor patient survival. | Zhang et al., 2013 |
| miR-101/miR-10b*/miR-139-5p/miR-152/miR-29b/miR-455-5p | 21 NEECs | OS | Reduced expression of miRNA-101, miR-10b*,miR-139-5p, miR-152, miR-29b and miR-455-5p was significantly correlated with shorter OS. | Hiroki et al., 2010 |
| miR-152/miR-29b/miR-455-5p | 21 NEECs | PFS | Reduced expression of miR-152, miR-29b and miR-455-5p was significantly correlated with shorter PFS. | Hiroki et al., 2010 |
| miR-129-2 | 74 ECs | OS | Hypermethylation of miR-129-2 was associated with shorter patient OS. | Huang et al., 2009 |
| miR-100 | 73 EECs | OS | Reduced expression of miR-100 was associated with poor patient OS. | Torres et al., 2012 |
| miR-503 | 48 EECs | OS | Reduced expression of miR-503 was associated with poor patient OS. | Xu et al., 2013 |
| miR-199a | 141ECs, including 128 EECs, 13 NEECs | PFS | Reduced expression of miR-199a was correlated with poor patient OS and PFS. | Cohn et al., 2010 |

OS, overall survival; PFS, progression-free survival.

the diagnostic and therapeutic value of tissue and plasma EC-associated miRNAs.

Using miRNA microarrays, Torres et al. (2013) managed to find miRNA signatures that classified with high accuracy tumor tissues (miR-92a/miR-410 and miR-92a/miR-205/miR-410; AUC, 0.977 and 0.984, respectively) and EEC plasma samples (miR-9/miR-1228 and miR-9/miR-92a; AUC, 0.909 and 0.913, respectively) (Torres et al., 2013). Additionally, miRNA signatures that could be independent prognostic markers of overall (miR-1228/miR-200c/miR-429) and progression-free (miR-1228/miR-429) survival were also found. In contrast, a profile of four serum miRNAs (miR-222, miR-223, miR-186 and miR-204) was found by Jia (2013) as a fingerprint for EEC detection with an AUC of 0.927, which was markedly higher than that of Ca125 (AUC, 0.673) (Jia et al., 2013). Most recently, Tsukamoto (2014) applied a next-generation sequencing method to identify two miRNA signatures (miR135b/miR195 and miR135b/miR30a-3p) which could distinguish between EEC and normal endometrial tissue samples, yielding a high AUC of 0.984 and 0.990, respectively (Tsukamoto et al., 2014). They also found miR-135b and miR-205 levels in plasma with AUCs of 0.9722 and 1.0, respectively (Tsukamoto et al., 2014). These preliminary studies showed that measurement of tissue and plasma EEC-associated miRNAs may be useful for early detection, diagnostic and follow-up tests for EEC.

MiRNA profiles have been correlated with disease outcome in multiple cancers (Li et al., 2010). However, the prognostic value of miRNAs in EC has not been systematically researched. Therefore, we performed a comprehensive review of the literature on this topic. A PubMed search was performed with a strategy that included various combinations of the keywords “microRNA”, “miRNA” and “endometrial cancer”. Studies (excluding review articles) were considered eligible if they met the following inclusion criteria: (1) discussed patients with EC and included both EEC and serous EC; (2) measured miRNA expression levels in tumor tissues; (3) investigated the survival or the correlation between miRNA expression and the clinical outcome. Table 1 shows the prognostic miRNAs in EC and related references. These combined observations suggest that miRNAs can be potentially important as biomarkers of EC prognosis and facilitate therapy management. On the other hand, although several miRNAs were shown to have prognostic value, no consensus miRNA signature was found to effectively predict the clinical outcome of EC. Moreover, the patient numbers included in all these studies were relatively small, indicating that more studies with larger sample sizes are needed to clarify the roles of miRNAs in EC.

Several studies focused on the relationship between chemoresistance and miRNA dysregulation. Upregulation of miR-34 could enhance the chemotherapeutic effect of cisplatin in the Ishikawa EC cell line (Jiang et al., 2013), while restoration of miR-200c enhanced cheomsensitivity to paclitaxel but not cisplatin (Cochrane et al., 2009). However, Wu et al. (2011) showed that miR-200b/200c/429 overexpression in EC correlated with resistance to cisplatin treatment by targeting the *AP-2α* tumor suppressor gene (Wu et al., 2011). Thus, the role of specific miRNAs in the treatment of EC remains unclear, and the contradictory results require further investigation. Although miRNAs have been associated with resistance to anti-endocrine therapy and radiotherapy in breast cancer (Mulrane et al., 2013), these relationships in EC have not been exploited yet.

## Conclusion

The aberrantly expressed miRNAs in EC have revealed novel mechanisms in endometrial tumorigenesis and progression. Moreover, the miRNA expression profiles in tissues and blood can potentially be used for the detection and surveillance of EC. Additionally, miRNAs are implicated in aggressive tumor behavior (i.e., type II EC) and chemotherapy resistance and may be a potentially useful tool for prognostic stratification and tailored therapy. However, the study of miRNAs in EC is a relatively new area. More effort is needed to clarify the key EC-related miRNAs as well as their signal transduction pathways, which will allow us to find ways to manipulate miRNAs for therapeutic benefit in a rational manner.

## References

Banno K., Yanokura M., Kisu I., Yamagami W., Susumu N. and Aoki D. (2013). MicroRNAs in endometrial cancer. Int. J. Clin. Oncol. 18, 186-192.

Bao W., Qiu H., Yang T., Luo X., Zhang H. and Wan X. (2013a). Upregulation of trkb promotes epithelial-mesenchymal transition and anoikis resistance in endometrial carcinoma. PLoS One 8, e70616.

Bao W., Wang H.H., Tian F.J., He X.Y., Qiu M.T., Wang J.Y., Zhang H.J., Wang L.H. and Wan X.P. (2013b). A trkb-stat3-mir-204-5p regulatory circuitry controls proliferation and invasion of endometrial carcinoma cells. Mol. Cancer 12, 155.

Bartel D.P. (2004). Micrornas: Genomics, biogenesis, mechanism, and function. Cell 116, 281-297.

Boren T., Xiong Y., Hakam A., Wenham R., Apte S., Wei Z., Kamath S., Chen D.T., Dressman H. and Lancaster J.M. (2008). Micrornas and their target messenger rnas associated with endometrial carcinogenesis. Gynecol. Oncol. 110, 206-215.

Cai J., Fang L., Huang Y., Li R., Yuan J., Yang Y., Zhu X., Chen B., Wu J. and Li M. (2013). Mir-205 targets pten and phlpp2 to augment akt signaling and drive malignant phenotypes in non-small cell lung cancer. Cancer Res. 73, 5402-5415.

Calin G.A., Ferracin M., Cimmino A., Di Leva G., Shimizu M., Wojcik S.E., Iorio M.V., Visone R., Sever N.I. and Fabbri M. (2005). A microrna signature associated with prognosis and progression in chronic lymphocytic leukemia. New Engl. J. Med. 353, 1793-1801.

Castilla M.A., Moreno-Bueno G., Romero-Perez L., Van De Vijver K., Biscuola M., Lopez-Garcia M.A., Prat J., Matias-Guiu X., Cano A., Oliva E. and Palacios J. (2011). Micro-RNA signature of the

epithelial-mesenchymal transition in endometrial carcinosarcoma. J. Pathol. 223, 72-80.

Chang C.J., Chao C.H., Xia W., Yang J.Y., Xiong Y., Li C.W., Yu W.H., Rehman S.K., Hsu J.L., Lee H.H., Liu M., Chen C.T., Yu D. and Hung M.C. (2011). P53 regulates epithelial-mesenchymal transition and stem cell properties through modulating mirnas. Nat. Cell Biol. 13, 317-323.

Chen X., Yan Q., Li S., Zhou L., Yang H., Yang Y., Liu X. and Wan X. (2012). Expression of the tumor suppressor mir-206 is associated with cellular proliferative inhibition and impairs invasion in erα-positive endometrioid adenocarcinoma. Cancer Lett. 314, 41-53.

Cheung L.W., Hennessy B.T., Li J., Yu S., Myers A.P., Djordjevic B., Lu Y., Stemke-Hale K., Dyer M.D., Zhang F., Ju Z., Cantley L.C., Scherer S.E., Liang H., Lu K.H., Broaddus R.R. and Mills G.B. (2011). High frequency of pik3r1 and pik3r2 mutations in endometrial cancer elucidates a novel mechanism for regulation of pten protein stability. Cancer Discov. 1, 170-185.

Choi C.H., Lee J.S., Kim S.R., Kim T.J., Lee J.W., Kim B.G. and Bae D.S. (2010). Clinical significance of pmtor expression in endometrioid endometrial carcinoma. Eur. J. Obstet. Gyn. R. B. 153, 207-210.

Chung T.K., Cheung T.H., Huen N.Y., Wong K.W., Lo K.W., Yim S.F., Siu N.S., Wong Y.M., Tsang P.T., Pang M.W., Yu M.Y., To K.F., Mok S.C., Wang V.W., Li C., Cheung A.Y., Doran G., Birrer M.J., Smith D.I. and Wong Y.F. (2009). Dysregulated micrornas and their predicted targets associated with endometrioid endometrial adenocarcinoma in hong kong women. Int. J. Cancer 124, 1358-1365.

Chung T.K., Lau T.S., Cheung T.H., Yim S.F., Lo K.W., Siu N.S., Chan L.K., Yu M.Y., Kwong J., Doran G., Barroilhet L.M., Ng A.S., Wong R.R., Wang V.W., Mok S.C., Smith D.I., Berkowitz R.S. and Wong Y.F. (2012). Dysregulation of microrna-204 mediates migration and invasion of endometrial cancer by regulating foxc1. Int. J. Cancer 130, 1036-1045.

Cochrane D.R., Spoelstra N.S., Howe E.N., Nordeen S.K. and Richer J.K. (2009). Microrna-200c mitigates invasiveness and restores sensitivity to microtubule-targeting chemotherapeutic agents. Mol. Cancer Ther. 8, 1055-1066.

Cochrane D.R., Howe E.N., Spoelstra N.S. and Richer J.K. (2010). Loss of mir-200c: A marker of aggressiveness and chemoresistance in female reproductive cancers. J. Oncol. 2010, 821717.

Cohn D.E., Fabbri M., Valeri N., Alder H., Ivanov I., Liu C.G., Croce C.M. and Resnick K.E. (2010). Comprehensive mirna profiling of surgically staged endometrial cancer. Am. J. Obstet. Gynecol. 202, 656 e1-8.

Colas E., Pedrola N., Devis L., Ertekin T., Campoy I., Martinez E., Llaurado M., Rigau M., Olivan M., Garcia M., Cabrera S., Gil-Moreno A., Xercavins J., Castellvi J., Garcia A., Ramon y Cajal S., Moreno-Bueno G., Dolcet X., Alameda F., Palacios J., Prat J., Doll A., Matias-Guiu X., Abal M. and Reventos J. (2012). The emt signaling pathways in endometrial carcinoma. Clin. Transl. Oncol. 14, 715-720.

Devor E.J., Hovey A.M., Goodheart M.J., Ramachandran S. and Leslie K.K. (2011). Microrna expression profiling of endometrial endometrioid adenocarcinomas and serous adenocarcinomas reveals profiles containing shared, unique and differentiating groups of micrornas. Oncol. Rep. 26, 995.

Di Cristofano A. and Ellenson L.H. (2007). Endometrial carcinoma. Annu. Rev. Pathol. 2, 57-85.

Diaz-Martin J., Diaz-Lopez A., Moreno-Bueno G., Castilla M.A., Rosa-Rosa J.M., Cano A. and Palacios J. (2014). A core microrna signature associated with inducers of the epithelial-to-mesenchymal transition. J. Pathol. 232, 319-329.

Dong P., Kaneuchi M., Watari H., Hamada J., Sudo S., Ju J. and Sakuragi N. (2011). Microrna-194 inhibits epithelial to mesenchymal transition of endometrial cancer cells by targeting oncogene bmi-1. Mol. Cancer 10, 99.

Dong P., Karaayvaz M., Jia N., Kaneuchi M., Hamada J., Watari H., Sudo S., Ju J. and Sakuragi N. (2013). Mutant p53 gain-of-function induces epithelial-mesenchymal transition through modulation of the mir-130b-zeb1 axis. Oncogene 32, 3286-3295.

Dong P., Kaneuchi M., Watari H., Sudo S. and Sakuragi N. (2014). Microrna-106b modulates epithelial-mesenchymal transition by targeting twist1 in invasive endometrial cancer cell lines. Mol. Carcinogen. 53, 349-359.

Duggan B.D., Felix J.C., Muderspach L.I., Tourgeman D., Zheng J. and Shibata D. (1994). Microsatellite instability in sporadic endometrial carcinoma. J. Natl. Cancer. Inst. 86, 1216-1221.

Frankel L.B., Christoffersen N.R., Jacobsen A., Lindow M., Krogh A. and Lund A.H. (2008). Programmed cell death 4 (pdcd4) is an important functional target of the microrna mir-21 in breast cancer cells. J. Biol. Chem. 283, 1026-1033.

Gao M., Sun P., Wang J., Zhao D. and Wei L. (2006). Expression of estrogen receptor–related receptor isoforms and clinical significance in endometrial adenocarcinoma. Int. J. Gynecol. Cancer 16, 827-833.

He L., Thomson J.M., Hemann M.T., Hernando-Monge E., Mu D., Goodson S., Powers S., Cordon-Cardo C., Lowe S.W. and Hannon G.J. (2005). A microrna polycistron as a potential human oncogene. Nature 435, 828-833.

Hiroki E., Akahira J., Suzuki F., Nagase S., Ito K., Suzuki T., Sasano H. and Yaegashi N. (2010). Changes in microrna expression levels correlate with clinicopathological features and prognoses in endometrial serous adenocarcinomas. Cancer Sci. 101, 241-249.

Hiroki E., Suzuki F., Akahira J.i., Nagase S., Ito K., Sugawara J.i., Miki Y., Suzuki T., Sasano H. and Yaegashi N. (2012). Microrna-34b functions as a potential tumor suppressor in endometrial serous adenocarcinoma. Int. J. Cancer 131, E395-E404.

Howe E.N., Cochrane D.R. and Richer J.K. (2011). Targets of mir-200c mediate suppression of cell motility and anoikis resistance. Breast Cancer Res. 13, R45.

Huang Y.W., Liu J.C., Deatherage D.E., Luo J., Mutch D.G., Goodfellow P.J., Miller D.S. and Huang T.H. (2009). Epigenetic repression of microrna-129-2 leads to overexpression of sox4 oncogene in endometrial cancer. Cancer Res. 69, 9038-9046.

Huang Y.W., Kuo C.T., Chen J.H., Goodfellow P.J., Huang T.H., Rader J.S. and Uyar D.S. (2014). Hypermethylation of mir-203 in endometrial carcinomas. Gynecol. Oncol. 133, 340-345.

Hunten S., Siemens H., Kaller M. and Hermeking H. (2013). The p53/microrna network in cancer: Experimental and bioinformatics approaches. Adv. Exp. Med. Biol. 774, 77-101.

Huszar M., Pfeifer M., Schirmer U., Kiefel H., Konecny G.E., Ben-Arie A., Edler L., Munch M., Muller-Holzner E., Jerabek-Klestil S., Abdel-Azim S., Marth C., Zeimet A.G., Altevogt P. and Fogel M. (2010). Up-regulation of l1cam is linked to loss of hormone receptors and e-cadherin in aggressive subtypes of endometrial carcinomas. J . Pathol . 220, 551-561.

Jia W., Wu Y., Zhang Q., Gao G., Zhang C. and Xiang Y. (2013).

Identification of four serum micrornas from a genome-wide serum microrna expression profile as potential non-invasive biomarkers for endometrioid endometrial cancer. Oncol. Lett. 6, 261-267.

Jiang F., Liu T., He Y., Yan Q., Chen X., Wang H. and Wan X. (2011). Mir-125b promotes proliferation and migration of type ii endometrial carcinoma cells through targeting tp53inp1 tumor suppressor in vitro and in vivo. BMC Cancer 11, 425.

Jiang L., Meng W., Zeng J., Hu H. and Lu L. (2013). Mir-34c oligonucleotide enhances chemosensitivity of ishikawa cell to cisplatin by inducing apoptosis. Cell Biol. Int. 37, 577-583.

Karaayvaz M., Zhang C., Liang S., Shroyer K.R. and Ju J. (2012). Prognostic significance of mir-205 in endometrial cancer. PLoS One 7, e35158.

Klinge C.M. (2012). Mirnas and estrogen action. Trends Endocrin. Met. 23, 223-233.

Kong X., Xu X., Yan Y., Guo F., Li J., Hu Y., Zhou H. and Xun Q. (2014). Estrogen regulates the tumour suppressor mirna-30c and its target gene, mta-1, in endometrial cancer. PLoS One 9, e90810.

Kuhn E., Wu R.-C., Guan B., Wu G., Zhang J., Wang Y., Song L., Yuan X., Wei L. and Roden R.B. (2012). Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses. J. Natl. Cancer Inst. 104, 1503-1513.

Kuokkanen S., Chen B., Ojalvo L., Benard L., Santoro N. and Pollard J.W. (2010). Genomic profiling of microrna and messenger rnas reveals hormonal regulation in microrna expression in human endometrium. Biol. Reprod. 82, 791-801.

Lam E.W., Shah K. and Brosens J.J. (2012). The diversity of sex steroid action: The role of micro-rnas and foxo transcription factors in cycling endometrium and cancer. J. Endocrinol. 212, 13-25.

Le Gallo M., O'Hara A.J., Rudd M.L., Urick M.E., Hansen N.F., O'Neil N.J., Price J.C., Zhang S., England B.M. and Godwin A.K. (2012). Exome sequencing of serous endometrial tumors identifies recurrent somatic mutations in chromatin-remodeling and ubiquitin ligase complex genes. Nature Genet. 44, 1310-1315.

Le M.T., Teh C., Shyh-Chang N., Xie H., Zhou B., Korzh V., Lodish H.F. and Lim B. (2009). Microrna-125b is a novel negative regulator of p53. Genes Dev. 23, 862-876.

Lee J.W., Park Y.A., Choi J.J., Lee Y.Y., Kim C.J., Choi C., Kim T.J., Lee N.W., Kim B.G. and Bae D.S. (2011). The expression of the mirna-200 family in endometrial endometrioid carcinoma. Gynecol. Oncol. 120, 56-62.

Lee H., Choi H.J., Kang C.S., Lee H.J., Lee W.S. and Park C.S. (2012). Expression of mirnas and pten in endometrial specimens ranging from histologically normal to hyperplasia and endometrial adenocarcinoma. Modern Pathol. 25, 1508-1515.

Lee T.S., Jeon H.W., Kim Y.B., Kim Y.A., Kim M.A. and Kang S.B. (2013). Aberrant microrna expression in endometrial carcinoma using formalin-fixed paraffin-embedded (ffpe) tissues. PLoS One 8, e81421.

Leskela S., Leandro-Garcia L.J., Mendiola M., Barriuso J., Inglada-Perez L., Munoz I., Martinez-Delgado B., Redondo A., de Santiago J., Robledo M., Hardisson D. and Rodriguez-Antona C. (2011). The mir-200 family controls beta-tubulin iii expression and is associated with paclitaxel-based treatment response and progression-free survival in ovarian cancer patients. Endocr-Related Cancer 18, 85-95.

Li S.D., Zhang J.R., Wang Y.Q. and Wan X.P. (2010). The role of micrornas in ovarian cancer initiation and progression. J. Cell. Mol. Med. 14, 2240-2249.

Li S., Hu R., Wang C., Guo F., Li X. and Wang S. (2014). Mir-22 inhibits proliferation and invasion in estrogen receptor α-positive endometrial endometrioid carcinomas cells. Mol. Med. Rep. 9, 2393-2399.

Liu B., Che Q., Qiu H., Bao W., Chen X., Lu W., Li B. and Wan X. (2014). Elevated mir-222-3p promotes proliferation and invasion of endometrial carcinoma via targeting erα. PLoS One 9, e87563.

Ma L., Teruya-Feldstein J. and Weinberg R.A. (2007). Tumour invasion and metastasis initiated by microrna-10b in breast cancer. Nature 449, 682-688.

Ma W.J., Lv G.D., Tuersun A., Liu Q., Liu H., Zheng S.T., Huang C.G., Feng J.G., Wang X., Lin R.Y., Sheyhidin I. and Lu X.M. (2011). Role of microrna-21 and effect on pten in kazakh's esophageal squamous cell carcinoma. Mol. Biol. Rep. 38, 3253-3260.

McConechy M.K., Ding J., Cheang M.C., Wiegand K.C., Senz J., Tone A.A., Yang W., Prentice L.M., Tse K. and Zeng T. (2012). Use of mutation profiles to refine the classification of endometrial carcinomas. J. Pathol. 228, 20-30.

Meng F., Henson R., Lang M., Wehbe H., Maheshwari S., Mendell J.T., Jiang J., Schmittgen T.D. and Patel T. (2006). Involvement of human micro-rna in growth and response to chemotherapy in human cholangiocarcinoma cell lines. Gastroenterology 130, 2113-2129.

Mulrane L., McGee S.F., Gallagher W.M. and O'Connor D.P. (2013). Mirna dysregulation in breast cancer. Cancer Res. 73, 6554-6562.

Myatt S.S., Wang J., Monteiro L.J., Christian M., Ho K.K., Fusi L., Dina R.E., Brosens J.J., Ghaem-Maghami S. and Lam E.W. (2010). Definition of microrna that repress expression of the tumor suppressor gene foxo1 in endometrial cancer. Cancer Res. 70, 367-377.

Network C.G.A.R. (2013). Integrated genomic characterization of endometrial carcinoma. Nature 497, 67-73.

Nishida N., Yokobori T., Mimori K., Sudo T., Tanaka F., Shibata K., Ishii H., Doki Y., Kuwano H. and Mori M. (2011). Microrna mir-125b is a prognostic marker in human colorectal cancer. Int. J. Oncol. 38, 1437-1443.

Pan Q., Luo X., Toloubeydokhti T. and Chegini N. (2007). The expression profile of micro-rna in endometrium and endometriosis and the influence of ovarian steroids on their expression. Mol. Hum. Reprod. 13, 797-806.

Panda H., Pelakh L., Chuang T.D., Luo X., Bukulmez O. and Chegini N. (2012). Endometrial mir-200c is altered during transformation into cancerous states and targets the expression of zebs, vegfa, flt1, ikkbeta, klf9, and fbln5. Reprod. Sci. 19, 786-796.

Pandey D.P. and Picard D. (2009). Mir-22 inhibits estrogen signaling by directly targeting the estrogen receptor α mrna. Mol. Cell. Biol. 29, 3783-3790.

Park Y.A., Lee J.W., Choi J.J., Jeon H.K., Cho Y., Choi C., Kim T.J., Lee N.W., Kim B.G. and Bae D.S. (2012). The interactions between microrna-200c and brd7 in endometrial carcinoma. Gynecol. Oncol. 124, 125-133.

Qin X., Yan L., Zhao X., Li C. and Fu Y. (2012). Microrna-21 overexpression contributes to cell proliferation by targeting pten in endometrioid endometrial cancer. Oncol. Lett. 4, 1290-1296.

Qu C., Liang Z., Huang J., Zhao R., Su C., Wang S., Wang X., Zhang R., Lee M.H. and Yang H. (2012). Mir-205 determines the radioresistance of human nasopharyngeal carcinoma by directly targeting pten. Cell Cycle 11, 785-796.

Ratner E.S., Tuck D., Richter C., Nallur S., Patel R.M., Schultz V., Hui P., Schwartz P.E., Rutherford T.J. and Weidhaas J.B. (2010).

Microrna signatures differentiate uterine cancer tumor subtypes. Gynecol. Oncol. 118, 251-257.

Schirmer U., Doberstein K., Rupp A.K., Bretz N.P., Wuttig D., Kiefel H., Breunig C., Fiegl H., Muller-Holzner E., Zeillinger R., Schuster E., Zeimet A.G., Sultmann H. and Altevogt P. (2014). Role of mir-34a as a suppressor of l1cam in endometrial carcinoma. Oncotarget 5, 462-472.

Sebastianelli A., Renaud M.C., Gregoire J., Roy M. and Plante M. (2010). Preoperative ca 125 tumour marker in endometrial cancer: Correlation with advanced stage disease. J. Obstet. Gynaecol. Can. 32, 856-860.

Shang C., Lu Y.M. and Meng L.R. (2012). Microrna-125b down-regulation mediates endometrial cancer invasion by targeting erbb2. Med. Sci. Monit.18, BR149-155.

Siegel R., Naishadham D. and Jemal A. (2013). Cancer statistics, 2013. CA Cancer J. Clin. 63, 11-30.

Slomovitz B.M. and Coleman R.L. (2012). The pi3k/akt/mtor pathway as a therapeutic target in endometrial cancer. Clin. Cancer Res. 18, 5856-5864.

Snowdon J., Zhang X., Childs T., Tron V.A. and Feilotter H. (2011). The microrna-200 family is upregulated in endometrial carcinoma. PLoS One 6, e22828.

Su N., Qiu H., Chen Y., Yang T., Yan Q. and Wan X. (2013). Mir-205 promotes tumor proliferation and invasion through targeting esrrg in endometrial carcinoma. Oncol. Rep. 29, 2297-2302.

Torres A., Torres K., Pesci A., Ceccaroni M., Paszkowski T., Cassandrini P., Zamboni G. and Maciejewski R. (2012). Deregulation of mir-100, mir-99a and mir-199b in tissues and plasma coexists with increased expression of mtor kinase in endometrioid endometrial carcinoma. BMC Cancer 12, 369.

Torres A., Torres K., Pesci A., Ceccaroni M., Paszkowski T., Cassandrini P., Zamboni G. and Maciejewski R. (2013). Diagnostic and prognostic significance of mirna signatures in tissues and plasma of endometrioid endometrial carcinoma patients. Int. J. Cancer 132, 1633-1645.

Tsukamoto O., Miura K., Mishima H., Abe S., Kaneuchi M., Higashijima A., Miura S., Kinoshita A., Yoshiura K. and Masuzaki H. (2014). Identification of endometrioid endometrial carcinoma-associated micrornas in tissue and plasma. Gynecol. Oncol. 132, 715-721.

Valeri N., Gasparini P., Fabbri M., Braconi C., Veronese A., Lovat F., Adair B., Vannini I., Fanini F., Bottoni A., Costinean S., Sandhu S.K., Nuovo G.J., Alder H., Gafa R., Calore F., Ferracin M., Lanza G., Volinia S., Negrini M., Mcllhatton M.A., Amadori D., Fishel R. and Croce C.M. (2010). Modulation of mismatch repair and genomic stability by mir-155. Proc. Natl. Acad. Sci. USA 107, 6982-6987.

Wang D., Zheng W., Wang S.M., Wang J.B., Wei W.Q., Liang H., Qiao Y.L. and Boffetta P. (2012). Estimation of cancer incidence and mortality attributable to overweight, obesity, and physical inactivity in china. Nutr. Cancer 64, 48-56.

Ward E.C., Hoekstra A.V., Blok L.J., Hanifi-Moghaddam P., Lurain J.R., Singh D.K., Buttin B.M., Schink J.C. and Kim J.J. (2008). The regulation and function of the forkhead transcription factor, forkhead box o1, is dependent on the progesterone receptor in endometrial carcinoma. Endocrinology 149, 1942-1950.

Wu W., Lin Z., Zhuang Z. and Liang X. (2009). Expression profile of mammalian micrornas in endometrioid adenocarcinoma. Eur. J. Cancer Prev. 18, 50-55.

Wu Y., Xiao Y., Ding X., Zhuo Y., Ren P., Zhou C. and Zhou J. (2011). A mir-200b/200c/429-binding site polymorphism in the 3' untranslated region of the ap-2alpha gene is associated with cisplatin resistance. PLoS One 6, e29043.

Wu D., Huang H.J., He C.N. and Wang K.Y. (2013). Microrna-199a-3p regulates endometrial cancer cell proliferation by targeting mammalian target of rapamycin (mtor). Int. J. Gynecol. Cancer 23, 1191-1197.

Xu Y.Y., Wu H.J., Ma H.D., Xu L.P., Huo Y. and Yin L.R. (2013). Microrna-503 suppresses proliferation and cell-cycle progression of endometrioid endometrial cancer by negatively regulating cyclin d1. FEBS J. 280, 3768-3779.

Yeramian A., Moreno-Bueno G., Dolcet X., Catasus L., Abal M., Colas E., Reventos J., Palacios J., Prat J. and Matias-Guiu X. (2013). Endometrial carcinoma: Molecular alterations involved in tumor development and progression. Oncogene 32, 403-413.

Zhang S. and Yu D. (2010). Pi(3)king apart pten's role in cancer. Clin. Cancer Res. 16, 4325-4330.

Zhang R., He Y., Zhang X., Xing B., Sheng Y., Lu H. and Wei Z. (2012). Estrogen receptor-regulated micrornas contribute to the bcl2/bax imbalance in endometrial adenocarcinoma and precancerous lesions. Cancer Lett. 314, 155-165.

Zhang X., Dong Y., Ti H., Zhao J., Wang Y., Li T. and Zhang B. (2013). Down-regulation of mir-145 and mir-143 might be associated with DNA methyltransferase 3b overexpression and worse prognosis in endometrioid carcinomas. Hum. Pathol. 44, 2571-2580.

Zhou J., Song T., Gong S., Zhong M. and Su G. (2010). Microrna regulation of the expression of the estrogen receptor in endometrial cancer. Mol. Med. Rep. 3, 387-392.

Zhou H., Xu X., Xun Q., Yu D., Ling J., Guo F., Yan Y., Shi J. and Hu Y. (2012). Microrna-30c negatively regulates endometrial cancer cells by targeting metastasis-associated gene-1. Oncol. Rep. 27, 807-812.

Zighelboim I., Goodfellow P.J., Gao F., Gibb R.K., Powell M.A., Rader J.S. and Mutch D.G. (2007). Microsatellite instability and epigenetic inactivation of mlh1 and outcome of patients with endometrial carcinomas of the endometrioid type. J. Clin. Oncol. 25, 2042-2048.

Accepted November 26, 2014