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Review

Differential role of microRNAs in prognosis, diagnosis, and therapy of ovarian cancer

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ABSTRACT

Ovarian cancer (OC) is the most lethal of malignant gynecological cancers, and has a very poor prognosis, frequently, attributable to late diagnosis and responsiveness to chemotherapy. In spite of the technological and medical approaches over the past four decades, involving the progression of several biological markers (mRNA and proteins biomarkers), the mortality rate of OC remains a challenge due to its late diagnosis, which is expressly ascribed to low specificities and sensitivities. Consequently, there is a crucial need for novel diagnostic and prognostic markers that can advance and initiate more individualized treatment, finally increasing survival of the patients. MiRNAs are non-coding RNAs that control target genes post transcriptionally. They are included in tumorigenesis, apoptosis, proliferation, invasion, metastasis, and chemoresistance. Several studies have within the last decade demonstrated that miRNAs are dysregulated in OC and have possibilities as diagnostic and prognostic biomarkers for OC. Additionally; recent studies have also focused on miRNAs as predictors of chemotherapy sensitivities and their potential as therapeutic targets. In this review, we discuss the current data involving the accumulating evidence of the altered expression of miRNAs in OC, their role in diagnosis, prognosis, and forecast of response to therapy. Given the heterogeneity of this disease, it is likely that advances in long-term survival might be also attained by translating the recent insights of miRNAs participation in OC into new targeted therapies that will have a crucial effect on the management of ovarian cancer.

Contents

1. Introduction . . . 593
2. MicroRNAs and cancer . . . 593
3. MiRNA and ovarian cancer . . . 593
4. MiRNA expression profiles in ovarian cancer . . . 594
5. MiRNAs might serve as potential prognostic biomarker . . . 594
6. MiRNAs as a diagnostic tool in OC . . . 595
7. Molecular signaling pathways involved in miRNA-mediated regulation of OC . . . 596
8. Roles of miRs in ovarian carcinoma chemotherapy . . . 597
9. MiRNAs as therapeutic tools in OC . . . 598
Conflict of interest . . . 599
Acknowledgment . . . 599
References . . . 599

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1. Introduction

Ovarian cancer (OC) is the main cause of death from gynecological malignancies, and the fifth most frequent cancer death among women worldwide [1]. OC happens in 1 of 2500 postmenopausal women in the United States and accounts for 5–6% of all cancer-related mortalities [2]. The 5-year survival rate of OC ranges from 30 to 90%, depending on the distribution of disease at diagnosis. When OC is diagnosed at early stages, the survival rate is close to 90%; Unluckily, the large number of patients is identified when they have late-stage disease [3]. One reason for this high mortality rate is the lack of an early detection method for ovarian carcinoma. Epithelial ovarian cancer (EOC) accounts for more than 90% of all OCs, and is frequently ascribed to as 'The Silent Killer' caused by lack of early symptoms. More than 70% of patients diagnosed with OC, are diagnosed at a progressed stage resulting in a 5-year overall survival <30% [4]. Standard therapy for advanced OC is surgery combined with neo adjuvant chemotherapy, and despite improvements in chemotherapy many patients experience chemotherapy resistance and relapses. Diagnostic tools for OC today principally involve pelvic examination, transvaginal ultrasound, and serum cancer antigen 125 (CA125) measurements. However, these methods frequently fail to diagnose OC at an early stage. CA125 is the only serum biomarker utilized routinely for OC, and although quite specific (99%), the sensitivity for early stage disease in postmenopausal women is only 50–60% [5]. Consequently, novel approaches for detecting early stage ovarian cancer are crucially needed. Another reason of the high mortality rate is the difficulty of treating disseminated or recurrent ovarian tumor. Although the clinical response rate after platinum- and taxane-based chemotherapy is often high initially, subsequent relapses and repetitive therapies utilizing cytotoxic chemotherapies lead to an acquired resistance to those treatments. Consequently, most patients that suffer relapses finally capitulate to their disease [6]. Our enhanced understanding of the fundamental biology of ovarian tumor etiology and chemoresistance has led to the progression of molecular targeted therapies. Many small-molecule inhibitors and monoclonal antibodies that target multiple critical cancer characteristics, are now entering clinical trials However, new attempts are needed to determine new and better markers/therapeutics to aid the diagnostic and healing process of ovarian cancer [3]. Among these, the recently identified miRNAs establish a novel layer of gene expression regulation and have been involved in the etiology of ovarian cancer. The present review summarizes the current status and knowledge of microRNA expression in OC and the potential clinical relevance in diagnosis, prognosis, and treatment of OC.

2. MicroRNAs and cancer

MicroRNAs (miRs) are approximately 22-nucleotide noncoding RNAs, are highly conserved among a wide range of species, and are generally included in posttranscriptional gene regulation [7]. MiRNAs are discovered to be irregularly expressed in cancer, revealing that they may function as either oncogenes or tumor suppressor. Overexpressed miRs may act as oncogenes through down-regulating tumor suppressor genes, while the down-regulated miRs may function as tumor suppressor genes by negatively regulating oncogenes [8–10]. A potential link between miRs and cancer was first described in chronic lymphocytic leukemia, where miR-15 and miR-16 were discovered to be deleted or down-regulated in the vast majority of cancers [11]. Since then, a large number of studies have found different miRs irregularly expressed in several human malignancies [12]. Surprisingly, about 50% of annotated human miRNAs are affiliated with cancer and located at fragile sites, which are areas of the genome affiliated with cancer [13].

Several mechanisms leading to aberrant expression of miRs in tumor have been reported, involving chromosomal rearrangements, genomic copy number change, epigenetic alterations, defects in miR biogenesis pathway and regulation by transcriptional factors [14]. MiRs negatively control genes expression by binding to the 3′ untranslated region (UTR) of target mRNAs. Since miRs do not require entirely complementary, target sites and identify short sites complementary to their 5′ seed region (nucleotides 2–8 of the miRs), one miR can control hundreds of mRNAs and multiple miRs can control an individual mRNA [15]. Significant intuitions into the mechanisms of miR function in cancer have been provided through the showing that miRs are included in known oncogenic pathways. For example, the three human RAS oncogenes (H-, K-, and N-RAS) all include let-7 sites in their 3′ UTR [16]. Interestingly, the let-7 family of miRs, which is typically down-regulated in different cancers, has been demonstrated to negatively control the RAS oncogenes in lung tumors, therefore function as tumor suppressor genes [16,17].

Similarly, miR-15 and miR-16 have been revealed to target the BCL2 oncogene, leading to its down-regulation and apoptosis in leukemic cells [18]. As an example of miRs acting as oncogenes, miR-221 and miR-222 can target and prevent the expression of the p27Kip tumor suppressor [19]. Actually; high levels of these miRs were demonstrated to maintain low p27 protein and elevated proliferation. Another oncogenic pathway, the p53 pathway, also involves miR components. Indeed, the p53 tumor suppressor has been demonstrated to transcriptionally induce miR-34 following genotoxic stress and this induction is significant in mediating p53 function [20,21]. These studies only demonstrate a fraction of the explosion of publications emphasizing the role of miRs in cancer biology and revealing miR deregulation in different malignancies, involving ovarian cancer.

3. MiRNA and ovarian cancer

MiRNAs were originally found in Caenorhabditis elegans, and they are discovered in genomes of most eukaryotes, involving humans [22,23]. Recent researches have offered that miRNAs account for approximately 1%–5% of the human genome and control at least 30% of protein-coding genes [24,25]. To date, nearly 940 various miRNA molecules have been recognized within the human genome [26,27]. To enhance the survival rate in ovarian cancer patients, highly specific and more sensitive biomarkers should be found and progressed for ovarian cancer screening and early detection, as well as for survival prediction trough assisting monitoring of response to chemotherapeutic drugs. The first study offered that miRNAs also fulfill a significant role in ovarian cancer was published in 2006 and demonstrated that nearly 40% of the miRNA genes reveal modified DNA copy numbers [28]. In 2007, Iorio et al. were the first to analyze the global miRNA expression in human OC and compare the differential expression in carcinomas and normal ovarian tissue. They discovered miR-141, miR-200a, miR- 200b, and miR-200c to be up-regulated in carcinomas, and miR-125b1, miR-140, miR-145, and miR-199a to be down-regulated. MiR-140 is located on chromosome 6q22, which is often deleted in ovarian cancers, and this miRNA is thought to target genes affiliated with invasion, involving matrix metalloproteinase 13, fibroblast growth factor 2, and angiogenic VEGFA [29]. In ovarian cancer, miRNAs are engaged in different cellular functions ranging from tumorigenesis, cell cycle, apoptosis, proliferation, invasion, and metastasis to progression of chemoresistance. The role of miRNAs in ovarian cancer has been discovered mainly through expression profiling of miRNAs in various cancer types. Additionally, miRNAs also act as oncogenes

and tumor-suppressor genes; therefore they have a large potential to serve as crucial biomarkers for OC. Accordingly, miRNA biomarkers are more specific and sensitive than any other biomarkers inspected for the diagnosis and prognosis of OC [30,31].

4. MiRNA expression profiles in ovarian cancer

A number of studies have utilized different gene expression profiling approaches to study miR expression in ovarian cancer. An integrative genomic approach that involved miR microarray, array-based comparative genomic hybridization, cDNA microarray, and tissue array was utilized to appraise miR alterations in epithelial ovarian cancer [32]. The authors discovered that both genomic losses and epigenetic changes may be responsible for miR down-regulation. Out of 35 miRs dysregulated between ovarian cancer and the normal controls (immortalized ovarian surface epithelial cells), 31 (88.6%) were under expressed in cancer tissues compared with normal tissues, including the tumor suppressor miRs, let-7d [16], and miR-127 [33]. Iorio et al. demonstrated various miR expression profiles between ovarian cancer tissues/cell lines and normal tissues Of 29 miRs, they demonstrated that only 4 (miR-141, miR-200a, miR-200b, and miR-200c) were over expressed and 25 miRNAs were down-regulated, involving miR-199a, miR-140, miR-145, and miR-125b-1 in the cancer samples [29]. Additionally, they understood that miR signatures were various between ovarian carcinoma histotypes (serous, endometrioid, clear cell, and mucinous). Calura et al. analyzed miR profiles characteristic of each EOC histotype at stage 1 and discovered robust miR markers for clear cell and mucinous histotypes. The clear cell histotype is characterized by higher expression of miR-30a-5p and miR-30a-3p, whereas mucinous histotype displays higher levels of miR-192 and miR-194 [34]. Nam et al. in their study demonstrated the miR expression profiles of 20 serous ovarian carcinomas utilizing a miRNA microarray and compared them with normal samples [35]. In ovarian cancer, 11 miRs were over expressed. (miR-16, miR-20a, miR-21, miR-23a,miR 23b,miR-27a,miR- 93, miR-141, miR-200a, miR-200b, and miR-200c) and 12 were down-regulated (miR-10b, miR 26a, miR-29a, miR-99a, miR-100, miR-125a, miR-125b, miR-143, miR-145, miR-199a, miR-214, and let-7b). Therefore, these reports demonstrated similar sets of dysregulated miRs. Vang et al. analyzed the miR expression profiles of primary serous ovarian cancers and their respective omental metastases utilizing miRNA qPCR arrays [36]. Seventeen miRs exhibited various expressions in omental lesions in comparison with primary tumors. Significantly, among these, miR 146a and miR-150 were enhanced in omental metastases, controlling intensification of spheroid formation and cisplatin resistance. Thirteen miRs were under expressed in high-grade tumors compared with low-grade tumors. Consequently, under expression was higher in late-stage tumors as compared with early-stage cancers, offering a tumor suppressor function for the down-regulated miRs. Among 44 miRs down-regulated in late-stage cancers, three miRs, miR-15a, miR-34a, and miR-34b are believed to be tumor suppressors [14]. Utilizing array-based comparative genomic hybridization, these authors discovered that genomic regions containing miR genes frequently showed copy number abnormalities [28]. Particularly, copy number losses of the region involving miR-218-1 and SLIT2 were observed in 15.5% of ovarian carcinomas. There was a positive association between miR copy number alterations and the miR expression levels of 73.1% of them miR genes. Additionally, experiments with demethylating agents offered that up to 33% of miRs may be regulated through epigenetic mechanisms. The Cancer Genome Atlas project has analyzed mRNA expression, miRNA expression, promoter methylation, and DNA copy number in a total of 489 high-grade serous ovarian adenocarcinomas [37] They demonstrated that high-grade serous ovarian cancer was distinguished by TP53 mutations in almost every tumor (96%). Additionally, there was a low but statistically remarkable prevalence of recurrent somatic mutations in 8 other genes involving NF1, BRCA1, BRCA2, RB and CDK12.In addition, they demonstrated that ovarian cancers could be divided into 4 transcriptional subtypes, 3 miR subtypes, and 4 promoter methylation subtypes. Integrated genomic analysis showed a miRNA-regulatory network that identified a robust integrated mesenchymal subtype affiliated with poor survival in 459 cases of serous ovarian cancer and 560 cases independent of cohort data [38]. Eight key miRs (miR-25, miR-29c, miR-101, miR-128, miR-141, miR-182, miR-200a, and miR-506) were identified and prophesied to regulate 89% of the targets in this network., Studies also revealed that between normal ovarian cells and epithelial ovarian cancers, miR-199a*, miR-214, miR-200, miR-100, and let-7 family being the most highly variously expressed candidates [14,39]. The miR-200 family of miRNAs, which are abundantly expressed in epithelial tissues, contains five members (miR-200a, miR-200b, miR-200c, miR-141, and miR-429). These miRNAs are organized in two clusters along the human genome. MiR-200a, miR-200b, and miR-429 are clustered on chromosome 1, whereas miR-200c and miR-141 are located on chromosome 12 [40] several studies have reported alterations in the expression of different members of the miR-200 family and offered their critical roles in the pathogenesis of ovarian carcinoma. The miR-200 family is among the most remarkably up-regulated miRNAs in EOC. These studies revealed that miR-200a and miR-200c were over expressed in three types of ovarian cancers: serous, endometrioid, and clear cell carcinomas. However, miR-200b and miR-141 are over expressed only in endometrioid and serous subtypes, offering that the role of the miR-200 family in ovarian cancer is more complicated and diverse than initially thought [29]. The let-7 (lethal-7) family of miRNA, containing of 13 various miRNAs, is located and distributed on nine various chromosomes in humans [41]. The expression of the let-7 family is remarkably reduced in multiple human tumors. Low expression level of let-7 is affiliated with poor survival of cancer patients [42]. The let-7 family of miRNAs suppresses multiple ovarian cancer oncogenes, like KRAS, HRAS, c-MYC, and HMGA-2. Remarkably, the genomic region harboring let-7a-3/let- 7b locus was deleted in 44% of ovarian tumor samples studied. However, restored expression of let-7b remarkably decreased ovarian cancer growth both in vitro and in vivo [16,43]. Consequently different miRs have been recognized as a crucial prognostic biomarkers and promise utility in future studies.

5. MiRNAs might serve as potential prognostic biomarker

Since miRNAs are frequently reported dysregulated in cancer and often have tissue-specific expression, they seem to be novel and attractive potential indicators for tumor. [44]. Various studies have demonstrated that irregular miRNA expression can be utilized as a prognostic marker to examine the disease outcome during the treatment regimen. For example, in ovarian cancers, loss of let-7 and over expression of HMGA2 is remarkably affiliated with unfavorable prognosis. Therefore, the ratio of HMGA2 to let-7 has been utilized for prognosis of ovarian cancer; higher ratio of HMGA2/let-7 demonstrates poor survival ($<$10%) compared with a lower ratio (40%) [40]. Additionally, let-7 utilized as a prognostic marker in ovarian cancer is under expressed in chemotherapy-resistant patients and affiliated with shorter development-free survival, consequently, it may serve as a biomarker to remark disease outcome and survival in ovarian cancer patients [42]. Accordingly, the miR-200 family has been discovered as a prognostic marker in several studies of OC. In a study by Hu et al. [45], 55 patients with stage III and IV OC, involving all histological subtypes, were explored and they discovered

expression of the miR-200 family cluster, involving miR- 200a/b/c and miR-429 to be remarkably lower in patients with recurrent disease compared to recurrence free patients. Eitan et al. [46] in their study by where the relation of miRNA expression to prognosis, reported Similar results, investigated in 57 stage I or stage III OC patients with either serous or endometroid histology, and discovered miR- 200a, miR-34, and miR-449b to be the most down-regulated miRNAs in progressed OC (stage III), and high miR-200a expression to be affiliated with early stage disease (stage I) and a more favorable outcome. Additionally, in another large study of 107 OC patients, involving all histological subtypes and stages, it was revealed that patients with high-grade OC combined with high miR-200a levels have an enhanced survival compared to patients with low miR-200a levels [47]. MiR-9 and miR-223 are associated with the recurrence of ovarian cancer and may be utilized as prognostic markers for disease outcome in ovarian cancer [48]. Lately, miR-30d has been observed to be over expressed in patients with platinum-based chemo sensitive response than in patients with chemo-resistant response. Additionally, In this research, miR-30d was observed to be down-regulated in recurrent ovarian cancer patients [49]. Moreover, miRNA expression patterns were analyzed utilizing tissues and cell lines of ovarian cancer; miR-221 was observed to be the most constantly up-regulated and the let-7 family members were the most frequently down-regulated miRNAs in ovarian tumors. These finding offered that these miRNAs may serve as critical biomarkers for disease outcome [13]. Other studies have identified several miRNAs that could be crucial prognostic markers for OC. In a study by Lee et al. [49] exploring miRNA expression in patients with OC compared to benign ovarian cancers and borderline tumors they revealed that higher expression of miR-30c, miR-30d, miR30e-3p, and miR-181d were independent prognostic markers for disease-free survival. Others have recognized low expression of miR-34c and miR-422b in high-grade OC to be affiliated with declined disease-specific survival [50]. Corneyet al. demonstrated that down-regulation of miR-34b/c in late stage OC and affiliated with mesenchymal-to epithelial transition (MET) [51]. Kim et al. [52] found a remarkable up-regulation of miR-519a to be affiliated with poor survival outcome. The down-regulated expression of miR-22 in OC is associated with overall survival and development-free survival; therefore it may serve as an effective prognostic factor for OC patients [53]. The most considerable studies that have identified critical prognostic miRNAs are listed in Table 1.

6. MiRNAs as a diagnostic tool in OC

Among the different preventive measures considered, early detection has long been the key to successful therapy of multiple life-threatening diseases and malignancies, involving ovarian cancer. The irregular expression pattern of miRNAs can be a potential tool to diagnose ovarian cancer in its earliest stages. Several reports have previously demonstrated this miRNA feature for various tumor types. The first report of miRNA dysregulation in ovarian cancer came from Iorio et al.: miRs expression profiles were demonstrated to distinguish between ovarian-cancer samples, and normal ovaries [29]. MiR-200a and miR-141 were recognized as highly up-regulated in cancer, while miR-199a, miR-140, miR-145, and miR-125b1 were most remarkably down-regulated. Additionally specific miRNA dysregulation was also utilized to differentiate the histological subtypes of ovarian tumors. For example, miR-200a and miR-200c were over expressed in all subtypes (mucinous, endometrioid, and clear cells), miR-200b and miR-141 were over expressed in serous as well as endometrioid carcinomas, and miR-21, miR-203, and miR-205 were over expressed only in endometrioid carcinomas. Actually, miR-145 was under expressed in serous and clear-cell carcinomas, while miR-222 was under expressed in both endometrioid and clear-cell carcinomas. Coukos et al. demonstrated a large down regulation of miRNAs in ovarian-cancer cell lines and cancer specimens [32]. Other study has demonstrated remarkable down-regulated expression of serum miR-145 in patients with malignant ovarian cancer and benign ovarian cancer compared with that in healthy controls, and results offered that miR-145 can powerfully serve as an critical indicator for the detection of ovarian and other human cancers [59]. Nam et al. determined 23 irregularly expressed miRNAs in at least 60% of ovarian-cancer specimens with miR-21 as the most over expressed (85% samples) and miR-125b (95% samples) most down-regulated miRNAs [35]. Yang et al. determined 36 miRNAs variously expressed between normal ovarian cells and cancers, involving miR-199a*, miR-214, miR-200a which were discovered over expressed in 53, 56, and 43% tumor tissues respectively, and affiliated with high-grade and late-stage cancers. miR-100 was identified instead as downregulated in 76% of tumors [39]. In contrast with these data, Eitan et al. demonstrated miR-200a, miR-34a, and miR-449b as the most down-regulated miRNAs in the progressed (stage III) ovarian tumors with miR-200a affiliate in the early-stage disease to an improved overall survival [46]. Additionally, miR-200a was recognized as forecaster of favorable outcome in another profiling study of a cohort of 55 progressed ovarian cancers [45]. In addition, Marchini et al. identified miR-200c that is affiliated with development-free survival, overall survival, or both in multivariate analysis of stage I ovarian cancers [56]. Hypomethylation of miRNA genes is the most important epigenetic mechanism for up-regulation of miR-21, miR-203, and miR-205 compared with healthy ovarian tissues [29]. Another study has reported that over expression of miRNAs is dependent on the amplification of miRNA genes in ovarian tumor [32]. Among the 35 miRNAs analyzed, four miRNAs (miR-26, miR-182, miR-103, and miR-26a) were remarkably up-regulated, while two miRNAs (let-7d and miR-127) were

Table 1
Potential prognostic miRs for ovarian cancer.

miRNA	Alteration	Patient	Prognosis	End Point	Ref
miR-21	Upregulated	EOC	Poor	OS	[54]
miR-221	Upregulated	EOC	Poor	OS	[55]
miR-200a	Upregulated	EOC	Good	RFS,OS	[45]
miR-200c	Upregulated	EOC (Stage 1)	Good	PFS,OS	[56]
Let-7	Downregulated	EOC	Poor	Decreased OS	[35,42]
miR-22	Downregulated	EOC	Good	OS	[53]
miR-519a	Downregulated	EOC	Poor	Decreased OS	[52]
miR-30c,d and miR-30e-3p	Upregulated	EOC	Good	Improved OS and DFS	[49]
miR-34b,c	Downregulated	EOC	Poor	Decreased DSS	[50,51]
miR-203	Upregulated	EOC	Poor	DFS, OS	[57]
miR-187	Upregulated	EOC	Good	RFS, OS	[58]

EOC; epithelial ovarian cancer, OS, overall survival; PFS, progression-free survival, DSS; disease-specific survival, DFS: disease-free survival, RFS; recurrent-free survival.

highly down-regulated. These studies demonstrated that changes in copy number and epigenetic silencing of miRNA genes are the two mechanisms of irregular expression of miRNAs in ovarian cancer [32].Consequently, miR-30c, miR-30d, and miR-30e are frequently up-regulated, while miR-493 is down-regulated in ovarian tumors compared with that in normal HOSE cell lines. However, miR-30a has been recognized as a clear cell-specific miRNA in ovarian cancer [60]. In a recent study, comparative and detailed miRNA expression profiling was accomplished in different tissues and malignant ovarian carcinomas utilizing quantitative real-time PCR (qPCR) to discover the relationship between frequently dysregulated miRNAs and clinicopathologic variables, response to treatment, survival, and their connection with Her-2/neu status in ovarian tumors. This study clearly identified that expression levels of the four miRNAs (miR-30c, miR-30d, miR-30e-3p, and miR-370) is remarkably higher in ovarian cancer than that in benign ovarian tissue, whereas, three miRNAs (miR-181d, miR-30a-3p, miR-532-5p) are remarkably various between borderline and ovarian carcinoma. Critically, miR-370, which is significantly up-regulated in early stage of ovarian carcinoma, can be utilized as a biomarker for early detection of ovarian cancer. Additionally, the down-regulation of miR-30c, miR-30d, miR-30e-3p, and miR-532-5p is affiliated with the over expression of Her2/neu oncogene, while the up-regulation of miR-30a-3p and miR-181d is connected with well-differentiated carcinomas (grade 1) compared with poorly differentiated carcinomas (grade 3), demonstrating the diagnostic potential of multiple miRNA species for various staging and grading of ovarian carcinoma [49]. Aside from the expression profiling of miRNA in various tissues, blood-based serum and plasma miRNA expression is also well documented and may be utilized as surrogate noninvasive biomarkers. Resnick et al. compared 21 serum miRs between epithelial ovarian cancer patients and normal ovary [61]. MiR-21, miR-29a, miR-92, miR-93, and miR-126 were remarkably up-regulated in the serum of ovarian cancer patients compared to controls, whereas miR-99b, miR-127, and miR-155 were remarkably down regulated. Hausler et al. examined the whole blood-derived miR profiles of ovarian carcinoma patients [62]. A comparison between ovarian cancer patients and healthy controls detected 147 remarkably deregulated miRs. Particularly, miR-30c-1-3p was highly over expressed and miR-181a-3p, miR-342-3p, and miR-450b-5p were remarkably under expressed in ovarian cancer patients. Kan et al. discovered that miR-200a, miR-200b, and miR-200c were remarkably elevated in the serum of patients and offered that their presence could be utilized as a predictor of ovarian carcinoma [63]. Chung et al. showed that serum miR-26a, miR-132, miR-145, and let-7b could be considered powerful candidates as novel biomarkers of serous ovarian cancer [64]. Suryawanshi et al. identified 3 various miR signatures between healthy controls, patients with endometriosis, and patients with endometriosis-connected ovarian cancer [65]. They offered that these signatures might serve as useful diagnostic markers for the discrimination of these diseases, which is often clinically difficult. Zheng et al. reported that plasma miR-205 and let-7f could be utilized as biomarkers for ovarian cancer detection, especially in patients with stage 1 disease [66]. These attempts potentially support the idea that the detection of ovarian carcinoma-affiliated miRs from the peripheral blood could become an important tool for early diagnosis of this disease in future clinical practice. Enhancing the sensitivity and lowering the cost of such detection methods are both main goals for progressing the application of detecting serum miR in cancer patients. MiRs that are potentially useful for the diagnosis or detection of ovarian cancer are summarized in Table 2.

7. Molecular signaling pathways involved in miRNA-mediated regulation of OC

MiRNAs control various molecular signaling pathways of ovarian cancer pathogenesis by interacting with multiple target genes, and they modulate the functions of these genes across various tumor types. For example, the RAS oncogenes are well-known targets of the let-7 cluster [16], which have been demonstrated to be down-regulated in ovarian carcinoma by several groups. Other let-7 targets, including HMGA2, CDK6, cMYC, and STAT 3 are likely relevant to tumorigenesis [68]. Another study has offered that let-7a plays crucial roles in carcinogenesis, proliferation, and invasion, possibly by regulating the cell cycle through the NIRF/p53/p21/CDK signaling pathway [69]. The transforming growth factor-β (TGF-β) signaling pathway is one of the best characterized pathways known to play a critical role in ovarian cancer development, particularly in epithelial mesenchymal transition (EMT), through modulation by miR-181a. The key target genes of the TGF-β signaling pathway are the two receptor-regulated SMADs, namely, Smad2 and Smad3, involving Smad7. Additionally, TGF-β plays a pivotal role in EMT by suppressing E-cadherin expression in epithelial cancer cells (the TGF-β/SMAD signaling pathway) [70]. Similarly, the tumor suppressor gene WT1, which encodes a transcription factor, is a putative target of miR-212. Unlike the previous examples, which were described in other systems, miR-214 was shown to target PTEN in ovarian carcinoma, explaining its ability to regulate survival and drug resistance [39]. The p53 pathway is another pathway with critical miR components that were studied in ovarian carcinoma. MiR-34b and miR-34c, two known transcriptional targets of p53, have been revealed to be down-regulated in ovarian carcinoma [32]. Surprisingly, their over expression can repress proliferation and colony formation in soft agar in neoplastic epithelial ovarian cells, providing functional relevance of this pathway in ovarian

Table 2
Potential diagnostic miRs for ovarian cancer.

miRNA	Alteration	Tumor histology	Sample	Ref
miR-21, miR-203, miR-205	Upregulated	EAC	Exosome	[67]
miR-200a,c	Upregulated	All subtypes	Serum	[29]
miR-141, miR-200b	Upregulated	SAC, EAC	Serum	[29]
miR-145	Downregulated	SAC, CAC	Serum	[29,64]
miR-222	Downregulated	EAC, CAC	Serum	[29]
miR-132, miR-145, miR-26a, let7b	Downregulated	SAC	Serum	[64]
miR-30c-1-3p	Upregulated	SAC, EAC	Whole blood	[62]
miR-181a-3p, miR-342-3p, miR-450b-5p	Downregulated	SAC, EAC	Whole blood	[62]
miR-205	Upregulated	SAC, CAC, EAC, MAC	Plasma	[66]
Let-7f	Downregulated	SAC, CAC, EAC, MAC	Plasma	[66]
miR-16, miR-21, miR-191	Upregulated	CAC, EAC	Plasma	[65]
miR-4284, miR-191	Upregulated	SAC	Plasma	[65]

SAC: serous adenocarcinoma; CAC: clear cell adenocarcinoma; EAC: endometrioid adenocarcinoma; MAC: mucinous adenocarcinoma.

carcinogenesis [71]. Additionally, OC is characterized through changes in epidermal growth factor receptor (EGFR), PI3K/AKT/mTOR signaling, and mutations or epigenetic losses of BRCA1/2, PTEN, and TP53 [72]. In the pathogenesis of ovarian cancer, transformation of epithelial cells to mesenchymal cells marks the inception of cancer progression and invasion. The miR-200 family of miRNAs plays a crucial role in this transition by targeting ZEB-1 and ZEB-2, the transcriptional suppressor of E-cadherin genes [73]. For EMT induction, the cells are activated by external stimuli, like TGF-β or PDGF-D, which activate the expression of transcriptional suppressor ZEB1/2 and reduces the expression of miR-200 [74]. MiR-34-a/b/c induced by p53 is down-regulated in ovarian cancer. The p53 mutation or loss-of-function advances EMT of cancer cells by enhancing the expression of Snail1 protein as the miR-34 family of miRNAs represses Snail1 activity when it binds to highly conserved 3′untranslated region in Snail1 and its regulatory molecules, involving β catenin, LEF1, and Axin2.Thus, mutated p53 down-regulates miR-34a/b/c to maintain the level of Snail1 protein, which is a zinc-finger transcriptional repressor that regulates EMT programs of cancer cells [51,75]. Additionally, miR-21 located on chromosome 17q23 is up-regulated in most cancers and plays an important role in neoplastic transformation, invasion, and metastatic processes. MiR-21 prevents apoptosis in cancer cells by targeting PTEN and PDCD4 and triggering the AKT pathway [76]. The enhanced expression of miR-221 and miR-222, which are located on X-chromosome, prevents apoptosis by down regulating cell cycle genes, namely, CDK1B (p27) and CDK1C (p57) [77] (Fig. 1).

8. Roles of miRs in ovarian carcinoma chemotherapy

One of the critical challenges in OC therapy is the development of chemotherapy resistance. About 20% of all primary OC patients are resistant to the standard platinum-based chemotherapy resulting in a fast, most often catastrophic, disease course. Out of the 80% initially responsiveness to chemotherapy almost all patients will finally experience relapse and develop drug resistance, and the acquired resistance often leaves no other attainable curative treatment [8,78].

One of the first miRNAs identified to be remarkably dysregulated in chemotherapy-resistant EOC is the let-7i, and it was additionally observed that decreased levels of let-7i also was associated with shorter survival [42]. Another expression profiling study in a panel of cisplatin-, paclitaxel-, and cyclosporin A-resistant ovarian cancer cells showed the expressions of let-7e, miR-30c, miR-125b, miR-130a, and miR-335 in all the resistant cell lines [79]. Whereas analyzing their downstream targets, the researcher discovered a direct relationship between under expression of miR-130a with up-regulation of M-CSF, a gene previously known to be over expressed in ovarian cancer. Laios et al. demonstrate where primary and recurrent cases of ovarian carcinomas were compared, 60 miRs were discovered dysregulated more than twofold between primary and recurrent disease [48]. In contrast to some studies demonstrating a majority of miRs to be down-regulated in cancer tissues, a marked over expression of miRs in recurrent compared with primary tumors was observed (52 miRs showed over expression and 8 demonstrated down regulation of >twofold in recurrent versus primary tumors). miR-223 (up) and miR-9 (down) were the most highly dysregulated genes in the recurrent versus primary samples [48].

An over expression of five miRNAs (miR-27a, miR-23a, miR-449b, miR-21, miR-24-2) revealed an association with poorer survival [46]. Additionally, let-7a expression has also been linked to the chemotherapeutic response, where the advantageous effect of the addition of paclitaxel to platinium therapy was better in patients with low let-7a levels [80]. In a recent patient cohort

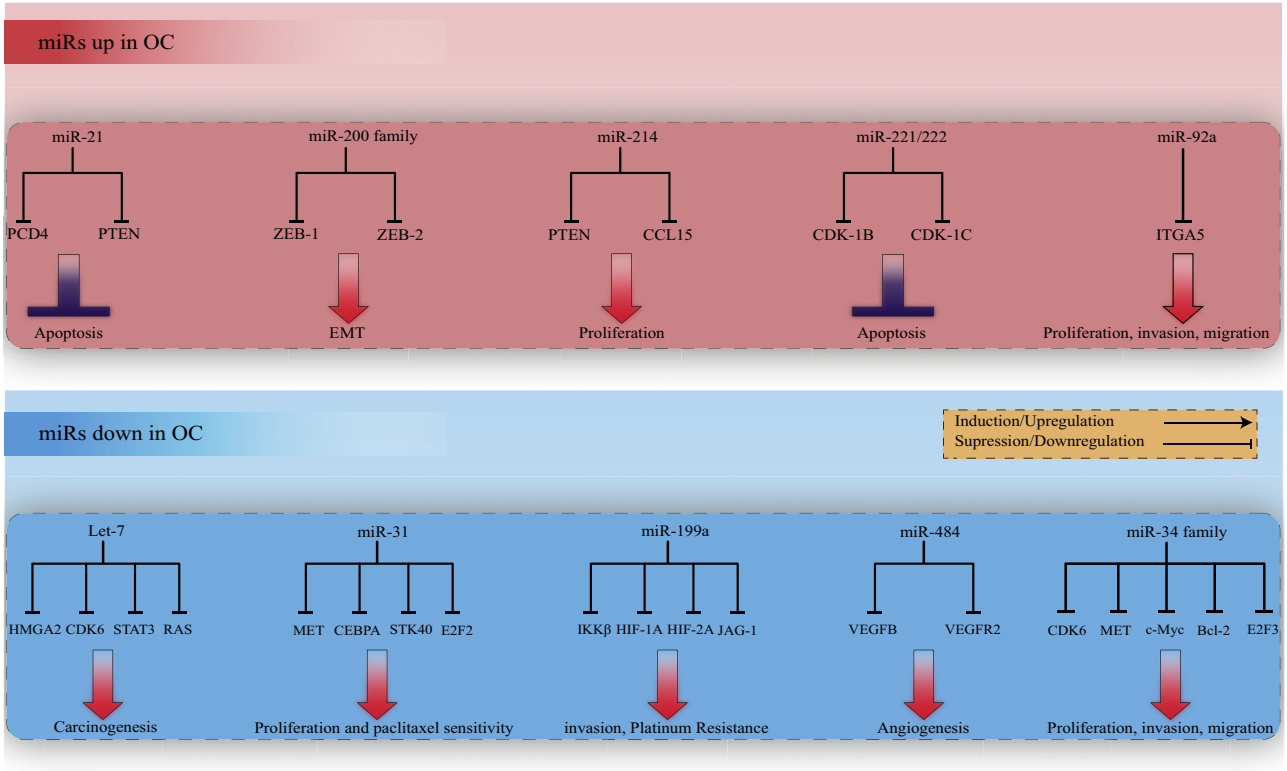

Fig. 1. Schematic representation of selected known targets for miRs that are frequently altered in ovarian carcinoma. The miRs that are up-regulated (red boxes) target genes that have negative effects on cell growth. These miRs may represent targets for therapeutic interventions, while miRs frequently down-regulated in ovarian carcinoma (shown in blue box) typically target genes that have growth promoting functions.

study, Vecchione et al. [81], analyzed miRNA expression in 198 OC specimen, and reported three miRNAs (miR-484, miR-642 and miR-217) that were under expressed in chemoresistant patients, whereas Parikh et al. reported miR-181a as a predictor of tumor recurrence and chemoresistance in high-grade OC. They revealed that miR-181a expression was remarkably higher in tumor biopsies that were taken after patients have recurred, compared to the matched-tumor biopsies taken at primary surgery [70].

9. MiRNAs as therapeutic tools in OC

With the progression in cancer profiling, therapies will soon be customized for each individual. Because each miR controls the expression of hundreds of different genes, miRs can function as master coordinators, effectively controlling and coordinating multiple cellular pathways and proceedings [82]. Therefore, miRs have been offered as possible therapeutic weapons against cancer. As evidence has demonstrated, miRNAs can function as either oncogenes or tumor suppressor genes, and correction of the changed miRNA expression is an attractive target for cancer treatments. Correction of the alteration can be done either by using miRNA mimics (miRNA replacement therapy) to restore loss-of-function or by suppression of the over expressed oncomiRs using antisense miRs (miRNA inhibition therapy) [83]. The first and the only 'anticancer miRNA drug' MRX34 that is a miR-34 miRNA mimic has entered Phase I clinical trials in patients with advanced hepatocellular carcinoma heralding the entry of miRNAs into cancer treatments in clinical settings. Engrossingly, miR-34 family of miRNAs was found to be regularly under expressed in EOC and this under expression was more evident in EOC patients with mutations in TP53 and was connected with metastatic clinical stage [51]. In the same study, it was further indicated that miR-34 replacement therapy in the metastatic SKOV3 ovarian cancer cells remarkably reduced proliferation, migration and invasion. Despite the fact that there is currently no miRNA drug in clinical settings in EOC, MRX34 could provide with a stimulating possibility of clinical translation in EOC patients in future.

Members of the miR-200 family (miR-141, miR-200a, miR-200b, miR-200c, and miR-429) are downregulated in the majority of ovarian cancers, as previously discussed [29,35]. Marchini et al. demonstrated that low levels of miR-200c can anticipate poor survival and are a biomarker of relapse in stage I epithelial ovarian cancer [56]. The miR-200 family plays a critical role in the inhibition of epithelial-to-mesenchymal transition (EMT) and cancer cell migration, metastasis, and invasion by directly targeting ZEB1 (zinc finger E-box-binding homeobox 1) and ZEB2 [47,84]. Both miR-141 and miR-200a target p38 and modify the oxidative stress response, touching tumorigenesis and chemosensitivity [47]. miR-200a or miR-200c suppress cancer stem-like cell populations [84,85]. Pecot et al. reported that miR-200 members suppress angiogenesis through direct and indirect mechanisms by targeting interleukin-8 and CXCL1 released from the tumor epithelial and tumor cells. They indicated the therapeutic potential of miR-200 delivery in treating ovarian tumor or other malignancies [86].

Chen et al. reported that miR-199a regulates IKK expression, which modifies the inflammatory microenvironment in ovarian cancer [87]. Yin et al. indicated that TWIST1 controlled the IKK/NF-??B and PTEN/AKT pathways by the miR-199a-2/miR-214 cluster [88]. MiR-199a also targets CD44 to inhibit the tumorigenicity and multidrug resistance of ovarian cancer initiating cells [89]. Epigenetic silencing of miR-199b-5p is connected with chemoresistance in ovarian cancer through the activation of JAG1/Notch1 signaling [90]. Yang et al. indicated that miR-214 induced cell survival and cisplatin resistance by direct targeting of PTEN and inactivation of the AKT pathway [39]. Joshi et al. showed that the expression of miR-199a is decreased in cancer cells by hypoxic stimuli, and exogenous expression of miR-199a reduced cell migration and metastasis of ovarian cancer cells through targeting the 3′-UTRs of HIF-1a and HIF-2a [91].

Johnson et al. indicated that the let-7 family negatively controls let-60/RAS, whose 3′-UTR contains multiple let-7 complementary sites [16]. In ovarian cancer, let-7 is under expressed. Let-7 also targets the embryonic gene high mobility group A2 (HMGA2) more effectively than RAS during early cancer progression [40,92]. Shell et al. reported that let-7 and HMGA2 can be foreseers of prognosis and that loss of let-7 expression shows less differentiated cancer [40]. High-grade serous ovarian carcinoma (HG-SOC) is a heterogeneous, poorly classified, and lethal disease. Lately, *meta*-analysis of its transcriptome showed let-7b as an unfavorable prognostic biomarker that can anticipate molecular and clinical subclasses of HG-SOC [93].

MiR-92a is in the miR-17/92 family cluster, which includes miR-17, miR-18, miR-19a, mir-19b, miR-20, and miR-92. Ohyagi-Hara et al. demonstrated the participation of miR-92a in the expression of integrin alpha-5, a known key player in ovarian cancer adhesion and diffusion [94,95]. The levels of integrin alpha-5 and miR-92a expression were considerably and inversely correlated in ovarian cancer cells. The contrived expression of miR-92a in cancer cells notably inhibited peritoneal diffusion in vivo, offering that targeting miR-92a may confirm to be a novel and efficient gene therapy for patients with ovarian cancer.

Table 3
Potential therapeutic miRs for ovarian cancer.

miRNA	Alteration	Target	Cellular function	Ref
miR-200a and miR-141	Mixed	p38, MAPK14	Oxidative stress response	[47]
miR-200c	Downregulated	ZEB1, ZEB2	EMT, migration, invasion	[98,99]
miR-200b	Downregulated	IL8, CXCL1	Metastasis, angiogenesis	[86]
miR-141	Upregulated	KEAP1	Cisplatin resistance	[100]
Let-7e	Downregulated	EZH2, CCD1	Overexpression increases platinum sensitivity	[101]
Let-7i	Downregulated	H-RAS, HMGA2	Overexpression increases platinum sensitivity	[42]
miR-199a/miR-214	Upregulated	IKKb/NFκB, PTWN/AKT	Stemness	[88]
miR-92a	Downregulated	ITGA5	Overexpression inhibits cell Adhesion. Reduces peritoneal metastasis	[95]
miR-484	Downregulated	VEGFB, VEGFR2	Overexpression increases Chemosensitivity. Control angiogenesis	[81]
miR-187	Upregulated	Dab2	Increased levels of miR-187 inhibits EMT	[58]

Creighton et al. comprehensively profiled the expression of miRs and mRNAs in serous ovarian cancers, cell lines, and normal ovarian epithelium [96]. They demonstrated that miR-31, the least 6 BioMed Research International regulated miR in serous ovarian cancer, inhibited the cell cycle regulator E2F2, suppressed proliferation, and induced apoptosis. They discovered that loss of miR-31 is connected with defects in the TP53 (also called p53) pathway and functions in serous ovarian cancer, offering that patients with cancers that are deficient in TP53 activity might benefit from therapeutic delivery of miR-31.

Nishimura et al. showed miR-520d-3p as a tumor suppressor upstream of EPHA2, whose expression correlated with favorable results in clinical cohorts [97]. Dual suppression of EPHA2, using EPHA2 siRNA and nanoliposomes loaded with miR-520d-3p, indicated better antitumor efficacy than either monotherapy in vivo. These data accentuate the applicability of combined miRNA-siRNA therapy for cancer or other diseases. MiRs that are potentially useful for the treatment of ovarian cancer are summarized in Table 3.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

None.

References

[1] R. Siegel, D. Naishadham, A. Jemal, Cancer statistics 2012, CA. Cancer J. Clin. 62 (2012) 10–29.
[2] A. Jemal, R. Siegel, E. Ward, Y. Hao, J. Xu, T. Murray, et al., Cancer statistics 2008, CA. Cancer J. Clin. 58 (2008) 71–96.
[3] G. Di Leva, C.M. Croce, miRNA profiling of cancer, Curr. Opin. Genet. Dev. 23 (2013) 3–11.
[4] J. Prat, Staging classification for cancer of the ovary, fallopian tube, and peritoneum, Int. J. Gynecol. Obstet. 124 (2014) 1–5.
[5] C. van Haaften-Day, Y. Shen, F. Xu, Y. Yu, A. Berchuck, L.J. Havrilesky, et al., OVX1, macrophage-colony stimulating factor, and CA-125-II as tumor markers for epithelial ovarian carcinoma, Cancer 92 (2001) 2837–2844.
[6] R.F. Ozols, B.N. Bundy, B.E. Greer, J.M. Fowler, D. Clarke-Pearson, R.A. Burger, et al., Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study, J. Clin. Oncol. 21 (2003) 3194–3200.
[7] Y. Kinose, K. Sawada, K. Nakamura, T. Kimura, The role of microRNAs in ovarian cancer, BioMed Res. Int. 2014 (2014).
[8] G.W. Prahm, C. Høgdall, E. Høgdall, Current status on microRNAs as biomarkers for ovarian cancer, Apmis, (2016) .
[9] M. Hemmatzadeh, H. Mohammadi, F. Jadidi-Niaragh, F. Asghari, M. Yousefi, The role of oncomirs in the pathogenesis and treatment of breast cancer, Biomed. Pharmacother. 78 (2016) 129–139.
[10] M. Hemmatzadeh, H. Mohammadi, M. Karimi, M.H. Musavishenas, B. Baradaran, Differential role of microRNAs in the pathogenesis and treatment of Esophageal cancer, Biomed. Pharmacother. 82 (2016) 509–519.
[11] G.A. Calin, C.D. Dumitru, M. Shimizu, R. Bichi, S. Zupo, E. Noch, et al., Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia, Proc. Natl. Acad. Sci. 99 (2002) 15524–15529.
[12] W. Zhang, J.E. Dahlberg, W. Tam, MicroRNAs in tumorigenesis: a primer, Am. J. Pathol. 171 (2007) 728–738.
[13] M.K. Pal, S.P. Jaiswar, V.N. Dwivedi, A.K. Tripathi, A. Dwivedi, P. Sankhwar, MicroRNA: a new and promising potential biomarker for diagnosis and prognosis of ovarian cancer, Cancer Biol. Med. 12 (2015) 328.
[14] N. Dahiya, P.J. Morin, MicroRNAs in ovarian carcinomas, Endocr. Relat. Cancer 17 (2010) F77–F89.
[15] B.P. Lewis, I.-h. Shih, M.W. Jones-Rhoades, D.P. Bartel, C.B. Burge, Prediction of mammalian microRNA targets, Cell 115 (2003) 787–798.
[16] S.M. Johnson, H. Grosshans, J. Shingara, M. Byrom, R. Jarvis, A. Cheng, et al., RAS is regulated by the let-7 microRNA family, Cell 120 (2005) 635–647.
[17] M.S. Kumar, S.J. Erkeland, R.E. Pester, C.Y. Chen, M.S. Ebert, P.A. Sharp, et al., Suppression of non-small cell lung tumor development by the let-7 microRNA family, Proc. Natl. Acad. Sci. 105 (2008) 3903–3908.
[18] A. Cimmino, G.A. Calin, M. Fabbri, M.V. Iorio, M. Ferracin, M. Shimizu, et al., miR-15 and miR-16 induce apoptosis by targeting BCL2, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 13944–13949.
[19] C. le Sage, R. Nagel, D.A. Egan, M. Schrier, E. Mesman, A. Mangiola, et al., Regulation of the p27Kip1 tumor suppressor by miR-221 and miR-222 promotes cancer cell proliferation, EMBO J. 26 (2007) 3699–3708.
[20] T.-C. Chang, E.A. Wentzel, O.A. Kent, K. Ramachandran, M. Mullendore, K.H. Lee, et al., Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis, Mol. Cell 26 (2007) 745–752.
[21] H. Hermeking, p53 Enters the microRNA world, Cancer Cell 12 (2007) 414–418.
[22] B. Wightman, I. Ha, G. Ruvkun, Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans, Cell 75 (1993) 855–862.
[23] M.P. Perron, P. Provost, Protein interactions and complexes in human microRNA biogenesis and function, ABBV Front Biosci. 13 (2008) 2537.
[24] N. Rajewsky, MicroRNA target predictions in animals, Nat. Genet. 38 (2006) S8–S13.
[25] W. Liu, S.-Y. Mao, W.-Y. Zhu, Impact of tiny miRNAs on cancers, World J. Gastroenterol. 13 (2007) 497.
[26] B.R. Cullen, Transcription and processing of human microRNA precursors, Mol. Cell 16 (2004) 861–865.
[27] S. Griffiths-Jones, H.K. Saini, S. van Dongen, A.J. Enright, miRBase: tools for microRNA genomics, Nucl. Acids Res. 36 (2008) D154–D158.
[28] L. Zhang, J. Huang, N. Yang, J. Greshock, M.S. Megraw, A. Giannakakis, et al., microRNAs exhibit high frequency genomic alterations in human cancer, Proc. Natl. Acad. Sci. 103 (2006) 9136–9141.
[29] M.V. Iorio, R. Visone, G. Di Leva, V. Donati, F. Petrocca, P. Casalini, et al., MicroRNA signatures in human ovarian cancer, Cancer Res. 67 (2007) 8699–8707.
[30] W.C. Cho, MicroRNAs: potential biomarkers for cancer diagnosis prognosis and targets for therapy, Int. J. Biochem. Cell Biol. 42 (2010) 1273–1281.
[31] W.C. Cho, Great potential of miRNAs as predictive and prognostic markers for cancer, Expert Rev. Mol. Diagn. 12 (2012) 315–318.
[32] L. Zhang, S. Volinia, T. Bonome, G.A. Calin, J. Greshock, N. Yang, et al., Genomic and epigenetic alterations deregulate microRNA expression in human epithelial ovarian cancer, Proc. Natl. Acad. Sci. 105 (2008) 7004–7009.
[33] Y. Saito, G. Liang, G. Egger, J.M. Friedman, J.C. Chuang, G.A. Coetzee, et al., Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells, Cancer Cell 9 (2006) 435–443.
[34] E. Calura, R. Fruscio, L. Paracchini, E. Bignotti, A. Ravaggi, P. Martini, et al., miRNA landscape in stage I epithelial ovarian cancer defines the histotype specificities, Clin. Cancer Res. 19 (2013) 4114–4123.
[35] E.J. Nam, H. Yoon, S.W. Kim, H. Kim, Y.T. Kim, J.H. Kim, et al., MicroRNA expression profiles in serous ovarian carcinoma, Clin. Cancer Res. 14 (2008) 2690–2695.
[36] S. Vang, H.-T. Wu, A. Fischer, D.H. Miller, S. MacLaughlan, E. Douglass, et al., Identification of ovarian cancer metastatic miRNAs, PLoS One 8 (2013) e58226.
[37] C.G.A.R. Network, Integrated genomic analyses of ovarian carcinoma, Nature 474 (2011) 609–615.
[38] D. Yang, Y. Sun, L. Hu, H. Zheng, P. Ji, C.V. Pecot, et al., Integrated analyses identify a master microRNA regulatory network for the mesenchymal subtype in serous ovarian cancer, Cancer Cell 23 (2013) 186–199.
[39] H. Yang, W. Kong, L. He, J.-J. Zhao, J.D. O'Donnell, J. Wang, et al., MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN, Cancer Res. 68 (2008) 425–433.
[40] S. Shell, S.-M. Park, A.R. Radjabi, R. Schickel, E.O. Kistner, D.A. Jewell, et al., Let-7 expression defines two differentiation stages of cancer, Proc. Natl. Acad. Sci. 104 (2007) 11400–11405.
[41] S. Roush, F.J. Slack, The let-7 family of microRNAs, Trends Cell Biol. 18 (2008) 505–516.
[42] N. Yang, S. Kaur, S. Volinia, J. Greshock, H. Lassus, K. Hasegawa, et al., MicroRNA microarray identifies Let-7i as a novel biomarker and therapeutic target in human epithelial ovarian cancer, Cancer Res. 68 (2008) 10307–10314.
[43] I. Büssing, F.J. Slack, H. Großhans, let-7 microRNAs in development, stem cells and cancer, Trends Mol. Med. 14 (2008) 400–409.
[44] K.P. Prahm, M.A. Karlsen, E. Høgdall, N.M. Scheller, L. Lundvall, L. Nedergaard, et al., The prognostic value of dividing epithelial ovarian cancer into type I and type II tumors based on pathologic characteristics, Gynecol. Oncol. 136 (2015) 205–211.
[45] X. Hu, D.M. Macdonald, P.C. Huettner, Z. Feng, I.M. El Naqa, J.K. Schwarz, et al., A miR-200 microRNA cluster as prognostic marker in advanced ovarian cancer, Gynecol. Oncol. 114 (2009) 457–464.
[46] R. Eitan, M. Kushnir, G. Lithwick-Yanai, M.B. David, M. Hoshen, M. Glezerman, et al., Tumor microRNA expression patterns associated with resistance to platinum based chemotherapy and survival in ovarian cancer patients, Gynecol. Oncol. 114 (2009) 253–259.
[47] B. Mateescu, L. Batista, M. Cardon, T. Gruosso, Y. de Feraudy, O. Mariani, et al., miR-141 and miR-200a act on ovarian tumorigenesis by controlling oxidative stress response, Nat. Med. 17 (2011) 1627–1635.
[48] A. Laios, S. O'Toole, R. Flavin, C. Martin, L. Kelly, M. Ring, et al., Potential role of miR-9 and miR-223 in recurrent ovarian cancer, Mol. Cancer 7 (2008) 1.
[49] H. Lee, C.S. Park, G. Deftereos, J. Morihara, J.E. Stern, S.E. Hawes, et al., MicroRNA expression in ovarian carcinoma and its correlation with clinicopathological features, World J. Surg. Oncol. 10 (2012) 1.

[50] C.-H. Lee, S. Subramanian, A.H. Beck, I. Espinosa, J. Senz, S.X. Zhu, et al., MicroRNA profiling of BRCA1/2 mutation-carrying and non-mutation-carrying high-grade serous carcinomas of ovary, PLoS One 4 (2009) e7314.
[51] D.C. Corney, C.-I. Hwang, A. Matoso, M. Vogt, A. Flesken-Nikitin, A.K. Godwin, et al., Frequent downregulation of miR-34 family in human ovarian cancers, Clin. Cancer Res. 16 (2010) 1119–1128.
[52] T.H. Kim, Y.K. Kim, Y. Kwon, J.H. Heo, H. Kang, G. Kim, et al., Deregulation of miR-519a, 153, and 485-5p and its clinicopathological relevance in ovarian epithelial tumours, Histopathology 57 (2010) 734–743.
[53] W.-N. Wan, Y.-X. Zhang, X.-M. Wang, Y.-J. Liu, Y.-Q. Zhang, Y.-H. Que, et al., ATAD2 is highly expressed in ovarian carcinomas and indicates poor prognosis, Asian Pac. J. Cancer Prev. 15 (2014) 2777–2783.
[54] Y.-Z. Xu, Q.-H. Xi, W.-L. Ge, X.-Q. Zhang, Identification of serum microRNA-21 as a biomarker for early detection and prognosis in human epithelial ovarian cancer, Asian Pac. J. Cancer Prev. 14 (2013) 1057–1060.
[55] F. Hong, Y. Li, Y. Xu, L. Zhu, Prognostic significance of serum microRNA-221 expression in human epithelial ovarian cancer, J. Int. Med. Res. (2013) 0300060513475759.
[56] S. Marchini, D. Cavalieri, R. Fruscio, E. Calura, D. Garavaglia, I.F. Nerini, et al., Association between miR-200c and the survival of patients with stage I epithelial ovarian cancer: a retrospective study of two independent tumour tissue collections, Lancet Oncol. 12 (2011) 273–285.
[57] S. Wang, X. Zhao, J. Wang, Y. Wen, L. Zhang, D. Wang, et al., Upregulation of microRNA-203 is associated with advanced tumor progression and poor prognosis in epithelial ovarian cancer, Med. Oncol. 30 (2013) 1–7.
[58] A. Chao, C. Lin, Y. Lee, C. Tsai, P. Wei, S. Hsueh, et al., Regulation of ovarian cancer progression by microRNA-187 through targeting Disabled homolog-2, Oncogene 31 (2012) 764–775.
[59] H. Liang, Z. Jiang, G. Xie, Y. Lu, Serum microRNA-145 as a novel biomarker in human ovarian cancer, Tumor Biol. 36 (2015) 5305–5313.
[60] S.K. Wyman, R.K. Parkin, P.S. Mitchell, B.R. Fritz, K. O'Briant, A.K. Godwin, et al., Repertoire of microRNAs in epithelial ovarian cancer as determined by next generation sequencing of small RNA cDNA libraries, PLoS One 4 (2009) e5311.
[61] K.E. Resnick, H. Alder, J.P. Hagan, D.L. Richardson, C.M. Croce, D.E. Cohn, The detection of differentially expressed microRNAs from the serum of ovarian cancer patients using a novel real-time PCR platform, Gynecol. Oncol. 112 (2009) 55–59.
[62] S. Häusler, A. Keller, P. Chandran, K. Ziegler, K. Zipp, S. Heuer, et al., Whole blood-derived miRNA profiles as potential new tools for ovarian cancer screening, Br. J. Cancer 103 (2010) 693–700.
[63] C.W. Kan, M.A. Hahn, G.B. Gard, J. Maidens, J.Y. Huh, D.J. Marsh, et al., Elevated levels of circulating microRNA-200 family members correlate with serous epithelial ovarian cancer, BMC Cancer 12 (2012) 1.
[64] Y.-W. Chung, H.-S. Bae, J.-Y. Song, J.K. Lee, N.W. Lee, T. Kim, et al., Detection of microRNA as novel biomarkers of epithelial ovarian cancer from the serum of ovarian cancer patient, Int. J. Gynecol. Cancer 23 (2013) 673–679.
[65] S. Suryawanshi, A.M. Vlad, H.-M. Lin, G. Mantia-Smaldone, R. Laskey, M. Lee, et al., Plasma microRNAs as novel biomarkers for endometriosis and endometriosis-associated ovarian cancer, Clin. Cancer Res. 19 (2013) 1213–1224.
[66] H. Zheng, L. Zhang, Y. Zhao, D. Yang, F. Song, Y. Wen, et al., Plasma miRNAs as diagnostic and prognostic biomarkers for ovarian cancer, PLoS One 8 (2013) e77853.
[67] D.D. Taylor, C. Gercel-Taylor, MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer, Gynecol. Oncol. 110 (2008) 13–21.
[68] M.E. Peter, Let-7 and miR-200 microRNAs: guardians against pluripotency and cancer progression, Cell Cycle 8 (2009) 843–852.
[69] X. Wang, L. Cao, Y. Wang, X. Wang, N. Liu, Y. You, Regulation of let-7 and its target oncogenes (Review), Oncol. Lett. 3 (2012) 955–960.
[70] C. A. Parikh, P. Lee, S. Joseph, A. Marchini, V. Kolev Baccarini, et al., microRNA-181a has a critical role in ovarian cancer progression through the regulation of the epithelial–mesenchymal transition, Nat. Commun. 5 (2014).
[71] D.C. Corney, A. Flesken-Nikitin, A.K. Godwin, W. Wang, A.Y. Nikitin, MicroRNA-34b and MicroRNA-34c are targets of p53 and cooperate in control of cell proliferation and adhesion-independent growth, Cancer Res. 67 (2007) 8433–8438.
[72] E. Calura, P. Martini, G. Sales, L. Beltrame, G. Chiorino, M. D'Incalci, et al., Wiring miRNAs to pathways: a topological approach to integrate miRNA and mRNA expression profiles, Nucl. Acids Res. 42 (2014) e96.
[73] P.A. Gregory, A.G. Bert, E.L. Paterson, S.C. Barry, A. Tsykin, G. Farshid, et al., The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1, Nat. Cell Biol. 10 (2008) 593–601.
[74] M. Korpal, E.S. Lee, G. Hu, Y. Kang, The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2, J. Biol. Chem. 283 (2008) 14910–14914.
[75] N.H. Kim, H.S. Kim, X.-Y. Li, I. Lee, H.-S. Choi, S.E. Kang, et al., A p53/miRNA-34 axis regulates Snail1-dependent cancer cell epithelial–mesenchymal transition, J. Cell Biol. 195 (2011) 417–433.
[76] Y. Lou, X. Yang, F. Wang, Z. Cui, Y. Huang, MicroRNA-21 promotes the cell proliferation, invasion and migration abilities in ovarian epithelial carcinomas through inhibiting the expression of PTEN protein, Int. J. Mol. Med. 26 (2010) 819.
[77] R. Medina, S.K. Zaidi, C.-G. Liu, J.L. Stein, C.M. Croce, G.S. Stein, MicroRNAs 221 and 222 bypass quiescence and compromise cell survival, Cancer Res. 68 (2008) 2773–2780.
[78] L.E. Weinberg, G. Rodriguez, J.A. Hurteau, The role of neoadjuvant chemotherapy in treating advanced epithelial ovarian cancer, J. Surg. Oncol. 101 (2010) 334–343.
[79] A. Sorrentino, C.-G. Liu, A. Addario, C. Peschle, G. Scambia, C. Ferlini, Role of microRNAs in drug-resistant ovarian cancer cells, Gynecol. Oncol. 111 (2008) 478–486.
[80] L. Lu, P. Schwartz, L. Scarampi, T. Rutherford, E.M. Canuto, H. Yu, et al., MicroRNA let-7a: a potential marker for selection of paclitaxel in ovarian cancer management, Gynecol. Oncol. 122 (2011) 366–371.
[81] A. Vecchione, B. Belletti, F. Lovat, S. Volinia, G. Chiappetta, S. Giglio, et al., A microRNA signature defines chemoresistance in ovarian cancer through modulation of angiogenesis, Proc. Natl. Acad. Sci. 110 (2013) 9845–9850.
[82] G. Di Leva, M. Garofalo, C.M. Croce, MicroRNAs in cancer, Annu. Rev. Pathol. 9 (2014) 287.
[83] Z. Li, T.M. Rana, Therapeutic targeting of microRNAs: current status and future challenges, Nat. Rev. Drug Discov. 13 (2014) 622–638.
[84] Q. Wu, R. Guo, M. Lin, B. Zhou, Y. Wang, MicroRNA-200a inhibits CD133/1+ ovarian cancer stem cells migration and invasion by targeting E-cadherin repressor ZEB2, Gynecol. Oncol. 122 (2011) 149–154.
[85] D. Chen, Y. Zhang, J. Wang, J. Chen, C. Yang, K. Cai, et al., MicroRNA-200c overexpression inhibits tumorigenicity and metastasis of CD117+ CD44+ ovarian cancer stem cells by regulating epithelial-mesenchymal transition, J. Ovar. Res. 6 (2013) 1.
[86] C.V. Pecot, R. Rupaimoole, D. Yang, R. Akbani, C. Ivan, C. Lu, et al., Tumour angiogenesis regulation by the miR-200 family, Nat. Commun. 4 (2013).
[87] R. Chen, A. Alvero, D. Silasi, M. Kelly, S. Fest, I. Visintin, et al., Regulation of IKKβ by miR-199a affects NF-(B activity in ovarian cancer cells, Oncogene 27 (2008) 4712–4723.
[88] G. Yin, R. Chen, A.B. Alvero, H.-H. Fu, J. Holmberg, C. Glackin, et al., TWISTing stemness, inflammation and proliferation of epithelial ovarian cancer cells through MIR199A2/214, Oncogene 29 (2010) 3545–3553.
[89] W. Cheng, T. Liu, X. Wan, Y. Gao, H. Wang, MicroRNA-199a targets CD44 to suppress the tumorigenicity and multidrug resistance of ovarian cancer-initiating cells, FEBS J. 279 (2012) 2047–2059.
[90] M.X. Liu, M.K. Siu, S.S. Liu, J.W. Yam, H.Y. Ngan, D.W. Chan, Epigenetic silencing of microRNA-199b-5p is associated with acquired chemoresistance via activation of JAG1-Notch1 signaling in ovarian cancer, Oncotarget 5 (2014) 944.
[91] H.P. Joshi, I.V. Subramanian, E.K. Schnettler, G. Ghosh, R. Rupaimoole, C. Evans, et al., Dynamin 2 along with microRNA-199a reciprocally regulate hypoxia-inducible factors and ovarian cancer metastasis, Proc. Natl. Acad. Sci. 111 (2014) 5331–5336.
[92] S.-M. Park, S. Shell, A.R. Radjabi, R. Schickel, C. Feig, B. Boyerinas, et al., Let-7 prevents early cancer progression by suppressing expression of the embryonic gene HMGA2, Cell Cycle 6 (2007) 2585–2590.
[93] Z. Tang, G.S. Ow, J.P. Thiery, A.V. Ivshina, V.A. Kuznetsov, Meta-analysis of transcriptome reveals let-7b as an unfavorable prognostic biomarker and predicts molecular and clinical subclasses in high-grade serous ovarian carcinoma, Int. J. Cancer 134 (2014) 306–318.
[94] K. Sawada, A.K. Mitra, A.R. Radjabi, V. Bhaskar, E.O. Kistner, M. Tretiakova, et al., Loss of E-cadherin promotes ovarian cancer metastasis via α5-integrin, which is a therapeutic target, Cancer Res. 68 (2008) 2329–2339.
[95] C. Ohyagi-Hara, K. Sawada, S. Kamiura, Y. Tomita, A. Isobe, K. Hashimoto, et al., miR-92a inhibits peritoneal dissemination of ovarian cancer cells by inhibiting integrin α5 expression, Am. J. Pathol. 182 (2013) 1876–1889.
[96] C.J. Creighton, M.D. Fountain, Z. Yu, A.K. Nagaraja, H. Zhu, M. Khan, et al., Molecular profiling uncovers a p53-associated role for microRNA-31 in inhibiting the proliferation of serous ovarian carcinomas and other cancers, Cancer Res. 70 (2010) 1906–1915.
[97] M. Nishimura, E.-J. Jung, M.Y. Shah, C. Lu, R. Spizzo, M. Shimizu, et al., Therapeutic synergy between microRNA and siRNA in ovarian cancer treatment, Cancer Discov. 3 (2013) 1302–1315.
[98] D. Chen, J. Wang, Y. Zhang, J. Chen, C. Yang, W. Cao, et al., Effect of down-regulated transcriptional repressor ZEB1 on the epithelial-mesenchymal transition of ovarian cancer cells, Int. J. Gynecol. Cancer 23 (2013) 1357–1366.
[99] Y.-m. Lu, C. Shang, Y.-l. Ou, D. Yin, Y.-N. Li, X. Li, et al., miR-200c modulates ovarian cancer cell metastasis potential by targeting zinc finger E-box-binding homeobox 2 (ZEB2) expression, Med. Oncol. 31 (2014) 1–11.
[100] M. Van Jaarsveld, J. Helleman, A. Boersma, P. Van Kuijk, W. Van Ijcken, E. Despierre, et al., miR-141 regulates KEAP1 and modulates cisplatin sensitivity in ovarian cancer cells, Oncogene 32 (2013) 4284–4293.
[101] J. Cai, C. Yang, Q. Yang, H. Ding, J. Jia, J. Guo, et al., Deregulation of let-7e in epithelial ovarian cancer promotes the development of resistance to cisplatin, Oncogenesis 2 (2013) e75.