Chapter

Functions of miRNAs in the Development, Diagnosis, and Treatment of Ovarian Carcinoma

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Abstract

miRNAs (miRNA) are small RNA molecules that are not to expressed to proteins. Their size is 20–22 nucleotides in length and they are highly conserved molecules among the species. miRNAs are synthesized in the nucleus as a primary miRNA. Primary miRNA is transferred to cytoplasm by Xpo5 protein (exportin-5) and then is processed by Dicer enzyme to a 22-nucleotide-sized long mature miRNA. miRNAs are differentially expressed in different diseases and are released into plasma by normal and tumor tissues during the cell metabolism. Ovarian carcinoma is the deadliest cancer among women. When the disease was diagnosed, the disease usually progressed. Currently, there is no biological marker to detect ovarian carcinoma at an early stage. Furthermore, there is a need for markers that are sensitive to chemotherapy changes and early detection of the disease. Because of this, miRNAs can be detected in plasma and can be used as highly significant biological markers and therapeutic targets for ovarian carcinoma. When the literature of the last 5 years is searched, there are many studies about miRNA and ovarian carcinoma. In this chapter, studies examining the relationship between ovarian carcinoma and miRNA from different angles are summarized under different sections.

Keywords: miRNAs, ovarian carcinoma, diagnosis and treatment

1. Introduction

Ovarian cancer (OC) is the sixth common cancer in women in the United States. According to GLOBOCAN data published in 2018, 295,414 new cases of ovarian cancer have been reported in the world. A total of 184,799 of these cases have been reported to have died due to ovarian carcinoma. The patients who died because of ovarian carcinoma had constituted 62.5% of the cases diagnosed in 2018 [1]. Ovarian carcinoma is diagnosed in women at peri- and postmenopausal status frequently [2].

Genetics, syndromes (breast and ovarian carcinoma syndrome and Lynch syndrome), family history, personal history of cancer or endometriosis, increasing age, reproductive history and infertility, hormone replacement therapy, and obesity are factors that may increase the risk of ovarian carcinoma. However, oral contraceptive usage, having pregnancy before age 26, breastfeeding, removal of the ovaries and fallopian tubes, hysterectomy, and tubal ligation are factors that may reduce the risk of ovarian carcinoma. Ovarian carcinoma comprises a heterogeneous group of

tumors with different histologic subtypes which have particular genetic structures and different response to treatment. The most common histological subtype is epithelial ovarian carcinomas accounting for about 90% of cases and can be classified as serous, endometrioid, and clear-cell and mucinous carcinomas [3, 4].

However, a majority of women are diagnosed in an advanced stage because of the asymptomatic issue in the early stage and due to the lack of an adequate early detection screening method [5]. Ovarian cancer still remains as one of the leading causes of cancer-related deaths, and the treatments could be improved using predictive biomarkers to measure a response to ovarian cancer therapy. Currently, there is no available proven single biomarker in the clinical use for detecting ovarian carcinoma in the early stage with adequate sensitivity and specificity. To solve this problem, researchers have aimed at the identification and validation of novel biomarkers for the early detection of ovarian carcinoma using new technologies. Diagnostic markers for population screening would be a simple blood testing with 95% specificity and sensitivity.

Similar to regulatory RNAs, microRNAs (miRNAs) are frequently deregulated in carcinogenesis. In ovarian tumorigenesis, numerous miRNAs were found altered, and some of these genes might represent ideal targets for diagnosis, prognosis, and treatment [6].

This chapter will focus on the recent advancements in miRNAs in the diagnosis, prognosis, and the treatments resistant to ovarian carcinoma.

2. Methods

PubMed search was performed using the keywords "ovarian carcinoma and miRNA" to prepare a comprehensive literature review. The results were filtered by published manuscripts in the last 5 years. A total of 193 associated papers, and review articles were found in the initial search. Additional searches were performed using the keywords genetic markers in ovarian cancer, multidrug resistance in ovarian cancer, and prognostic markers to supplement the information. 180 papers were selected for inclusion in the manuscript following the careful review of the abstracts. This chapter was written using the data of 3 meta-analyses, 20 reviews, and 67 original papers published in the last 5 years.

3. Biogenesis and functions of miRNAs

MicroRNAs (miRNAs) are a class of small noncoding RNA molecules which regulate gene expression at the posttranscriptional level [7, 8]. Thousands of miRNA sequences have been identified in a wide range of organisms after the discovery of small noncoding RNAs [9, 10] and have currently been shown to be highly conserved among a wide range of species [11]. The miRNA database contains 38,589 entries representing hairpin precursor miRNAs, expressing 48,885 mature miRNA for 271 species (http://microrna.sanger.ac.uk). Each miRNA directly or indirectly regulates approximately 100 mRNA transcripts; however, a single gene coding protein could be regulated by more than one miRNA.

MicroRNAs are transcribed by RNA polymerase II or III, generating primary transcripts as short RNA hairpin structures (pre-miRNA) which are subsequently processed by cytoplasmic RNase III-type enzymes, Drosha and Dicer. The processed, mature miRNA incorporates into the RNA-induced silencing protein complex (RISC) to regulate the function of genes through degradation of mRNA and inhibition of translation [12, 13]. RISC usually binds to the 3′-UTR region of

target mRNAs to repress translation. The degree of translation depends on the degree of complementarity between miRNA and target mRNA. miRNAs usually bind to specific sequences with partial complementarity on target RNA transcripts, called microRNA response elements (MREs), which result in translational repression in humans [14, 15].

MicroRNAs were shown to have a crucial function in oncogenesis by regulating cell proliferation, cell differentiation, and apoptosis as oncogenes or tumor suppressors. The deregulation of miRNAs was suggested to be involved in a mechanism for cancer development. Also, miRNAs have been used as potential diagnostic or therapeutic targets in cancer treatment.

3.1 Important miRNAs as diagnostic and prognostic biomarkers and therapeutic targets in ovarian carcinoma

Ovarian carcinoma is the most lethal cancer among gynecological malignancies. Therefore, there is still a need for good diagnostic markers to detect the disease at an early stage and good prognostic markers to follow the effects of therapeutic agents during the chemotherapy of patients with ovarian carcinoma. Li et al. investigated the miR-193b expression level in the tissues of patients diagnosed with ovarian carcinoma and ovarian carcinoma cell lines. They found the aberrant expression level of miR-193b in the tissue of ovarian carcinoma patients. miR-193b showed decreased expression in tumor tissues of patients with ovarian carcinoma and was correlated with FIGO stage, histologic grade, ascites, lymph node metastasis, tumor size, and also poor survival. Therefore, they suggested that the level of miR193b expression could be a potential biomarker for ovarian carcinoma patients [16]. Fukagawa et al. investigated the expression level of miR-135a-3p in the serum of ovarian carcinoma patients compared to ovarian cysts and normal ovarian tissue and also analyzed the expression level of miR-135a-3p in ovarian carcinoma cell lines such as SKOV3, ES2, and xenograft under cisplatin and paclitaxel. According to their result, they suggested that the miR-135a-3p expression could be used as a noninvasive biomarker in serum of patients with ovarian carcinoma in the diagnosis and follow-up of the disease [17]. Zuberi et al. evaluated the impact of the miR-125b expression level in patients with ovarian carcinoma and found that the expression level of miR-125b was statistically significant and that it was increased in serum specimens of patients with ovarian carcinoma compared to the levels in serum specimens of the healthy controls. They also demonstrated that the upregulation of miR-125b was associated with FIGO stage and lymph node involvement and distant metastasis and was correlated with hypermethylation of some tumor suppressor genes such as p16, p14, BRCA1, DAPK1, PTEN, and RASSF1A. Their results suggested that the expression level of mi-125b might be an early diagnostic biomarker to predict distant metastasis and lymph node status [18]. Zhang et al. investigated miR-613 expression in tissue of patients with ovarian carcinoma compared to matched normal adjacent tissue of patients. They found that low expression of miR-613 was associated with the FIGO stage, tumor grade, lymph node involvement, short progression-free survival (PFS), and overall survival (OS) in ovarian carcinoma patients. Their results indicated that miR-613 might be a good prognostic biomarker in patients with retinoblastoma [19]. Yanaihara et al. searched five miRNAs such as miR-132, miR-9, miR-126, miR-34a, and miR-21 in 12 high-grade serous ovarian carcinoma and 15 clear-cell ovarian carcinoma patients. They found that five miRNAs showed statistically higher expression in patients with clear-cell ovarian carcinoma. They also investigated further biological significance of miR-9 expression especially and demonstrated that miR-9 might have distinguished histologic subtypes of ovarian carcinoma and might be used a therapeutic

target for treatment of ovarian carcinoma [20]. Yang et al. showed that miR-506 was associated with poor prognosis in ovarian carcinoma (OC) patients [21]. Sun et al. demonstrated in their study that miR-506 expression was correlated with early FIGO stage and good and longer survival [22]. The results of both studies suggested that miR-506 might be used as a prognostic biomarker. Yuan et al. showed that miR-494 had an antitumor effect in the tissue of OC patients and that miR-494 suppressed the cell proliferation and cell migration in epithelial ovarian carcinoma through the c-myc gene [23].

Agostini et al. studied 155 tissues of ovarian carcinoma including 30 sex cord-stromal tumors, 22 borderline tumors, and 103 ovarian carcinomas and investigated the HMGA2 gene and its two miRNA targets in the study. They found that let-7a and miR-30c were highly decreased in all tumors in the study. Their results showed that Let-7a and miR30c were deregulated in OC patients, and the cause of deregulation in let-7a and miR30c might be due to the genomic imbalances, and the genomic imbalances resulted with the upregulation of HMGA2 gene. They suggested further research to better understand the associations between genetic imbalance and miRNA expression and prognostic and diagnostic importance in ovarian carcinoma [24]. Ma et al. investigated the expression level of miR-486-5p and its target, OLFM4 gene. Their results suggested that the decreased expression level of OLFM4 was associated with higher-grade FIGO tumors and poor differentiation. OLFM4 is downregulated by miR-486-5p which contributed to the tumorigenesis of ovarian carcinoma, and the opposite might be possible. OLFM4 and miR-485-5p might be the therapeutic targets for ovarian carcinoma [25]. Teng et al. published an article explaining an association between DNMT3A/3B and miR-29b. The results showed that the downregulation of miR29b was controlled by high levels of DNMT3A/3B expression. The results were suggested that was a cross talk and feedback between DNMT3A/3B and miR-29b and that the expression of miR-29b negatively controlled DNMTs, especially DNMT3A/3B. The findings showed that miR-29b and inhibitors of DNMT3A/B might be therapeutic target for patients with ovarian carcinoma [26]. According to articles published by different authors, miR-199 was downregulated in epithelial ovarian carcinoma and targeted to c-Met, HIF1-alpha, HIF2-beta, and IKK-beta proteins. Therefore, c-Met and/or miR-199 might be a target for patients with metastatic ovarian carcinoma [27–29]. Although many studies have been conducted so far, there are many candidate molecules that can be used in the diagnosis and prognosis of ovarian cancer; however, most of them should be validated with larger patient groups.

3.2 miRNAs responsible for drug resistance in treatment of ovarian carcinoma

The response of a patient with ovarian cancer to chemotherapy is actually the most important factor determining the survival of the patient. The primary treatment for ovarian cancer is surgery. After surgery, the first-line treatment is platinum-based combination [cisplatin or carboplatin and/or taxane (paclitaxel)] [30]. The majority of patients, almost 70%, receive this treatment and show complete remission. Patients were extremely sensitive to chemotherapy when they first received the treatment, and this situation changed during the next relapse period. The pharmacokinetics and pharmacodynamics of platinum-based therapies are known to be influenced by germ line genetic factors [31].

It is stated that many events associated with cisplatin resistance may be effective. It has been thought that these mechanisms can be generated by genetic and epigenetic alterations and miRNAs [32]. It is known that women with BRCA1 and BRCA2 gene mutations had better response to chemotherapy and had longer survival. It was reported that the mechanism underlying situation was associated with miR-9 in

animal models. miR-9 downregulates the BRCA1 gene, causing the DNA repair mechanism not to function, and thus increases the sensitivity to chemotherapy. In a study by Sun et al., It was shown that miR-9 overexpression in 58 tumor tissue samples was associated with BRCA1 gene mutation. Accordingly, these patients have been reported to be extremely sensitive to chemotherapy, especially platinum-based drugs and PARP inhibitors [33]. Furthermore, a similar relationship between BRCA1-miR-9 is present between the miR-93 and the PTEN gene. High miR-93 and low PTEN expressions were investigated in ovarian carcinoma cell lines which were OVCAR3 and SKOV3 with and without platinum resistance. In this study by Fu et al., the relationship between PTEN-miR-93 was also shown in tumor tissues of 10 ovarian cancer patients [34]. Let-7 expression has been reported to play a role in the response to chemotherapy. In particular, when paclitaxel was added to platinum regimen, it was shown that chemotherapy is beneficial in patients with low expression of let-7 [35]. It has been reported that high-level expression of miR622 is responsible for the development of resistance to platinum drugs and PARP inhibitors in patients with high-grade serous ovarian cancer with BRCA1 mutation. It is emphasized that this effect of miR622 can be affected by correcting the disorders in the homologous recombination mechanism [36]. The blockade of PD-L1, PD-1, and CTLA-4, which are immune system inhibitor receptors, has been extremely successful in some advanced cancers. High expression of miR-424 (322), especially in tumors, prolongs progression-free survival in ovarian cancer patients. miR-424 (322) blocks PD-L1 and CD80 expressions. The expression of miR424 (322) with PD-L1 immune checkpoint inhibitors is corrected, i.e., it is converted to normal. In in vivo and in vitro conditions, the restoration of miR424 (322), i.e., normalization, eliminates the resistance to chemotherapy by activation of the T cell immune response via blocking PD-L1. There is a synergetic development of chemotherapy and immunotherapy. PD-L1 and chemoresistance are controlled via miRNAs [37]. In the literature, there are a number of studies showing the relationship between miRNAs and chemosensitivity and chemoresistance. Some miRNAs have a highly significant role in the use of combined therapies such as chemotherapy and immunotherapy. There is no doubt that the success of cancer treatments will increase as the relationship between miRNA molecules and cancer treatments is determined. However, there is no doubt that more studies should be done to use these molecules as standard in the clinic.

3.3 Important polymorphisms and mutations of miRNA processing and binding sites in ovarian carcinoma

3.3.1 3′UTR miRNA binding site of the KRAS gene

In 2008, Ratner et al. identified a germ line SNP in 3′UTR of the KRAS oncogene (rs61764370). The functional KRAS-variant was disrupted by the binding of let-7 to 3′UTR region of KRAS gene [38]. In 2010, Ratner et al. reported that a single nucleotide polymorphism (SNP), rs61764370, located in the 3′UTR of the *KRAS* oncogene was associated with the risk of unselected epithelial ovarian cancer [39]. They also showed that the variant was associated with hereditary ovarian cancer patients carrying *BRCA1* mutations and ovarian cancer patients with family history not carrying *BRCA1* or *BRCA2* [39]. This SNP was thought to be a strong candidate for cancer risk. These observations suggested that miRNAs can function as tumor suppressors or oncogenes [40]. An assay has subsequently been marketed to determine genotype at rs61764370 as a commercial test to determine the risk in women with a family history of ovarian cancer (http://www.miradx.com). However, in June 2011, Pharoah et al. showed in an extensive study with 8.669 unselected cases

of invasive epithelial ovarian cancer and 10.012 controls that the SNP was clinically useless for risk prediction in sporadic or familial ovarian cancer [41].

3.3.2 3'UTR miRNA binding site of the BRCA1 and BRCA2

BRCA1/2 mutations and targeted miRNAs to BRCA genes were demonstrated in many studies in the last decade [42] [43–45]. Moskwa et al. suggested that tumors overexpressing miRNAs such as miR-182 which target BRCA proteins can also be susceptible to PARP inhibition.

They suggested that the high level of miR-182 expression may affect BRCA1 regulation for sporadic breast tumors. The changing level of miR-182 expression in different types of breast tumor cell lines affected the level of protein expression of BRCA1 and changed the sensitivity to PARP1 inhibition, both in breast cancer cell lines and in xenograft models [42]. Bioinformatic tools showed a binding site for miR-146a and miR-146b-5p in the upstream of BRCA1. This information suggested that BRCA1 gene can be downregulated by miR-146a and miR-146b-5p in basal-like breast cancer cell lines and triple-negative breast tumors. This downregulation of BRCA1 increased a cell proliferation and a reduced homologous recombination repair rate controlled by BRCA1. Garcia et al. showed that the highest levels of miR-146a and/or miR-146b-5p were found in basal-like epithelial mammary tumor cell lines and breast tumors with triple-negative histology, and also the characteristics of these types of tumors are the closest tumors having carriers of BRCA1 mutations [43–45]. miRNAs are known to regulate tumor suppressor genes and oncogenes. The genetic alterations in the binding sites of miRNAs on DNA sequence of miRNA could affect the expression of tumor suppressor genes and oncogenes. Shen et al. searched the selected 17 miRNAs which have an important role in the development of breast cancer in 42 patients with familial breast carcinoma. miR-30c-1 and miR-17 among 17 miRNAs were only observed in noncarriers of BRCA1/2 mutations. They showed that these two miRNAs, miR-30c-1 and miR-17, resulted in conformational changes in their secondary structures and altered the expression in functional assays. They also showed that miR-17 could bind to the 3′UTR of BRCA1 mRNAs. Their results suggested that functional genetic alterations in miRNA genes can potentially alter the regulation of BRCA1 gene which is important for breast cancer [45]. The same perspective and scenario may be valid for patients with sporadic ovarian carcinoma having an overexpression of BRCA1, and the effect of PARP inhibitors can also be increased by eliminating BRCA expression via miR182 in ovarian carcinoma.

3.4 miRNAs as angiogenetic and metastatic biomarkers in ovarian carcinoma

The major challenge in treatment of ovarian carcinoma is the lack of good diagnostic and prognostic factors to follow and to diagnose in each stage of the disease. Li et al. established the study using SKOV3 and OVCAR3 ovarian carcinoma cell lines. They demonstrated that miR-125a-5p, miR125b-5p, miR22-3p, miR205-5p, and miR-152 were significantly downregulated in SKOV3 cell lines and also showed the negative correlation between miR-152 and expression level of ERBB3. The findings of the study showed that miR-152 was associated with the regulation of the proliferation and metastasis of ovarian cancer cells via the repression of ERBB3 expression. miR-152 is an important molecule to suppress the proliferation, invasion, and migration of ovarian carcinoma cell lines. Their results suggested that miR-152 may be a potential therapeutic target for ovarian carcinoma [46].

The interaction between HOTAIR and both miR-214 and miR-217 was shown in the study of Dong et al. on SKOV3 ovarian carcinoma cell line. Their results demonstrated that HOTAIR, which had an interaction with PIK3R3, regulated the proliferation, migration, and invasion in SKOV3 ovarian cell line via miR-214 and miR-217 [47].

Li et al. investigated miR-340 expression in five different ovarian carcinoma cell lines such as OVCAR3, CAOV3, HO-8910, ES-2, A2780, and FTE187. They showed that miR-340 was decreased in ovarian carcinoma cell lines and induced apoptosis in cells with downregulation of NF-ΚB1 to inhibit metastasis in ovarian carcinoma cell lines. They emphasized that miR-340-NF-ΚB1 interaction might be a potential therapeutic target or agent for patients with ovarian carcinoma [48].

Wang et al. examined the expression of MTA1 and miR-30c in ovarian cancer line, SKOV3, and normal human ovarian surface epithelial cell line, HOSE. They found that miR-30c expression was significantly reduced when MTA1 expression was higher and localized in the cytoplasm of the cells. Their results suggested that MTA1 and miR30c expression were altered in ovarian carcinoma cell line and might be associated in invasion and metastasis of patients with ovarian carcinoma [49].

3.5 Important miRNAs in exosomal and peripheral circulations in ovarian carcinoma

Numerous studies demonstrated the clinical importance of circulating miRNAs as diagnostic and prognostic biomarkers in all types of cancer. Circulating miRNAs in ovarian cancer were published in many studies using blood plasma, serum, ascites, and urine.

3.5.1 Exosomal miRNAs

The first study was published by Taylor et al. demonstrating that the levels of eight exosomal microRNAs extracted from sera which were miR-21, miR-141, miR-200a, miR-200c, miR-200b, miR-203, miR-205, and miR-214 were elevated at an advanced-stage ovarian carcinoma [50, 51]. The miRNA signature of exosomes showed that the circulating miRNAs can present the characteristics of the tumor.

3.5.2 miRNAs in sera

Many researchers investigated different miRNAs in the sera of OC patients [51–59].The microRNAs miR182, miR200a, miR200b, and miR200c from miR200 family were investigated by Kan et al. in the sera of OC patients and healthy controls. They found significant differences between patients and controls and suggested that miR200b and miR200c had a power to discriminate serous ovarian cancer from healthy controls and had a potential as a biomarker of sera [53]. Chung et al. showed that the miR-132, miR-26a, miR-let7b, miR-145, and miR-143 were decreased in serum specimens of patients with ovarian carcinoma and healthy individuals [54]. Xu et al. showed significantly higher miR-21 levels in sera of patients with epithelial ovarian cancer than the levels in healthy controls. They also indicated the correlation between the increased miR-21 expression in sera and advanced FIGO stage, high tumor grade, and shortened overall survival. Their findings suggested that serum miR-21 may be a novel diagnostic and prognostic marker and could be used as a therapeutic target in advanced-stage ovarian carcinoma [55]. Hong et al. investigated the serum levels of miR-221 in patients with epithelial ovarian carcinoma and in controls. miR-221 was found to be upregulated in patients with EOC compared with the healthy controls. The expression level

of serum miR-221 was significantly associated with the International Federation of Gynecology and Obstetrics (FIGO) stage and tumor grade. In addition, higher serum miR-221 expression was shown to be an independent prognostic factor for epithelial ovarian carcinoma [56].

3.5.3 miRNAs in plasma

Some other scientists used plasma in investigating the circulating biomarkers for ovarian carcinoma [60–63]. Zheng et al. showed higher plasma miR-205 and lower let-7f expression in patients with ovarian carcinoma than in healthy controls. The joint use of both MiR-205 and let-7f provided higher diagnostic accuracy for epithelial ovarian carcinoma, especially in patients with stage I disease. They also demonstrated that the combination of these two miRNAs and carbohydrate antigen-125 (CA-125) further improved the accuracy of detection of epithelial carcinoma in plasma samples and that the elevated miR-483-5p expression was found in patients with ovarian carcinoma with stages III and IV compared with stages I and II. Moreover, they demonstrated that lower levels of let-7f was predictive for poor prognosis in patients with epithelial ovarian carcinoma. Their findings suggested that plasma miR-205 and let-7f can be biomarkers for ovarian cancer detection and prognosis [60]. Shapira et al. assessed the expression levels of 754 miRNAs in presurgical plasma samples of 42 women with serous epithelial ovarian cancer and 36 plasma samples collected from women who had a benign pelvic mass at surgery. There were six miRNAs, miR-106b, miR-126, miR-150, miR-17, miR-20a, and miR-92a which were distinguished as benign in histology before surgery. They showed that 10 miRNAs in plasma can distinguish healthy controls from women with ovarian cancer and a benign neoplasm before surgery. In the comparison of healthy controls with patient's plasma samples, they found that five miRNAs, miR-1274a, miR-30b, miR-30c, miR-625-3p, and miR720, were differentially expressed and also that the level of miR-139-5p, miR-142-3p, miR-484, miR-486, and miR-660 were higher in healthy controls when analyzed against patients having benign mass in their body. They demonstrated that MiR-720 and miR-20a were higher in women who died 2 years after their diagnosis, and women who survived 44 years after diagnosis had higher levels of miR-223, miR-126-3p, and miR-1290 in their plasma before surgery [62].

3.5.4 miRNAs in ascites

Vaksman et al. investigated the effusion supernatants in 86 patients with ovarian carcinoma. In the study, they demonstrated that there were significant associations between clinicopathologic parameters and the levels of miR-21, miR-23a, miR-23b, miR-29a, miR-99a, miR-125b, miR-200c, miR-320a, and miR-484 and also between miRNAs 21, 23b, and 29a and poor survival. It was shown that the higher expression of miR-21 in metastatic ovarian carcinoma constituted chemoresistance in ovarian carcinoma, and the higher expression of miR-23a and miR-29a was associated with significantly shorter PFS [64].

3.5.5 miRNAs in urine

Researchers detected miRNAs on the urine of patients with ovarian carcinoma in the studies in the literature [65, 66]. Zavesky et al. investigated the expression of miRNAs in the urine of patients with ovarian carcinoma and endometrial carcinoma. They compared the expression levels of 18 miRNAs in OC patients before and after surgery. The expression levels of miR-92a, miR100, miR106b, and miR-200b were found significantly different between patients with ovarian carcinoma

and healthy controls. The expression levels of miR100 and miR106b were lower; however, the expression levels of miR-92a and miR-200b were higher in patients with ovarian carcinoma compared with the levels in healthy controls [65]. Zhou et al. examined the urine specimen obtained from 39 OC patients, from 26 patients with benign gynecologic disease, and from 30 healthy controls. They found that miR30a-5p was upregulated in OC patients compared with the healthy controls, and they also showed that the level of miR30a-5p can be used to follow excess tissues of ovarian carcinoma after surgery [66].

3.6 Important miRNAs for autophagy in ovarian carcinoma

Some miRNAs participated in the control of autophagy by regulating ATGs proteins [67]. Yang et al. showed that the higher expression of mir-30d regulated autophagy through inhibiting LC3B-I conversion to LC3B-II enzymes and formation of autophagosome. Their results suggested that mir-30d disrupts the process of autophagy targeting multiple genes in the autophagy pathway. The data suggested that miR-30d might participate to oncogenesis and be used in the cancer therapy strategy [68]. Dai et al. investigated the expression levels of miR29b that targeted to genes of myeloid cell leukemia sequence 1 (MCL1), mitogen-activated protein kinase 10 (MAPK10), and autophagy-related protein 9A (ATG9A) and suggested that lower level of miR29b was an independent poor prognostic marker in ovarian carcinoma [69]. He et al. examined the downregulation of ATG14 through EGR1-miR-152 in cisplatin resistance ovarian carcinoma cell lines of A2780, CP70, SKOV3, and DDP. They determined that miR-152 expression level was extremely low in the cisplatin-resistant cell lines. Therefore, they suggested that the overexpression of miR-152 might be a useful therapeutic strategy to overcome cisplatin resistance by inhibiting ATG14 expression in ovarian carcinoma [70].

3.7 Important miRNAs for invasion in ovarian carcinoma

Invasion into surrounding tissue is an important step of metastasis. Therefore, understanding the molecular mechanism of invasion may help to understand the metastasis process and identify novel biomarkers and therapeutic agents to treat and to protect patients against metastasis. Zhang et al. showed that there was a higher expression of miR-630 in 30 patients with ovarian carcinoma [71]. They also showed the effects of higher miR-360 expression in SKOV3 cell line. The results of the cell line study indicated that miR-630 targeted the KLF6 gene (Krüppel-like factor 6). KLF6 gene is responsible for cancer cell proliferation and migration. They demonstrated that miR-630 supported the epithelial cancer proliferation and invasion via targeting KLF6 gene, and overexpression of miR-630 stimulated growth of ovarian carcinoma tumor in vivo. Therefore, miR-630 was suggested to be a possible therapeutic target in ovarian carcinoma [71]. Sun et al. determined that the expression of miR-548c decreased in ovarian and endometrium carcinoma. Their results suggested that miR548c affected the expression of Twist. Higher expression level of Twist was shown in ovarian and endometrium carcinoma. Therefore, they emphasized that miR-548c might be used for therapeutic purposes to impress the expression level of TWIST in overexpressing tumors such as ovarian and endometrium carcinoma [72]. Wei et al. examined miR-205 expression level in 30 patients with ovarian carcinoma and in 12 normal ovarian tissues, and they found miR-205 overexpression in ovarian carcinoma tissue of patients. Also, the behavior of miR-205 was investigated in ovarian carcinoma cell lines of OVCAR5, OVCA8, and SKOV3. They determined that miR205 targeted to TCF21 gene (transcription factor 21) which significantly decreased in tumor tissue of OC patients [73]. They concluded that miR-205 was

associated with the invasive behavior of ovarian tumor cells by targeting and with the decrease of TCF21 expression. miR-205 and TCF21 were suggested to be used for anticancer purposes [73]. Human telomerase reverse transcriptase (hTERT) is another important molecule in ovarian carcinoma. Bai et al. investigated expression levels of miR-532 and miR-3064 and found that they were downregulated in 60 tumor tissues of ovarian cancer patients, and there was an association between the decreased miR-532 and miR-3064 and poor survival of patients with ovarian carcinoma. Bai et al. also demonstrated that miR-532 and miR-3064 targeted to hTERT gene and inhibited the proliferation, epithelial-mesenchymal transitions (EMT), and invasion of ovarian carcinoma cells. Their results showed that miR-3064 controlled the expression level of hTERT, and the role of miR-532 was limited in ovarian carcinoma. They suggested that both miR-532 and miR-3064 might be a good therapeutic agent for treatment of ovarian carcinoma [74].

3.8 An impact of miRNAs on epithelial-mesenchymal transitions (EMT) in ovarian carcinoma

3.8.1 miR-125a

The epithelial-to-mesenchymal transition (EMT) and its reversion, mesenchymal-to-epithelial transition (MET), are important mechanisms in carcinoma progression and tumor metastasis. The important regulators of this process are growth factors, transcription factors, and adhesion molecules in that the activity of microRNA (miRNA) is suggested to contribute to EMT, MET, and metastatic progression. In ovarian cancer cells, EMT induces by overexpression of EGFR which leads to transcriptional repression of the miR-125a. MiR125a is suggested to be a negative regulator of EMT. Therefore, the repression of miR-125a was suggested to be a potential novel therapeutic approach for invasive behavior of ovarian cancer [75].

3.8.2 miR-125b

miR-125b expression was lower in epithelial ovarian carcinoma. The expression of miR125b in ovarian carcinoma blocked the tumor invasion. The expression of miR125b was associated with EMT and also with the expression of SET gene. Functional studies showed that SET gene was a target for miR-125b. The downregulated SET gene may be observed during tumor migration [76].

3.8.3 miR-200 family

Various studies on miR-200 family showed that the miR-200 family was associated with the inhibition of cancer metastasis via epithelial-to-mesenchymal transition. mRNAs of SMAD and ZEB gene families are the key targets for the inhibition of cancer cell metastasis stimulated by miR-200 via EMT. ZEB2 has specific sequences on its' 3′ UTR region for miR-200a, miR-141, miR-200b, miR-200c, 429, miR-200a, and miR-141. ZEB1 and ZEB2 are transcriptional repressor of E-Cadherin [77]. Wang et al. determined that the higher expressions of miR-429 and miR-200 families in mesenchymal-like ovarian carcinoma cell lines elevated the MET and the sensitivity to cisplatin [78]. In addition, TET3 was a gene downregulated during the epithelial-mesenchymal transition (EMT) induced with TGF-β1 in ovarian carcinoma cell lines. miR-30d was associated as a downstream target of TET3 gene. miR-30d could not bind to the promoter of TET3 gene, and TGF-β1-associated EMT was stimulated owing to the demethylation on binding site of miR-30d [79].

3.9 Important miRNAs on survival in ovarian carcinoma

Fu et al. found higher miR-222-3p expression level in tumors of OC patients. They determined that the overexpression of miR-222-3p was associated with good survival in patients with epithelial ovarian carcinoma. As a further research, they also investigated biological function of miR-222-3p in cell lines and in mouse models. The data of the in vitro experiments determined that miR-222-3p suppressed the cell proliferation and migration in ovarian cancer cell lines and downregulated AKT activation by decreased phosphorylation of AKT protein. They showed that GNAI2 is a target for miR-222-3p and also induced PI3K/AKT pathway. They suggested that miR222-3p/GNAI2/AKT interactions might be used as a therapeutic target in ovarian carcinoma [80]. Zhou et al. showed that miR-595 is a significant biomarker to show poor prognosis in patients in ovarian carcinoma. They investigated miR-595 in tumors in epithelial ovarian carcinoma, and the lower expression of miR-595 was found associated with advanced FIGO stage and distant metastasis and short overall survival [81]. Shi et al. published a meta-analysis about miR-200 and miR-30. They showed that the expression levels of miR-200 family had significant association with overall survival (OS) and insignificant association with progression-free survival (PFS) in general evaluation. They also evaluated their results in subgroup analysis and found that an increased expression level of miR-200a, miR-200c, and miR-141 was associated with better PFS for patients with ovarian carcinoma. A higher expression level of miR-30 was associated with good overall survival and progression-free survival [82]. Therefore, they suggested that both miR200 family and miR-30 might be good prognostic biomarkers in patients with ovarian carcinoma. Kleeman et al. examined the prognostic and apoptotic potentials of miR-147b, miR-1912, and miR-3073a in ovarian carcinoma cell lines which have different genetic backgrounds such as SKOV3 (TP53 null), OVCAAR3 (TP53R248Q), TOV21G, TOV112D (TP53R175H), A2780, and A2780cis (TP53K351N) with/without adding the chemotherapeutic agent of carboplatin. They showed that the expression level of miR-147b and miR-1912 was higher after carboplatin treatment in ovarian cancer cell lines, while the expression level of miR-147b and miR-1912 was lower in untreated ovarian cancer cell line with carboplatin. They underlined that these two-miRNA were leaded pro apoptotic signals and decreased the expression level of Bcl2 and affected to median survival of ovarian carcinoma cell lines [83]. Yoshioka et al. published that the expression level of WNT7A gene was higher in 300 FFPE tissue of ovarian specimens including ovarian tumor, benign/borderline, and normal ovarian tissue. They used ovarian carcinoma cell lines and mouse models to characterize the role of WNT7A gene in ovarian tumor development and progression. They suggested that the re-expression of WNT7A gene could play an important role in malignant transformation of ovarian tissue and progression of ovarian carcinoma [84]. After the article was published by Yoshioka et al., MacLean et al. demonstrated that miR-15b expression targeted WNT7A gene and found an inverse association between WNT7A and miR-15b. Higher expression level of WNT7A gene and lower expression level of miR-15b were associated with poor survival in patients with ovarian carcinoma. Their data showed that WNT7A was controlled by miR-15b expression reduced by promoter methylation through the DNMT1 gene, a responsible methylation in the genome of ovarian carcinoma [85]. Sun et al. published meta-analysis on miR-9 and its prognostic importance in ovarian carcinoma. Their results revealed that the decreased expression level of miR-9 was found to be associated with poor overall survival (OS) and PFS in patients with ovarian carcinoma [86]. Wang et al. demonstrated that higher level expression of miR-532-5p was associated with the survival of patients with ovarian carcinoma in TCGA data and also ovarian carcinoma cell lines, such as SKOV3 and OVCAR3 [87].

4. Conclusion remarks

Over the last 5 years, a large number of studies have been carried out to reveal the relationship between ovarian carcinoma and miRNAs. All of these studies about miRNA are promising for early detection of ovarian cancer, monitoring treatment, determining chemotherapy resistance, and discovering new therapeutic agents. With more extensive studies in the future and the use of effective miRNA molecules found in the clinic, ovarian cancer will be more manageable and early detectable. There is a need for a large number of well-selected patient groups and validated studies for miRNAs to be involved and used in the routine clinic practice. However, when all studies are completed, it is undoubted that miRNAs will contribute to cancer diagnosis, prognosis, and development of new chemotherapeutic drugs and beneficial to individualized medicine. It will be understood that the effects of these small molecules are actually greater than it is thought in the future.

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