The Role of MicroRNA Molecules and MicroRNA-Regulating Machinery in the Pathogenesis and Progression of Epithelial Ovarian Cancer

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Abstract

MicroRNA molecules are small, single-stranded RNA molecules that function to regulate networks of genes. They play important roles in normal female reproductive tract biology, as well as in the pathogenesis and progression of epithelial ovarian cancer. DROSHA, DICER, and Argonaute proteins are components of the microRNA-regulatory machinery and mediate microRNA production and function. This review discusses aberrant expression of microRNA molecules and microRNA-regulating machinery associated with clinical features of epithelial ovarian cancer. Understanding the regulation of microRNA molecule production and function may facilitate the development of novel diagnostic and therapeutic strategies to improve the prognosis of women with epithelial ovarian cancer. Additionally, understanding microRNA molecules and microRNA-regulatory machinery associations with clinical features may influence prevention and early detection efforts.

1. Introduction

Ovarian cancer is the most lethal gynecologic malignancy and will claim more than 14,000 lives in 2017 in the United States (1). Epithelial ovarian cancer (EOC) is the most prevalent type of ovarian cancer, accounting for 90% of all ovarian cancers. It is characterized by distinct histological phenotypes including serous, endometrioid, clear-cell, and mucinous.

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Each histotype is thought to arise from distinct precursor lesions of the female reproductive tract (2). Molecularly, the landscape of each individual EOC histotype is distinct at the gene expression and genomic DNA level, allowing novel means to classify tumors beyond traditional histology (3, 4).

Early stage EOC has a 5-year survival of 92%, while late stage disease has a 5-year survival of only 29%. Unfortunately, 79% of women with EOC have late stage disease, defined as regional or distant metastasis, based on SEER data from 2006–2012 (1). Improved screening approaches to detect early stage disease and novel histotype- or molecular-marker specific therapies for the treatment of late stage disease are urgently needed. This review highlights clinical associations of microRNA molecules and microRNA machinery, including DROSHA, DICER, and Argonaute proteins, in EOC identified since our last review (5). The clinical relevance of these potential new biomarkers as prognostic, diagnostic, and therapeutic molecules are discussed.

2. Genesis of Mature MicroRNA Molecules

a. MicroRNA-Regulating Machinery

RNA polymerase II transcribes microRNA molecules from genomic DNA into a primary microRNA molecule (pri-miRNA). Pri-miRNA molecules are typically greater than 200 nucleotides in length with a characteristic stem loop structure. Furthermore, microRNA clusters containing multiple stem loop structures, each coding for a mature microRNA molecule, can be in the kilobase size range. Pri-miRNA molecules are recognized by DROSHA, an RNAse III, which cuts the double-stranded RNA into ~70-nucleotide precursor microRNA (pre-miRNA) in the nucleus. Pre-miRNA molecules are exported to the cytoplasm and are processed by DICER, an RNAse III, into two unique single-stranded mature microRNA molecules representing each side of the stem loop structure. Mature microRNA molecules are loaded onto the Argonaute-containing RNA-induced silencing complex (RISC). Within this structure, mature microRNA molecules function to repress gene expression by complementary binding of the 3' untranslated region (UTR) of the target gene to the miRNA seed sequence, nucleotides 2–8 of the mature miRNA molecule, leading to transcript degradation, and subsequent gene product loss (6). Studies have shown that microRNA-target genes play an important role in EOC cancer biology (7). Thus, microRNA molecules and their biogenesis regulation as mediated by microRNA machinery is clinically important.

b. Primer on MicroRNA Nomenclature

Understanding how microRNA molecules are named is important for understanding how closely related microRNA molecules are to each other in the context of clinical associations and molecular functions. MicroRNA molecules are sequentially named as they are discovered. For example, miR-21 was discovered and annotated in miRBase prior to miR-1307. Identical mature microRNA molecules of identical sequence may originate from different genomic loci with different primary microRNA molecule sequence due to the RNA processing. For example, miR-196a-1 and miR-196a-2 have identical mature microRNA sequence but originate from different genomic locations (*i.e.*, chromosome 17 versus

chromosome 12). This is different from microRNA molecules that have a closely related mature microRNA sequence such as miR-10a and miR-10b, which have a different mature sequence and are derived from different genomic locations. MiR-10a-5p and miR-10b-5p share the same seed sequence but different in one nucleotide in the mature sequence (8).

DICER processes each precursor microRNA into two mature molecules, with reverse complement sequence. Traditionally, the microRNA molecule with the greatest abundance was assigned the microRNA name (*i.e.*, miR-29c), while the mature microRNA molecule on the other arm was called the * form (*i.e.*, miR-29c*) (8). This nomenclature, based on abundance, was phased out, and a new nomenclature, based on the location of the mature microRNA on the 5' or 3' strand, was phased in. Thus, the miRNA-3p forms are not necessarily less abundant or less functional. The nomenclature is now based on sequence location on the stem look. Mature microRNA molecules are grouped into families based on identical seed sequence, which are nucleotides 2–8 of the mature molecule. This sequence serves to function in complementary binding to the 3'UTR, leading to downstream effects of transcript repression (8). MiRNA-5p and miRNA-3p molecules do not typically fall within the same microRNA family as they have a reverse complementary sequence. For example, the miR-10-5p family is comprised of miR-10a-5p and miR-10b-5p while miR-10a-3p and miR-10b-3p are each members of their own family. Finally, isomiRs are mature microRNA molecules that differ from the mature sequence by 1–2 nucleotides. For example, the miR-21+CA isomiR is formed from a unique tailing and trimming mechanism in proliferative diseases such as endometriosis and endometrial cancer. It contains the miR-21 mature sequence plus an additional two nucleotides (9). While isomiRs have not yet been described in EOC, these unique molecules represent an opportunity to be utilized as biomarkers.

3. Clinical Implications

a. Aberrant Expression of MicroRNA-Biogenesis Machinery Components in EOC

Multiple studies have examined the relative expression of DICER and DROSHA in EOC compared to control tissues. Choice of control tissue for comparison is critical in relative expression studies. Each histotype of ovarian cancer may arise from distinct precursor cells (2). For example, high-grade serous EOC may arise from the fallopian tube or ovarian surface epithelium (10–12). Endometrioid and clear-cell EOC may arise from a benign transformation of endometriosis (13, 14). For these reasons, we will define histotype and control tissues used for each study.

Using 50 cases of high-grade serous ovarian cancer, Flavin *et al* (15) revealed a significant upregulation of *DROSHA* and a trend towards upregulation in *DICER* by QPCR compared to normal ovary. Similarly, by immunohistochemistry in 37 samples, DICER showed a significant upregulation in high-grade serous ovarian cancer. High DICER expression was associated with an absence of lymph node metastasis and a low proliferation index. DICER expression did not correlate with disease free or overall survival (15). The authors did not comment on DROSHA expression by immunohistochemistry, nor did they comment on the association of DROSHA with clinical factors. Additionally, only high-grade serous EOC tumor samples were examined.

Merritt et al (16) examined *DICER* and *DROSHA* in 111 samples of EOC (2 endometrioid, 109 serous, 93 high grade, 18 low grade) by QPCR with validation by immunohistochemistry. Benign ovarian surface epithelium was used as a control. Using the bimodal expression of *DICER* and *DROSHA* in their dataset to classify tumors into low and high expression for *DICER* and *DROSHA*, they examined clinical associations. Low *DICER* expression was associated with advanced-stage disease and reduced median survival. Low *DROSHA* expression was associated with suboptimal cytoreduction and reduced median survival. Death from ovarian cancer was statistically associated with low levels of both *DICER* and *DROSHA* while high levels of both *DICER* and *DROSHA* were associated with increased median survival. Low *DICER* was a predictor of poor prognosis (hazard ratio, 2.10; 95% CI, 1.15 to 3.85) but low *DROSHA* was not. However, low *DICER* and low *DROSHA* was a predictor of death (hazard ratio, 4.00; 95% CI, 1.82 to 9.09). Cells with low *DICER* expression could not process shRNA, an important potential therapeutic consideration (16). A similar study using semi-quantitative RT PCR showed that *DICER* expression was downregulated in both benign and malignant ovarian tumors compared to normal ovary. However, the specific histotype of malignant ovarian tumors was not defined (17).

DICER expression was evaluated by immunohistochemistry in a large tissue microarray containing 87 serous and 39 non-serous ovarian tumors. DICER expression negatively correlated with node status and tumor grade. Low DICER expression in serous tumors was associated with poor overall survival. A similar trend was found for all tumors in the dataset but the analysis was not performed for specific histotypes. MicroRNA profiling in tumors with low DICER showed significant downregulation of many microRNA molecules compared to tumors with high DICER expression. Additionally, tumors with low DICER expression also had low estrogen receptor expression (18). Zhang et al (19) did not find any significant difference in *DICER* or *DROSHA* expression by QPCR or immunohistochemistry staining between early and late stage disease without evaluation of normal control tissues, although there were differences in microRNA expression levels (19).

Flavin et al (15) showed an association of high DICER expression associated with better prognosis tumors (*i.e.*, low metastatic lesions, low proliferative index tumors) but did not comment on low DICER expression being associated with poor prognosis tumors per se (15). Others have shown an association of poor survival with low expression of DICER (16, 18). However, Flavin et al did not find a significant association of DICER expression with survival rates (15). Clinical associations for DICER expression are intriguing for EOC. However, studies within the breast cancer literature have shown divergent expression results using different DICER antibodies based on hormone receptor status of the tissues (20). Additionally, each study in EOC determined a relative cut off value for "low" and "high" DICER expression. Prior to use of DICER expression in clinical care, these differences in cut off values and antibody use must be standardized.

A meta-analysis showed an overall association of low *DICER* expression with poor prognosis in multiple cancer types including ovarian cancer (21). Lower expression of microRNA machinery is associated with poor prognosis tumors, suggesting that global loss of microRNA regulation may underlie the pathophysiology of poor prognosis EOC. These

studies suggest that loss of DICER may act as loss of a tumor suppressor, leading to disease that is more aggressive. Finally, these studies also suggest that lack of DICER may influence attempts to treat tumors with small RNA molecules such as shRNA molecules.

Examination of expression of DICER, DROSHA, Argonaute 1 (AGO1), and Argonaute 2 (AGO2) in serous ovarian cancer revealed higher expression in metastatic lesions – either solid metastatic lesions or effusions – compared to the primary tumor (22). Thus, high levels of microRNA machinery may be required for disease progression.

b. Aberrant MicroRNA-Regulating Machinery Expression in Mouse Models

MicroRNA-regulating machinery is required for appropriate development of the female reproductive tract, as studies from mice have shown that full deletion of *Dicer* or *Ago2* leads to embryonic lethality (23, 24). Conditional deletion of *Dicer* or *Ago2*, allowing for postnatal studies with targeted deletion to the female reproductive tract using genetically engineered mouse models, revealed defects in female fertility (25). However, deletion of *Drosha* in mice does not affect fertility or female reproductive tract development (25). Importantly, none of these models result in a cancer phenotype, suggesting a critical role in normal female reproductive tract development and function, but not cancer initiation in the mouse, and thus, Dicer is not likely a true tumor suppressor.

Notably, loss of *Dicer* is critical to the development of high-grade serous EOC that begins in the oviduct of the mouse but also requires phosphatase and tensin homolog (*Pten*) deletion. In terms of translational importance, the histology of the ovarian tumors from anti-Müllerian hormone receptor type 2-*Cre* recombinase (*Amhr2$^{Cre/+}$); Dicer$^{flox/flox}$; Pten$^{flox/flox}$* mice recapitulated high-grade serous tumors from women. When the oviducts of *Amhr2$^{Cre/+}$; Dicer$^{f/f}$; Pten$^{f/f}$* mice were removed, the mice failed to develop ovarian tumors. Thus, this model represents an important model to study the origins and mechanism of disease processes from the oviduct (10). However, a majority [~96% of the Cancer Genome Atlas (TCGA) population] of high-grade serous EOC tumors from women contain mutations in tumor protein 53 (*TP53*) (26). Addition of a TP53 mutation to the *Amhr2$^{Cre/+}$; Dicer$^{f/f}$; Pten$^{f/f}$* mice (*Amhr2$^{Cre/+}$; Dicer$^{f/f}$; Pten$^{f/f}$; TP53^{R172H}* mice) with removal of oviduct revealed metastatic tumors arising from the ovary. However, loss of *Dicer* was not required as *Amhr2$^{Cre/+}$; Pten$^{f/f}$; TP53^{R172H}* mice developed similar metastatic lesions from the ovaries (12). Thus, loss of Dicer seems to be important for high-grade serous EOC arising from the oviduct but not for disease arising from the ovary. The role of specific cell types and specific genetic hits in the origin of EOC requires further study prior to translational extrapolation to disease in women.

Other genetically engineered mouse models of *Dicer* deletion have revealed that loss of two alleles of *Dicer* is protective against cancer development, while loss of one allele gives a more aggressive cancer phenotype. Specifically, conditional loss of one allele of *Dicer* had a faster rate of lung cancer formation on an oncogenic KRAS proto-oncogene, GTPase (*Kras^{G12D}*) background, while loss of both *Dicer* alleles led to inhibition of tumor formation (27). Similarly, *Dicer* haploinsufficiency on an oncogenic B-Raf proto-oncogene, serine/threonine kinase (*Braf) (V600E)* background led to increased metastasis in sarcomas (28). Loss of one allele of *Dicer* in the retinoblasts of mice led to aggressive retinoblastoma with

the inactivation of the retinoblastoma gene (29). Similarly, loss of one allele of *Dicer* with *Pten* in the prostate led to more aggressive tumors (30). These effects seem to be oncogene and tissue dependent, as conditional *Dicer* haploinsufficiency on an oncogenic MYC proto-oncogene, bHLH transcription factor (*c-Myc*) background does not facilitate cancers in B cells (31). One hypothesis supported by *in vitro* studies is that loss of one allele of *Dicer* affects microRNA processing, or total expression of microRNA molecules, with loss of one allele of *Dicer* affecting the ratio of miRNA-5p to miRNA-3p from the precursor microRNA (32–34). Further studies are needed to determine the effects of DICER on microRNA processing in the initiation and progression of cancer in other female reproductive tract cancers, such as EOC.

c. Genetic Alterations of MicroRNA Machinery Genes

EOC is a genetically heterogeneous disease. Examination of copy number loss of *DICER* in TCGA datasets revealed frequent loss of *DICER* in high-grade serous EOC, consistent with low levels of expression and association with poor clinical outcome (10). However, *DICER* functional mutations are not recurrent in high-grade serous ovarian cancer (16, 35, 36). Liang et al (37) studied single nucleotide polymorphisms from 8 miRNA processing genes and 134 microRNA-binding sites in genes in 339 EOC cases and 349 healthy controls. This work revealed that polymorphisms in specific microRNA binding sites in genes were associated with cancer risk, overall survival, and treatment response. In particular, a homozygous polymorphism in platelet derived growth factor C (*PDGFC*) showed the most statistically significant effect on survival (37). Single nucleotide polymorphisms in *DROSHA* were found to be associated with an increased risk of EOC diagnosis in a mostly Caucasian study population (37), but this association was not significant in a larger more ethnically diverse population (38). Other studies have shown no association between polymorphisms in microRNA binding sites or mature microRNA molecules with EOC clinical outcomes (39–41). Thus, use of single nucleotide polymorphisms in microRNA machinery genes, mature microRNA molecules, or microRNA binding sites in genes to determine the risk of EOC diagnosis has been not been replicated clinically. Larger studies and grouping samples according to newly published genetic changes (4) instead of histotype or grade may allow for results that are more replicable.

4. MicroRNA Molecules as Clinical Biomarkers for EOC

a. MicroRNA Molecules with Clinical Associations

In recent years, comprehensive profiling studies have revealed that microRNA molecules have distinct patterns of expression in EOC (Supplemental Tables 1–2). A majority of these studies have used high-grade serous EOC or grouped all EOC histotypes together during analysis. The choice of the control group for comparison has differed across many studies. Additionally, the microRNA-profiling platform has also differed. Thus, it is not surprising that the reproducibility of some microRNA profiling datasets have been called into question, as the comparisons, samples, and technical platforms are not the same (42). Attention to these details will be critical to deciphering important biomarkers.

Multiple studies have profiled microRNA molecules from clinical samples to determine if microRNA molecules would be good biomarkers for EOC (Supplemental Tables 1–2). Many of these large profiling studies aim to classify tumors into clinically important associations such as poor prognosis tumors, histotype, or chemotherapy responsive. Many of these studies do not limit samples to one particular histotype. Supplemental Tables 1 and 2 list the studies, brief details of experimental design including sample number, histotype, microRNA profiling platform, and validation sample set if applicable. There are 14 studies that use only serous histotype samples (Supplemental Table 1) and 13 studies that mix histotypes in the same study (Supplemental Table 2). Since our two previous reviews (5, 25), the published studies for comprehensive microRNA profiling studies in EOC have expanded greatly in number and sophistication of experimental design. Clinical associations of specific microRNA molecules in EOC tissues are listed in Supplemental Table 3. Thus, microRNA molecules hold promise for clinically useful biomarkers.

b. MicroRNA Molecules in Rare Histotypes of EOC

The molecular landscape of each histotype of EOC is distinct (3, 4). However, all patients are treated similarly with standard of care debulking surgery and chemotherapy regimens, with dismal "cure" rates of 20% (1). Notably, the presence of endometriosis, a benign pathologic growth of endometrium outside the uterus (43), leads to a 50% increase in the risk of ovarian cancer (44). Further, women with endometriosis are at higher risk of developing rare EOC subtypes, including clear-cell or endometrioid histotypes, as opposed to the more common high-grade serous disease (44). Therefore, a critical need exists to understand the genomic and pathophysiological differences between these histologic subtypes for early detection and for the development of histotype-specific therapies. Several studies have examined the role of microRNA molecules in these distinct EOC types.

MiR-132, miR-9, miR-126, miR-34a, and miR-21 were found to differentiate clear-cell from serous tumors. MiR-9, the most highly expressed of those five microRNA molecules in clear-cell samples, was found to be involved in cellular invasion *in vitro* (45). In a similar study, miR-510, miR-129-3p, miR-483 and miR-449a were found to be differentially expressed between serous and clear-cell ovarian tumors. All were associated with advanced tumor stage. Low expression of miR-129-3p or low expression of miR-510 was associated with poor overall survival (46). MiR-30a*, miR-30e* and miR-505* were the most upregulated miRNAs in clear-cell ovarian tumors compared with serous tumors (47). Lower expression of miR-30a*, miR-30e* and miR-505* were associated with poorer prognosis. Additionally, miR-134-3p was downregulated in CD44+/CD133+ ovarian cancer cells from clear-cell tumors. MiR-134-3p directly targeted RAB27A, which is involved in downregulation of stem cell markers and adhesions proteins (48). Overexpression of miR-21 was associated with endometriosis in clear-cell ovarian cancer, and miR-21 targets the tumor suppressor PTEN (49). Thus, microRNA molecules play a functional role in the regulation of gene expression in clear-cell ovarian cancer differently than high-grade serous ovarian cancer.

As a potential clinically relevant serum biomarker, miR-130a is elevated in the serum of women prior to surgery for clear-cell ovarian cancer and falls after surgery. Additionally,

miR-130a levels increase prior to CA-125 levels prior to disease recurrence, making miR-130a a promising biomarker (50). This was a well-normalized study in a specific histotype of ovarian cancer in a specific ethnic population. The results are promising and need further study in benign disease, normal control women, and other histotypes. A similarly important study showed a minimal signature of microRNA molecules detected in blood and the ability to determine whether a woman had endometriosis, clear-cell, endometrioid, or serous ovarian cancer (51). Thus, the clinical usefulness of microRNA molecules as biomarkers for EOC, in particular, subtype-specific histotypes, has not been sufficiently studied.

Multiple studies have highlighted the function of microRNA molecules in terms of endometrioid histotypes (52–54). Expression of miR-191 was increased in ovarian endometriosis and endometrioid EOC. Importantly, miR-191 overexpression *in vitro* decreased tumor necrosis factor alpha- (TNFα) induced apoptosis (52). Given the high expression of TNFα in the pelvic cavity of women with endometriosis (55), the failure of apoptosis due to high miR-191 may play a role in the over proliferation of endometrioid EOC associated with endometriosis. Additionally, miR-191 directly targets TIMP metallopeptidase inhibitor 3 (TIMP3) and loss of miR-191 leads to decreased cellular proliferation and decreased invasion *in vitro* (53). Furthermore, miR-370 is downregulated in endometrioid EOC compared to the normal ovary or other histotypes of EOC. Overexpression of miR-370 *in vitro* showed decreased proliferation and increased sensitivity to platinum. Similar results were revealed in xenograft studies with miR-370 (54). Thus, microRNA molecules may play significant roles in the underlying biology of endometrioid EOC.

c. MicroRNA Molecules in Bodily Fluids as Biomarkers

MicroRNA molecules offer promise as molecules for early detection. Urinary excretion of miR-30a-5p is found in serous ovarian cancer but not in other cancer types. After primary debulking surgery, less expression of miR-30a-5p is found in the urine (56). While Zhou et al (56) did not examine the expression of miR-30a-5p after recurrence of ovarian cancer, this microRNA may serve as a useful biomarker for determination of disease. Langhe et al (57) used a discovery set of five malignant high-grade serous and five benign serous cystadenomas to examine the expression of microRNA levels in blood. They determined a significant downregulation of let-7i-5p, miR-122, miR-152-5p and miR-25-3p in malignant disease compared to benign disease state (57). Thus, microRNA molecules may serve as biomarkers for pre-operative discrimination of benign and malignant disease. Table 1 lists the clinically relevant microRNA molecules as biomarkers for EOC and their associated clinical features.

d. MicroRNA Molecules as Markers of Treatment Specificity

A strategic priority of the NCI Gynecologic Cancer Steering Committee is identification of molecular and/or pathologic cancer subsets to drive therapy and improve outcomes. A large well-normalized study examined outcomes and expression of microRNA molecules in the blood of women with EOC in ICON7. This study aimed at assessing the safety and efficacy of adding the anti-angiogenesis immunologic therapy, specifically bevacizumab, to standard

therapy. The isolation of microRNA molecules from blood was well described, and the experimental design contained a discovery and validation cohort. MiR-1274a, miR-141, miR-200b, and miR-200c were associated with survival in the discovery studies. MiR-141 and miR-200b were similarly associated in the validation cohort containing all histotypes. MiR-200c was associated with better survival in women treated with bevacizumab compared to standard chemotherapy. Sub-classification of serous tumors revealed low miR-1274a associated with prolonged survival in discovery and validation groups (58). With the caveat that the study awaits independent replication, the results suggest the potential usefulness of miRNA profiles for the future choice of therapy regimens in EOC.

Petrillo et al (59) analyzed microRNA profiles from matched tumor samples before and after neoadjuvant chemotherapy. They found that samples collected after neoadjuvant chemotherapy (NACT) had distinct microRNA profiles and focused on microRNA molecules upregulated after NACT, hypothesizing that those microRNA molecules were necessary for chemotherapy resistance. They specifically studied miR-199, miR-29, miR-30, let-7, and miR-181 family members, as they were upregulated by QPCR in after NACT samples and associated with platinum resistance in other studies. MiR-199a-5p, miR-199a-3p, let-7a-5p, let-7g-5p, and miR-181a-5p were associated with worse progression-free survival. MiR-199a-5p, miR-199a-3p, miR-199b-5p, let-7g-5p, and miR-181a-5p were associated with worse overall survival. Multivariate analysis showed only let-7g-5p associated with overall survival with a hazard ratio of 1.1 (1.04–1.23) (59). Examination of P-SMAD2, an indirect target for miR-181a-5p, revealed a significant effect (hazard ratio 1.1 CI 1.0–1.2) on overall survival. Thus, these microRNA molecules and indirect targets may represent biomarkers of platinum resistance in a very specific group of patients. A potential concern, however, is represented by the rather modest hazard ratio, pointing to the need for large cohorts in any future validation study. Similar to studies in breast cancer, high expression of miR-622 in EOC was associated with loss of ku protein from the homologous recombination pathway and poor outcome. This suggests that miR-622 was associated with resistance to chemotherapy including poly ADP ribose polymerase (PARP) inhibitors (60). Since PARP inhibitors are now FDA approved for ovarian cancer therapy (61), this microRNA marker may be an additional marker useful for selecting appropriate candidates for this particular therapy.

e. Hypoxia Regulated MiRNA Molecules in EOC

Hypoxia plays an important role in microRNA molecule biogenesis and clinical oncology poor outcomes (62, 63). Hypoxia is important for DICER and DROSHA downregulation in EOC (64). Rupaimoole et al (64) found that hypoxic conditions downregulated *DICER* and *DROSHA* expression *in vitro* and *in vivo*. The expression levels of *DICER* and *DROSHA* and a panel of hypoxia markers showed an inverse correlation in EOC. Additionally, these studies revealed global microRNA downregulation following exposure to hypoxia. Examination of survival with a hypoxia metagene signature in TCGA datasets revealed an association of poor survival with high levels of hypoxia (64). MiR-199a-3p, miR-216b, miR-548d-5p, and miR-579 were found downregulated and 19 miRNAs were upregulated in ovarian cancer under hypoxia (65). Overexpression of miR-199a-3p reduces the invasion of

ovarian cancer cells in response to hypoxia (65). The role of hypoxia in microRNA molecule expression and function in EOC deserves additional study.

5. MicroRNA Molecules as Therapy for EOC

Given the ability of specific microRNA molecules to sensitize tumors to chemotherapy *in vitro*, studies have used microRNA molecules as adjuvant therapy with microRNA molecules in xenograft mouse models (Table 2). AntagomiR MiR-1307 treatment of mice with xenograft tumors resulted in a decrease in tumor size and an even further decrease in tumor size with paclitaxel treatment (66). Treatment of xenograft mouse models with miR-192-DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) leads to inhibition of angiogenesis and tumor growth (67). MiR-551b-3p is located in a genomic region frequently amplified in high-grade serous EOC (68). MiR-551b-3p overexpression in high-grade EOC is associated with decreased overall survival. Interestingly, miR-551-3p binds to the promoter of signal transducer and activator of transcription 3 (STAT3), leading to increased expression of STAT3. Treatment of mouse models with anti-miR-551b-3p via a liposomal delivery system decreased tumor burden *in vivo* (69). These few pre-clinical models show promise for treatment of EOC with molecules that regulate microRNA expression.

6. Challenges to Clinical Use of MicroRNA Molecules and MicroRNA-Regulatory Machinery in EOC

MicroRNA molecules hold promise as biomarkers for clinical associations, early markers for disease, and adjuvant therapy. However, most of the corresponding studies have yet to be replicated. Studies using biological fluids such as urine, serum, or plasma need to consider details such as phase of the menstrual cycle, effect of exogenous hormones or bioidentical compounds, type of sample collection, and processing of samples. The reference range or control group needs to be considered carefully. EOC as a disease arising from the ovary has been challenged. Many studies have compared EOC to normal ovarian epithelium, but the cell of origin for high-grade serous EOC may be fallopian tube epithelium. Limited studies on the more rare subtypes of EOC, such as endometrioid, clear-cell, or mucinous, need to be addressed because understanding the differences may lead to improved therapy for specific histotypes or specific molecular characteristics – possibly based on microRNA molecule expression. Treatment of patients with microRNA molecules needs further study in drug delivery and microRNA effects. However, these pre-clinical studies hold promise for the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Expression of microRNA-regulatory machinery may serve as unique biomarkers for prognosis in epithelial ovarian cancer

- MicroRNA molecules are promising biomarkers for epithelial ovarian cancer

- MicroRNA molecules are promising therapeutic adjuvants for epithelial ovarian cancer

- Further work is needed to understand the molecular mechanisms of microRNA molecules in subtypes of epithelial ovarian cancer

Table 1

MiRNAs as biomarkers for diagnosis of epithelial ovarian cancer

miRNA	Analysis and findings	ROC	Sensitivity	Specificity	Ref
miR-141	Serum samples: 74 EOC, 19 borderline, and 50 normal control High expression in EOC, especially late-stage disease with metastasis	0.75	0.69	0.72	(70)
miR-200c	Serum samples: 74 EOC, 19 borderline, and 50 normal control High expression in EOC without metastasis Expression variation across histotypes, with highest expression in serous	0.79	0.72	0.70	(70)
miR-125b	Serum samples: 54 controls with benign ovarian tumors and 135 patients with EOC High expression in EOC with no residual tumor after operation High expression in early stage disease	0.737	75.6%	68.5%	(71)
miR-125b	Serum samples: 70 EOC and 70 age-matched controls High expression in early stage disease High expression in no lymph node metastasis	0.728	62.3%	77.1%	(72)
miR-199a	Serum samples 70 EOC and 70 age-matched controls Low expression associated with aggressive tumor stage, lymph node metastasis, and distal metastasis	0.704	69.1%	95.7%	(73)
miR-200a	Serum samples: 70 EOC and 70 age-matched, cancer-free controls High expression in mucinous tumors High expression in metastatic tumors	0.810	80.6%	73.5%	(74)
miR-200c	Serum samples: 70 EOC and 70 age-matched, cancer-free controls High expression in advanced stage High expression in metastatic tumors	0.833	83.3%	73.1%	(74)
miR-200c	Serum samples: 70 EOC and 70 age-matched, cancer-free controls High expression in lymph node positive tumors	0.741	89.5%	60.8%	(74)
miR-1290	Plasma samples: 42 serous EOC, 36 benign neoplasm, and 23 age-matched healthy controls High expression associated with long overall survival	0.87	63.3%	100%	(75)
miR-30a-5p	Urine samples: 34 serous EOC and 25 healthy controls	0.862	No number		(56)

miRNA	Analysis and findings	ROC	Sensitivity	Specificity	Ref
miR-6076	Urine samples: 34 serous EOC and 25 healthy controls	0.693			(56)

Table 2

In vivo mouse models of miRNA therapy in epithelial ovarian cancer

miRNA Treatment	Method	Effect	Ref
miR-1307	A2780 cells subcutaneous injection	Chemotherapy sensitivity (Taxol)	(66)
miR-192	SKOV3ip1 cells intraperitoneal injection	Tumor growth	(67)
miR-506	HeyA8-IP2 and SKOV3-IP1 cells intraperitoneal injection	Invasion Metastasis Chemotherapy sensitivity (cisplatin and olaparib)	(76, 77)
miR-551b-3p	IGROV1 or HEYA8 cells intraperitoneal injection	Tumor growth Ascites formation	(69)
miR-6126	HeyA8 cells intraperitoneal injection	Tumor growth Angiogenesis	(78)