Review

Role of miRNAs in endometrial cancer

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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; McConkey 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, miR-210, 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, miR-204, miR-99b and miR-193b had decreased expression in cancer tissues (Banno et al., 2013). In this review, the role of miRNAs in the
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 carcinomas 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, mRNA 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-associated 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 ECC lines. This result seems counterintuitive given that miR-206 expression is elevated in more aggressive ERα-positive ECs. 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
MiRNAs overexpression in colorectal cancer was target core MMR proteins and induce MSI. For example, DNA sequences (Yeramian et al., 2013). MiRNAs can accumulation of mutations in coding and non-coding mismatch repair (MMR) deficiency leads to the non-EEC. In sporadic tumors, the MSI-associated 1994). MSI occurs more frequently in EEC (30%) than in normal endometria (Hiroki et al., 2012). The increased expression of mTOR kinase in EEC coexists with downregulation of its in-silico predicted 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
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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 trans repression of a large set of genes (Dong et al., 2013). In EC, the GOF p53 mutant has been found to bind directly and trans repress 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

<p>| Table 1. Prognostic value of miRNAs in EC. |
|-----------------------------|------------------|---------------------|------------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>miRNA(s)</th>
<th>Patients</th>
<th>Survival outcome</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-205</td>
<td>48 ECs, including 24EECs, 13NEECs, 11 other ECs</td>
<td>OS</td>
<td>High levels of miR-205 expression associated with poor patient OS</td>
<td>Karaayvaz et al., 2012</td>
</tr>
<tr>
<td>miR-130b</td>
<td>32 ECs, including 15EECs, 8NEECs, 9 other ECs</td>
<td>OS</td>
<td>High levels of miR-130b expression was associated with good patient OS.</td>
<td>Dong et al., 2013</td>
</tr>
<tr>
<td>miR-1228/miR-200c/miR-429</td>
<td>77 ECs</td>
<td>OS</td>
<td>MiRNA signature miR-1228/miR-200c/miR-429 overexpression predicted poor patient OS.</td>
<td>Torres et al., 2013</td>
</tr>
<tr>
<td>miR-1228/miR-429</td>
<td>77 ECs</td>
<td>PFS</td>
<td>MiRNA signature miR-1228/miR-429 overexpression predicted poor patient PFS.</td>
<td>Torres et al., 2013</td>
</tr>
<tr>
<td>miR-143/miR-145</td>
<td>107 ECs, including 85ECs, 22NECs</td>
<td>OS</td>
<td>Combination of DNMT3B overexpression and miR-145 or miR-143 downregulation was predictive of poor patient survival.</td>
<td>Zhang et al., 2013</td>
</tr>
<tr>
<td>miR-101/miR-10b'/miR-139-5p/miR-152/miR-29b/miR-455-5p</td>
<td>21 NEECs</td>
<td>OS</td>
<td>Reduced expression of miRNA-101, miR-10b',miR-139-5p, miR-152, miR-29b and miR-455-5p was significantly correlated with shorter OS.</td>
<td>Hiroki et al., 2010</td>
</tr>
<tr>
<td>miR-152/miR-29b/miR-455-5p</td>
<td>21 NEECs</td>
<td>PFS</td>
<td>Reduced expression of miR-152, miR-29b and miR-455-5p was significantly correlated with shorter PFS.</td>
<td>Hiroki et al., 2010</td>
</tr>
<tr>
<td>miR-129-2</td>
<td>74 ECs</td>
<td>OS</td>
<td>Hypermethylation of miR-129-2 was associated with shorter patient OS.</td>
<td>Huang et al., 2009</td>
</tr>
<tr>
<td>miR-100</td>
<td>73 ECs</td>
<td>OS</td>
<td>Reduced expression of miR-100 was associated with shorter patient OS.</td>
<td>Torres et al., 2012</td>
</tr>
<tr>
<td>miR-503</td>
<td>48 ECs</td>
<td>OS</td>
<td>Reduced expression of miR-503 was associated with shorter patient OS.</td>
<td>Xu et al., 2013</td>
</tr>
<tr>
<td>miR-199a</td>
<td>141ECs, including 128 ECs, 13 NEECs</td>
<td>PFS</td>
<td>Reduced expression of miR-199a was correlated with poor patient OS and PFS.</td>
<td>Cohn et al., 2010</td>
</tr>
</tbody>
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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 chemosensitivity 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.

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