Deregulated miRNA clusters in ovarian cancer: Imperative implications in personalized medicine

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Abstract Ovarian cancer (OC) is one of the most common and fatal types of gynecological cancer. OC is usually detected at the advanced stages of the disease, making it highly lethal. miRNAs are single-stranded, small non-coding RNAs with an approximate size ranging around 22 nt. Interestingly, a considerable proportion of miRNAs are organized in clusters with miRNA genes placed adjacent to one another, getting transcribed together to result in miRNA clusters (MCs). MCs comprise two or more miRNAs that follow the same orientation during transcription. Abnormal expression of the miRNA cluster has been identified as one of the key drivers in OC. MC exists both as tumor-suppressive and oncogenic clusters and has a significant role in OC pathogenesis by facilitating cancer cells to acquire various hallmarks. The present review...
Introduction

Ovarian cancer (OC) is the 7th most common cancer worldwide and is the most lethal type of gynecological malignancies. The GLOBOCAN estimates had reported 313,959 new victims and 207,252 fatalities due to OC in 2020. According to the American Cancer Society, in 2020, there were a total of 21,750 new OC cases and 13,940 deaths in the United States. Furthermore, in Europe, approximately 29,000 deaths were predicted due to OC in 2020. The Australian Institute of Health and Welfare estimated an incidence of 1,337 cases and 1,010 casualties in 2020 (http://www.aihw.gov.au/reports/cancer/cancer-data-in-australia). The high mortality rate of OC is attributed to its detection at an advanced stage, making it highly fatal. OC is very rarely detected in women below the age of 30 years, and the risk is greater with increasing age. OC is very frequently observed in postmenopausal women. The risk factors associated with OC include family history, ethnicity, genetic syndrome, \(BRCA1/BRCA2\) (breast cancer 1/2), and MMR (mismatch repair) gene mutations, endometriosis, age, obesity, nonsteroidal anti-inflammatory drugs, dietary factors, postmenopausal hormone therapy and smoking. The three prominent types of OC include sex-cord-stromal, germ cell and epithelial. Based on the histopathological characteristics, there are five primary subtypes of epithelial OC, which are low- and high-grade serous carcinoma, endometrioid, mucinous and clear cell. Owing to the vague array of symptoms, OC screening is very challenging. Physical examination, ultrasound, biopsy, blood tests, PET (positron emission tomography), CT (computerized tomography), and MRI (magnetic resonance imaging) scans are commonly used for the detection and diagnosis of OC. Blood-based biomarkers in combination with transvaginal ultrasound imaging have been utilized for the screening of OC. CA125 (cancer antigen 125) is a well-known tumor biomarker that has been used for OC detection. But, this blood-based biomarker has very low sensitivity as well as specificity, and because of this, CA125 is not recommended as a stand-alone screening method. However, the combination of transvaginal ultrasound coupled with screening for CA125 and HEP-4 (human epididymis protein 4) has been proposed as an efficient OC screening tool. Long term use of oral contraceptives has proven to be effective in preventing the risk of OC. On the other hand, the use of oral contraceptives should be equalized to prevent the possible risk of cervical and breast cancer.

Despite the availability of diagnostic tools and preventive interventions, the prognosis of OC is poor. Besides, the high mortality rate in OC is attributed to the nebulous nature of symptoms, diagnosis at an advanced stage, tumor cell heterogeneity, therapeutic resistance, metastasis, and relapse. Many previous studies have suggested that the use of molecular markers can significantly improve the clinical management of OC. This suggests the need to understand the disease at the molecular level and identify clinically relevant markers for diagnosis, prognosis and management of OC. Towards this, expression profiling of miRNAs can be employed for the clinical management of OC.

miRNAs were first discovered in \(C. e l e g a n s\) in 1993 and are single-stranded, non-coding RNAs with an approximate length of 22 nt. The mature miRNAs critically modulate target gene expression by translation repression or mRNA cleavage. Adjacently located miRNA genes get transcribed together to result in miRNA clusters (MC). These clusters contain 2 or more miRNA genes transcribed together in the same orientation. Many of the MCs are evolutionarily conserved and regulate diverse biological pathways by controlling the expression of protein-coding genes. Several studies have highlighted the involvement of MCs in OC progression by facilitating the acquisition of cancer hallmarks. Both the tumor-suppressive and tumor promoting roles of MCs are reported in OC. Various mechanistic studies have suggested that the MC members’ abnormal expression can result in ovarian tumorigenesis and metastasis. Towards this, the current review provides a comprehensive overview of the role of MCs in OC development. More specifically, the present review article focuses on the regulation and biological function of miRNA clusters in OC.

Regulators of MC expression in OC

Similar to protein-coding genes, MC expression is regulated by a variety of gene regulatory mechanisms, which include epigenetic changes, genetic alterations, transcription factors, and miRNA processing genes (Fig. 1). Current experimental evidences clearly describe the association between abnormal epigenetic changes and OC (Table 1). Altered DNA methylation, histone tail modifications, and miRNA expression have been reported during OC. The promoter regions of tumor-suppressive MC are hypermethylated, and downregulated in OC. For example, the miRNAs in the chromosome 14 cluster are identified as down regulated as a result of epigenetic modifications in EOC (epithelial ovarian cancer). Additionally, miRNA regulation of miRNA expression is reported in OC. Li et al have described the regulation of miR-133b (miR-1/133a cluster) expression by miR-145 (miR-143/145 cluster) via targeting c-MYC and DNM73A. Numerous MCs are found co-localized along with breakpoint regions, fragile sites, loss of heterozygosity (LOH) regions, regions with amplifications or deletion, all of which add up to its abnormal expression.
Dysregulation of miR-7a and miR-30c is linked to genomic imbalances in OC. Laddha et al have reported the loss of miR-379/miR-656 cluster in 14% of serous epithelial ovarian cancer (SEOC). On the contrary, miR-182 of miR-183/96/182 cluster was amplified in 28.9% of EOC. Genetic polymorphisms in MCs such as rs17147016 at miR-224, rs10771184 at miR-544, rs2075993 at miR-630 were strongly linked with OC. A strong association between the miR-17/92 cluster expression and rs3814113 polymorphism were linked to familial OC risk. Abnormal expression of TF-miRNA cluster axis participates in OC progression (Table 1). miR-199A2/214-TWIST1 axis critically regulates stemness of EOC cells. Guo et al have revealed miR-27b as a highly downregulated miRNA in OC cells lacking DGCR8 expression. DDX1 (dead-box helicase-1) gene was found to be upregulated in OC and was shown to promote miR-200 family miRNAs (miR-200a, −200b, −200c, miR-429, and miR-141) expression. These data suggest that genetic and epigenetic changes can significantly alter miRNA cluster expression in OC.

**Approaches for the analysis of miRNA/miRNA clusters**

The accurate detection and quantification of miRNAs has been challenging due to their unique features. Technological advancements have substantially improved the methods for miRNA isolation, amplification and profiling. miRNAs can be isolated from a wide range of samples including cell lines, serum, plasma, fresh or fixed tissue samples. Techniques such as immunoprecipitation with AGO2, electrophoresis-based size purification, and crosslinking immunoprecipitation (CLIP) have been employed for the isolation and analysis of miRNAs. Reverse transcription-quantitative PCR (RT-qPCR), microarray, and RNA sequencing (RNA-Seq) are the popular methods used for the profiling of miRNAs. For targeted miRNA analysis, RT-qPCR projects as a gold standard technique and offers absolute quantification even with low RNA inputs. Microarray analysis was the commonly used high-throughput technique for parallel examination of large number of miRNAs. This hybridization-based approach is best suited for the analysis of relative abundance of particular miRNAs among different group of samples. However, it does not facilitate absolute quantification and detection of novel miRNAs and isomiRs. Further, microarray-based analysis generally needs high RNA inputs due to its inadequate specificity, initial findings need to be validated by other methods such as Northern blot or RT-qPCR. The advent of small RNA sequencing platforms has allowed simultaneous identification and quantification of novel miRNAs, isomiRs and other small RNA species. High cost, complex workflow, and the requirement of computational infrastructure for data interpretation are the limitations of this approach. Recent techniques such as single molecule real-time sequencing (SMRT) assures less biased and faster analysis than other approaches. However, cost and high error rate hampers their usage. Though they have been employed in analyzing short RNA species, SMART approach is yet to be used in miRNA profiling.
| miRNA Cluster Name | No. of miRNAs | Alterations/Regulated by | Reference |
|--------------------|--------------|--------------------------|-----------|
| **Epigenetic Regulation** | | | |
| miR-382 | C14MC | 52 miRNAs | Promoter methylation | 181 |
| C14MC | 52 miRNAs | Hypermethylation | 182 |
| let-7a-3 | let-7a-3/let-7b | 3 miRNAs (let-7a-3, miR-4763, let-7b) | | 182 |
| miR-133b | miR-1/133a | 2 miRNAs (miR-1-2, miR-133a-1) | Hypermethylation | 26 |
| miR-15a/16 | miR-15a/16 | 2 miRNAs (miR-15a, miR-16-1) | Promoter methylation | 181 |
| miR-34b/c | miR-34b/c | 2 miRNAs (miR-34b and miR-34c) | Hypermethylation | 183 |
| miR-432 | C14MC | 52 miRNAs | Hypermethylation | 25 |
| miR-424/503 | miR-424/503 | 6 miRNAs (miR-424, miR-503, miR-542, miR-450a-2, miR-450a-1 and miR-450b) | Hypermethylation | 25 |
| miR-199a-3p | miR-199/214 | 3 miRNAs (miR-199a-5p, miR-199a-3p and miR-214) | Hypermethylation | 185 |
| miR-130b | miR-130b/301b | 2 miRNAs (miR-130b and miR-301b) | Hypermethylation | 186 |
| miR-203a | miR-203a/b | 2 miRNAs (miR-203a and miR-203b) | Hypermethylation | 186,187 |
| miR-127 | C14MC | 52 miRNAs | Hypermethylation | 187 |
| miR-137 | miR-137/2682 | 2 miRNAs (miR-137 and miR-2682) | Hypermethylation | 187 |
| miR-29b | miR-29a/b | 2 miRNAs (miR-29a and miR-29b-1) | Hypermethylation | 188 |
| miR-125b | miR-99a/let-7c/miR-125b | 3 miRNAs (miR-99a, miR-125b, let-7c) | Hypermethylation | 189 |
| miR-497 | miR-497/195 | 2 miRNAs (miR-195, miR-497) | Hypermethylation | 190 |
| miR-199b-5p | miR-199b/3154 | 2 miRNAs (miR-199b and miR-3154) | Hypermethylated | 191 |
| miR-191 | miR-191/425 | 4 miRNAs (miR-191–3p, miR-191–5p, miR-425–3p, miR-425–5p) | Hypomethylated | 187 |
| miR-133b | miR-206/133b | 2 miRNAs (miR-206, miR-133b) | miR-145 | 26 |
| **Genetic Regulation** | | | |
| miR-379/656 | miR-379/656 | 52 miRNAs | Loss | 29 |
| let-7a-3, let-7b | let-7a-3/let-7b | 3 miRNAs (let-7a-3, miR-4763, let-7b) | CNV- Loss | 192 |
| miR-30d | miR-30b/-30d | 2 miRNAs (miR-30b, miR-30d) | CNV- Gain | 193 |
| miR-143/145 | miR-143/145 | 2 miRNAs (miR-143, miR-145) | Loss of heterogeneity | 193 |
| miR-15a/16-1 | miR-15a/16-1 | 2 miRNAs (miR-15a, miR-16-1) | Deletion | 194 |
| miR-17/92 | miR-17/92 | 6 miRNAs (miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-20b) | Deletion | 194 |
| miR-182 | miR-183/96/182 | 3 miRNAs (miR-183, miR-96, miR-182) | Amplification | 25 |
| miR-224 | miR-224/452 | 2 miRNAs (miR-224, miR-452) | SNP (rs17147016) | 30 |
| miR-544 | miR-379/544 | 38 miRNAs | SNP (rs10771189) | 31 |
| miR-17/92 | miR-17/92 | 6 miRNAs (miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-20b) | SNP (rs3814113) | 31 |
| **Transcription Factors** | | | |
| miR-199A2/214 | miR-199a/214 | 3 miRNAs (miR-199a-5p, miR-199a-3p and miR-214) | TWIST1 | 32 |
| miR-199a | miR-199a | 3 miRNAs (miR-199a-3p and miR-214) | FOXD3 | 195 |
| miR-212/132 | miR-212/132 | 2 miRNAs (miR-212, miR-132) | SOX4/EZH2 | 80 |
| miR-222–3p | miR-221/222 | 2 miRNAs (miR-221, miR-222) | SNAI2 | 33 |
| miR-19a-3p | miR-17/92 | 6 miRNAs (miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-20b) | NF-κB | 196 |
| miR-92a | miR-17/92 | 6 miRNAs (miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-20b) | STAT3 | 197 |
| miR-17/92 | miR-17/92 | 6 miRNAs (miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-20b) | MYC | 87 |
Role of miRNA clusters in OC

Many mechanistic and functional investigations using *in vivo* and *in vitro* models have exhibited that abnormal expression of MCs crucially regulates OC progression (Fig. 2). The following sub-sections discuss the role of miRNA clusters in the context of OC. Table 2 summarizes the differentially expressed miRNA clusters in OC.

**miR-200c/141 as a regulator of metastasis**

This cluster, located at 12p13.31, encodes for miR-141 and miR-200c that are often abnormally expressed in various cancers including OC. The members of miR-200c/141 cluster regulate the expression of genes associated with growth, proliferation, migration, invasion, EMT, stemness, apoptosis, and chemosensitivity. Both tumor-suppressive and oncogenic functions have been assigned to miR-200c/141 cluster in cancers. In OC cells miR-200c/141 cluster increases cell proliferation and induces drug resistance via regulating the expression of KEAP1 (Kelch like ECH associated protein-1). The activation of EMT signaling cascade significantly fosters metastasis and may contribute to high mortality rate in OC. Forced expression of miR-200c in OC cells substantially reduced migratory and invasive potential by enhancing CDH1 (E-cadherin) expression. Due to its ability to reduce tumorigenicity and invasion of OC cells, miR-200c is proposed as an important therapeutic target. The list of validated targets and signaling pathways are shown in Table 3, miR-141 enhances anoikis resistance via targeting KLF12/SP1/survivin axis in OC. Besides, members of this cluster also target metastatic pathway genes. By targeting SIK1 (salt-inducible kinase 1) and KEAP1, miR-141 promotes cell proliferation and cisplatin resistance in OC. Together, these results suggest that miR-200c/141 cluster functions as both tumor-suppressive and oncogenic in OC and is vividly reported to regulate EMT and metastatic axis. Further, it may serve as a valuable therapeutic target and a prominent diagnostic marker.

**miR-200b/200a/429 modulates OC cell growth and proliferation**

miR-200b/200a/429 located at 1p36.33 belongs to miR-200 family and comprises miR-200b, miR-200a, and miR-429. Both downregulation and upregulation of the members of miR-200b/200a/429 cluster are reported in OC. For example, in T80 cells, overexpression of miR-200b/200a/429 promoted tumor growth *in vivo* by regulating ING5 (inhibitor of growth family-5). Moreover, this cluster targets Wnt/β-catenin and PI3K/AKT to promote its tumor regulatory functions. MiR-200a is often upregulated in OC tissues and participates in pathways facilitating tumor advancement. On the contrary, low level of miR-429 were found in OC cells. KIAA0101, an oncogene, is the direct target of miR-429 and are negatively correlated with one another. The ectopic miR-429 expression upsurges drug sensitivity and results in the induction of MET (mesenchymal to epithelial transition) in metastasizing OC cells. On upregulation, miR-200b-5p targeted ATAD2 (ATPase family AAA domain containing-2) and inhibited OC cell proliferation via PI3K/AKT pathway. Interestingly, nanoparticle mediated delivery of miR-200a and 200b reduced the metastatic burden with improved organization of the vasculature. These data clearly indicate that targeting miR-200b/200a/429 may have a significant impact on the clinical management of OC.

**miR-199a/214 in OC stemness and therapeutic resistance**

miR-199a/214, located at 1q24, encodes for miR-214, miR-199a-3p and miR-199a-5p, and is transcribed as a part of the transcription of DNM3OS (dynamin 3 opposite strand) using E-Box promoters. The members of the cluster participate in the development of various tissues, notably heart, bone, muscle, pancreatic, nervous system, nephrogenesis, and vascularization. At the cellular level, miR-199a/214 cluster controls proliferative, migratory, invasive ability, and cell cycle progression in OC cells. A study reported 56% and 53% of OC tissues showed upregulation of miR-214 and miR-199a, respectively. Interestingly, miR-214 and miR-199a have the potential to differentiate ovarian cancer stem cells into OC cells. OC cells possessing cell surface markers such as CD44+/CD117+ are known to render stemness and chemotherapeutic resistance. By transfecting CD44+/CD117+ cells with miR-199a, there is a substantial decrease in both protein and mRNA levels of CD44 with a concomitant decrease in ABCG2 (ATP binding cassette subfamily G member-2) expression. In OC, miR-214 displays an oncogenic function by targeting PTEN to activate AKT signaling and stimulates cisplatin resistance, cell survival, and radio-resistance. On the contrary, by targeting CTNNB1 (β-catenin), miR-214 acts as a tumor suppressor in OC. Collectively, abnormal expression of miR-199a/
miR-214 may promote stemness and therapeutic resistance in OC. Thus, modulation of miR-199a/214 expression may offer an opportunity to reverse the stemness and chemotherapeutic resistance in OC.

miR-183/182/96 in regulating apoptosis and chemoresistance

miR-183/182/96 located at 7q32.2 is a highly conserved MC that is expressed in the retina, sensory organs and pluripotent stem cells. miR-182, miR-183 and miR-96 are the members of this cluster and play a critical role during the pluripotent stem cell differentiation into sensory organs. miR-183/182/96 is one of the upregulated MCs in OC and modulates tumor growth, invasion, apoptosis and therapy resistance. Upregulated miR-183 has been shown to activate TGF-β/SMAD4 pathway by negative regulation of SMAD4 to promote OC. Importantly, by negatively regulating PDCD4 (programmed cell death-4), miR-182 induces growth, invasion, resistance to apoptosis, and resistance to cisplatin and taxol. Another study demonstrated that miR-182 overexpression induced apoptosis via caspase-3 and -9 activation in Caov-3 cells, thus demonstrating its tumor-suppressive function in OC. Both miR-96 and miR-182 are upregulated by the effect of leptin. It has been shown that the tumor promoting function of miR-96–5p could be annulled as an effect of CAV1 overexpression. Thus, deregulated expression of miR-183/182/96 may participate in pathways leading to growth, proliferation, invasion, apoptotic evasion, and induction of therapy resistance.

miR-23a/24–2/27a in OC cell growth and invasion

This cluster is located in 19p13.12 and encodes for miR-23a, miR-24-2, and miR-27a. Being an overexpressed MC in OC, the expression of members of this cluster is linked with clinical stage, lymph node metastasis and poor patient survival. By directly targeting ST7L (suppression of tumorigenicity-7-like), miR-23a activates Wnt/MAPK pathway and acts as anti-apoptotic and promoter of cell cycle progression in OC. MiR-23a inhibits DLG2 (discs large homolog-2) expression to foster tumor cell propagation and invasion via release of NANOG, OCT4 (octamer binding transcription factor-4), and BCL2 (BCL2 apoptosis regulator). miR-27a by targeting HIPK2 (homeodomain-interacting protein kinase 2) brings about paclitaxel (PTX) resistance in OC cells via MDR1/P-gp axis (multidrug resistance mutation 1/P-glycoprotein). Taken together, miR-23a/24–2/27a cluster functions as an oncogene and its upregulation stimulates growth, proliferation, and invasion via inhibition of apoptosis and induction of Wnt/MAPK and Wnt/β-catenin pathways to promote PTX resistance.

miR-212/132, a tumor-suppressive cluster in OC

miR-132 and miR-212 of miR-212/132 cluster are highly conserved vertebrate miRNAs mapped to 17p13.3 and are important for the morphogenesis of neurons, synaptic transmission, and angiogenesis. miR-212/132 locus was initially described to target CREB (cAMP-response element
| miRNA cluster | Chromosomal location | miRNAs in the cluster | OncomiR/Tumor suppressor | Model systems | Reference |
|---------------|----------------------|-----------------------|--------------------------|--------------|-----------|
| miR-200c/141 | 12p13.31             | miR-200c, miR-141     | OncomiR & Tumor suppressor | Cell lines (OVCAR-3, MES-OV, SKOV3) and human tissue samples | 47        |
| miR-200b/200a/429 | 1p36.33             | miR-200b, miR-200a, miR-429 | Tumor suppressor | Cell lines (OVCAR, A2780, T80) | 199       |
| miR-199a/214 | 1q24                 | miR-199a, miR-199a-3p | Tumor suppressor | Cell lines (SKOV3, A2780) and Human tissue samples | 32        |
| miR-183/182/96 | 7q32.2               | miR-183, miR-96, miR-182 | Tumor suppressor | Cell lines (OVCAR-3, SKOV3) and Human tissue samples | 200       |
| miR-23a/24–2/27a | 19p13.12            | miR-23a, miR-24-2, miR-27a | Tumor suppressor | Cell lines (OVCAR-3, SKOV3, A2780) and Human tissue samples | 75        |
| miR-23b/24–1/27b | 9q22.32             | miR-23b, miR-27b, miR-24-1 | Tumor suppressor | Cell lines (OVCAR-3, SKOV3) and Human tissue samples | 201       |
| miR-199a/214 | 1q23.33             | miRNA-106b, miR-93, miR-25 | Tumor suppressor | Cell lines (OVCAR-3) | 202       |
| miR-212/132 | 17p13.3             | miR-212, miR-132      | Tumor suppressor | Cell lines (SKOV-3, OVC008, A2780) | 79        |
| miR-221/222 | Xp11.3              | miR-221, miR-222     | Tumor suppressor | Cell lines (SKOV3, A2780) and Human tissue samples | 203       |
| miR-302/367 | 4q25                | miR-367, 302d, 302c-5p, 302c-3p, 302a-5p, 302a-3p, 302b-5p, 302b-3p, miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-92a | Tumor suppressor | Cell lines (SKOV3, A2780) and Human tissue samples | 204       |
| miR-17/92 | 13q31.3             | miR-371, miR-372, miR-373 | OncomiR & Tumor suppressor | Cell lines (OVCAR-3, SKOV3, CP70) and Human tissue samples | 101       |
| miR-306/514 | Xq27.3              | miR-506, -507, -508, -509, -510, -513, miR-514 | Tumor suppressor | Cell lines (A2780, SKOV3, OV3, ES2 and HOB910) and Human tissue samples | 101       |
| miR-143/145 | 5q33.1              | miR-143, miR-145     | Tumor suppressor | Cell lines (SKOV3, A2780, OV3, ES2 and HOB910) and Human tissue samples | 101       |
| miR-106a/363 | Xq26.2              | miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2, miR-363 | OncomiR & Tumor suppressor | Cell lines (OVCAR3, HO8910, SKOV3, ES2 and A2780) and Human tissue samples | 205,206   |
| miR-1-1/133a-2 | 20q13.33            | miR-1-1, miR-133a-2 | Tumor suppressor | Cell lines (HO-8910, OVCAR-3, W626, A2780 and SKOV-3) and Human tissue samples | 206       |
| miR-1-2/133a-1 | 18q11.2             | miR-1-2, miR-133a-1 | Tumor suppressor | Cell lines (HO-8910, OVCAR-3, W626, A2780 and SKOV-3) and Human tissue samples | 206       |
| miR-371/373 | 19q13.4             | miR-371, miR-372, miR-373 | OncomiR & Tumor suppressor | Cell lines (OVCAR3, A2780, SKOV3, CP70) and Human tissue samples | 207       |
| miR-379/656 | 19q13.4             | 52 miRNAs            | OncomiR & Tumor suppressor | Cell lines (OVCAR-3, Caov-3, HO8910, SKOV3, ES2, A2780, SW626) and Human tissue samples | 113       |
| C19MC        | 19q13.4             | 46 miRNAs            | OncomiR & Tumor suppressor | Cell lines (A2780, CAOV-3, SKOV3, HO8910, ES-2, OVCAR3) and Human tissue samples | 131       |
### Table 3  miRNAs cluster expression and their target in OC.

| miRNA cluster     | miRNAs in cluster | Expression          | Regulated by  | Signaling pathways | Targets                      | Reference       |
|-------------------|-------------------|---------------------|---------------|---------------------|-----------------------------|-----------------|
| miR-200c/141      | miR-200c, miR-141 | Downregulated       |               | EMT                 | KEAP1                       | 50,52,54,55,208–210 |
|                   |                   |                     |               | NF-κB               | CDH1                        |                 |
|                   |                   |                     |               | ZEB1/pSMAD          | SNAI1                        |                 |
|                   |                   |                     |               | JAK-STAT3           | ZEB2                        |                 |
|                   |                   |                     |               |                     | KLF12                        |                 |
|                   |                   |                     |               |                     | SIK1                         |                 |
|                   |                   |                     |               |                     | KEAP1                        |                 |
|                   |                   |                     |               |                     | KEAP1                        | 210             |
| miR-200b/          | miR-200b, miR-200a| Upregulated         |               | Wnt/β-catenin       | PCDH9 PTEN KIAA0101          | 55–57,59,209–211 |
| 200a/429          | miR-429           |                     |               | PI3K/AKT            | PTEN                         |                 |
|                   |                   |                     |               |                     | PTEN                         |                 |
|                   |                   |                     |               |                     | PTEN                         | 32,66,67,185,195,212,213 |
| miR-199a/214      | miR-199a-5p,      | Downregulated       | TWIST1        | IKKβ/NF-κB          | PTEN                         | 32,66,67,185,195,212,213 |
|                   | miR-199a-3p and   |                     | DNMT3         | TGF-β/PI3K/AKT      | PTEN                         |                 |
|                   | miR-214           |                     | FOXD3         |                     | PTEN                         |                 |
|                   |                   |                     |               |                     | NF-κB1                       |                 |
|                   |                   |                     |               |                     | DDR1                         | 32,66,67,185,195,212,213 |
|                   |                   |                     |               |                     | TGF-β2                       |                 |
|                   |                   |                     |               |                     | ABCG2                        |                 |
|                   |                   |                     |               |                     | Leptin CTNNB1                 |                 |
| miR-183/182/96    | miR-183, miR-96,  | Upregulated         | DNMT3A        | TGF-β/SMAD4         | SMAD4                        | 71–74,214,215   |
|                   | miR-182           |                     | Leptin        |                     | PDCD4                        |                 |
|                   |                   |                     | FOXD3         |                     | BRCA1                        |                 |
|                   |                   |                     |               |                     | MTSS1                        |                 |
|                   |                   |                     |               |                     | HMGA2                        |                 |
|                   |                   |                     |               |                     | FOXO3                         |                 |
|                   |                   |                     |               |                     | Sema 4D                       |                 |
| miR-23a/24–2/27a  | miR-23a, miR-24-2,| Upregulated         |               | NF-κB WNT/β-catenin | CAV1                         | 76–78,216–219   |
|                   | miR-27a           |                     |               |                     | IKK2                         |                 |
|                   |                   |                     |               |                     | ST7L                          |                 |
|                   |                   |                     |               |                     | DLG2                          |                 |
|                   |                   |                     |               |                     | NANO G                       |                 |
|                   |                   |                     |               |                     | OCT4                          |                 |
|                   |                   |                     |               |                     | BCL2                          |                 |
|                   |                   |                     |               |                     | CUL5                          |                 |
|                   |                   |                     |               |                     | FOXO1                         |                 |
|                   |                   |                     |               |                     | HIPK2                         |                 |
|                   |                   |                     |               |                     | BTG1                          |                 |
|                   |                   |                     |               |                     | FBLN5                         |                 |
| miR-23b/24–1/27b  | miR-23b, miR-27b, | Up/Downregulated    |               |                     | CCNG1                         | 34,220–223      |
|                   | miR-24-1          |                     |               |                     | RUNX2                         |                 |
|                   |                   |                     |               |                     | DGCR8                         |                 |
|                   |                   |                     |               |                     | VE-cadherin                   |                 |
|                   |                   |                     |               |                     | CXCL1                         |                 |
| miRNA Cluster | miRNAs | Regulation | Gene Function | Pathway |
|--------------|--------|------------|---------------|---------|
| miR-106b/25  | miR-106b, miR-93, miR-25 | Up/Downregulated | PTEN/AKT | RHOC, BIM, LATS2 |
| miR-212/132  | miR-212, miR-132 | Downregulated | — | PTEN, SOX4, HBEGF, MAP3K3, PEA15, E2F5, BMI1 |
| miR-221/222  | miR-221, miR-222 | Up/Downregulated | SNAI2, PI3K/AKT Wnt/β-catenin | PTEN, BMF, APAF1, ARF4 p27kip1, GNAI2, PDCD10 |
| miR-302/367  | miR-367, 302d, 302c-5p, 302c-3p, 302a-5p, 302a-3p, 302b-5p, 302b-3p | Downregulated | — | STAT3 signaling, CTNNB1 |
| miR-17/92    | miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-92a | Upregulated | NF-κB, PTEN/AKT, Hippo-YAP | ITGA5, ITGB1, LATS2, TRIP1, IPMK, IGFBP-3, YES1, PTEN |
| miR-506/514  | miR-506, -507, -508, -509, -510, -513, miR-514 | Downregulated | DQ786243, MALAT1, AKT/FOXO3A, MAPK1/ERK, CDK4/6, -FOXM1 | MTMR6, CREB1, CDK4, CDK6, iASPP, SIRT1, MAPK1, CCNA2, MMP7, BCL2, MCL1, BCL2L2, XIAP |
| miR-143/145  | miR-143, miR-145 | Downregulated | — | TGF-β, Hippo signaling |

(continued on next page)
| miRNA cluster          | miRNAs in cluster | Expression                  | Regulated by            | Signaling pathways             | Targets                                      | Reference       |
|------------------------|-------------------|-----------------------------|-------------------------|--------------------------------|----------------------------------------------|-----------------|
| miR-106a/363           | miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2, miR-363 | Up/Downregulated           | —                       | Hippo signaling                | TRIM2, TAK1, CSTB, PTEN, p130, BCL-10, Caspase-7, MCL1, PDCD4, NOB1, LATS2 | 108–112, 240–242 |
| miR-1-1/133a-2 and miR-1-2/133a-1 | miR-1-1, miR-133a-2, miR-1-2, miR-133a-1 | Downregulated              | —                       | Wnt/β-catenin                  | c-MET, IGF1, PYGB, LATS2, ATAD2, DKK1, CCNA1, p62, RAB22A | 243–245         |
| miR-371/373            | miR-371, miR-372, miR-373 | Up/Downregulated           | —                       | —                              | PI3K/AKT Wnt/β-catenin, APK/ERK1/2, NOTCH3, WNT, AKT, MYC | 142, 156, 246, 247 |
| miR-379/656            | 52 miRNAs         | Up/Downregulated           | —                       | —                              | SRM, GAPDH, RPL41, PRPF6, VIM, PAK2, FEN1, TAB1, NOTCH3, PIK3CA, PIK3CB, ENG, CUL4A, YY1, NOTCH1, c-MYC, FGFR2, CUL4A, IGF1R, CDCCP1, PLAGL2, RAB1A | 115–130, 248–252 |
binding protein) in neuronal cells. Subsequently, the expression of miR-212/132 was reported in non-neuronal cells. Abnormal expression of this cluster participates in oncogenesis. Majority of findings have analyzed the downregulation and tumor-suppressive function of miR-212/132 in OC. In vitro studies have shown that downregulation of miR-212/132 modulates the induction of EMT. In SKOV3 cells, miR-212 by targeting HBEGF (heparin binding EGF like growth factor) inhibits cell propagation, migration, and invasion. Forced expression of miR-212 suppressed PEA15 to inhibit OC cell proliferation via induction of apoptosis. miR-132, when upregulated, halts tumor migration and proliferation via downregulating E2F5. Interestingly, a study reported that the forced expression of miR-132 reversed cisplatin resistance. Collectively, miR-212/132 is a tumor-suppressive miRNA cluster and its re-expression could be attempted to overcome therapy resistance in OC.

Oncogenic and tumor-suppressive role of miR-17/92

This cluster is located on 13q31.3 within C13orf25 (chromosome 13 open reading frame-25), and is often dysregulated in neurodegenerative disorders, immune and cardiovascular diseases. This miRNA cluster is also denoted as oncomiR-1 and encodes for 6 miRNAs, namely miR-19a, miR-19b, miR-17, miR-20a, miR-18a, and miR-92a. The members of this cluster participate in pathways, notably cell cycle, tumor cell proliferation, apoptosis, and EMT. Many studies have revealed the oncogenic as well as tumor-suppressive nature of this MC. In PTX resistant OC cell lines, elevated level of miR-17/92 was observed. The over-expression of miR-92 in OC is involved in immune suppression, which is known to be regulated via LATS2/YAP1/PD-L1 pathway. Further, a study by Liu et al has reported miR-19b to be significantly upregulated in OC and enhances tumor migration and invasion by suppressing PTEN/AKT pathway. miR-20a enhanced tumor development by activating EMT in OVCAR3/DDP cells. Gong et al confirmed that miR-17 overexpression in OC cells suppressed adhesion and invading ability and impeded peritoneal metastasis in SKOV3 xenograft model via targeting ITGA5 (integrin α5) and ITGB1 (integrin-β1). miR-18a suppresses proliferation and promotes apoptosis in OC cells by targeting IPMK (inositol phosphate multikinase) and TRIAP1 (tumor protein p53-regulating inhibitor of apoptosis gene-1). Collectively, these data suggest the oncogenic and tumor-suppressive role of miR-17/92 cluster, and the regulation of this cluster could be attempted to be valuable in OC therapy.

miR-506/514 and its anti-tumor properties

This cluster comprises of 7 miRNAs, namely miR-506, -507, -508, -509, -510, -513, and miR-514 and is located at Xq27.3. The members of this cluster are usually downregulated and play a tumor-suppressive role in OC. Two studies have shown that the IncRNAs, DQ786243 and MALAT1 (metastasis-associated lung adenocarcinoma transcript-1) regulate miR-506 expression, and modulates OC cell growth
via targeting CREB1 and iASPP (inhibitor of apoptosis stimulating protein of p53), respectively. Liu and colleagues showed that this miRNA induced senescence and repressed the proliferation of OC cells by targeting CDK4/6-FOXM1 axis. miR-508 suppresses EMT, invasion, and migration through blocking the MAPK1/ERK pathway. This miRNA also targets CCNA2 (cyclin A2) and MMP7, thus inhibiting OC development. miR-509–3p re-sensitizes OC cells to cisplatin treatment via targeting BCL2, MCL1 (MCL1 apoptosis regulator), BCL2L2 (BCL2 like-2) and XIAP (X-linked inhibitor of apoptosis) resulting in apoptosis. Taken together, the miR-506/514 cluster exhibits anti-tumor properties in OC, and modulation of this axis could be significant towards OC therapeutics.

**miR-143/145 as a tumor-suppressive cluster**

This MC is located at 5q33.1, encodes for miR-143 and miR-145, and is widely studied for its function in vascular biology and pathology related to cardiovascular disease. Members of this MC are reported to regulate genes associated with cell proliferation, cell cycle progression, migration, invasion and apoptosis in several cancer types. miR-145 and miR-143 are downregulated in OC tissue samples and cell lines. Downregulation of miR-145 and miR-145/5p1/CDK6/Pgp/pRb axis is proposed as a key mechanism of chemoresistance in OC. Clinically, low expressions of miR-145 were linked to poor prognosis. Biologically, miR-145 hinders proliferation, migration and cancer dissemination by targeting MTDH (metadherin) in HGSOs (high grade serous ovarian cancer) via p53-miR-145-MTDH axis. Similar to miR-145, miR-143 expression is also considerably reduced in OC cell lines and tissues. Forced expression of this miRNA reduced the cancer hallmarks in SKOV3, ES2, and OVCAR3 cells via targeting TAK1 (transforming growth factor beta-activated kinase-1). Another study proposed that targeting TGF-β/miR-143–3p/CSTB axis can be used for clinical management of OC. These data demonstrate that the down regulation of members of this cluster is critical in OC. Targeting the network regulated by miR-143/145 cluster may have a significant impact on the clinical management of OC.

**miR-106a/363 modulates drug resistance**

This X-chromosome based MC encodes for 6 miRNAs, namely miR-18b, miR-19b-2, miR-106a, miR-92a, miR-20b, and miR-363. The members of this cluster exhibit a prominent role in facilitating the propagation of ovarian tumors and are also implicated in controlling multi-drug resistance in OC cells. In both OC cells and tissues, miR-106a expression was found to be significantly elevated and was shown to promote tumor growth, proliferation, and intrusin in OC cells by negatively regulating PTEN. Increased expression of miR-106a mediated proliferation and differentiation of HGSO via targeting p130 (RBL2). This miRNA showed upregulated expression in PTX resistant OC cell lines and reduced BCL10 and Caspase-7 expression. Another member of this cluster, miR-18b, whose upregulated expression boosts migratory as well as invasive properties of OC cells by directly targeting PTEN. Reduced level of miR-363 was observed in OC cells and tissues. The over-expression of this miRNA resulted in the decreased expression of NOB1 [NIN (RPN12) binding protein-1 homolog], which in turn suppressed tumor growth and proliferation. However, the rest of the members of miR-106a/363 cluster aren’t very well studied in OC. These data suggest oncogenic as well as tumor-suppressive functions of this MC in OC, and have a role in regulating multidrug resistance.

**miR-379/656 (chromosome 14 cluster) in metastasis and therapy resistance**

miR-379/656 cluster is also called chromosome 14 cluster or C14MC and is one of the largest MCs. miR-379/656 cluster harbors a total of 52 miRNAs and is located at 14q32.31 within the DLK1-DIO3 locus. In a genome-wide analysis on the expression profiles of miR-379/656 in different cancers, it was reported that about 14% of the miRNAs of this cluster were downregulated in ovarian serous cystadenocarcinoma. This study has provided evidence for this cluster to be tumor-suppressive. miR-127 is usually downregulated in OC and exerts its tumor-suppressive role by regulating its target gene BAG5 (BAG co-chaperone-5). Many studies have reported the expression of miR-134 to be lower in PTX resistant OC cells. A study has reported the role of miR-136 in PTX resistance and identified the oncogene NOTCH3 as its potential target. miR-370 demonstrated tumor-suppressive nature by regulating ENG (endoglin) in endometroid OC. Ectopic expression of miR-377 was revealed to negatively target CUL4A (cullin-4A) and reduce the metastatic ability of the cells. Additionally, it is also known to affect the activity of Wnt/β-catenin signaling by modulating the expression of MMP2 and MMP9. By targeting c-MYC, FGFR2 (fibroblast growth factor receptor 2), CUL4A and IGF1R, miR-494 impeded OC cell growth, proliferation, and migration. While the majority of the miRNAs of this cluster are reported to be downregulated and function as tumor suppressors in OC, a few of the members display an upregulated expression and function as oncomiRs. miR-299 displayed significantly higher expression levels in OC and it could facilitate tumor cell proliferation and migration by regulating OCT4. Likewise, miR-376a targets KLF15 (Kruppel like factor-15) and Caspase-8 and aids tumor progression. miR-485–5p and miR-539–3p target SRC and SPARCL1 (SPARC like-1) respectively, and promote OC progression.

**C19MC (chromosome 19 miRNA cluster) influences OC progression**

This is one of the largest clusters in the human genome located at chr19q13.42 and it contains about 46 miRNAs. C19MC is a primate specific cluster and has been shown to play both oncogenic as well as tumor-suppressive roles. Reduced expression of miR-498 was observed in OC, which in turn is correlated with poor prognosis and OS (overall survival). Ectopic expression of this tumor-suppressive miRNA in OC cells repressed tumor proliferation by targeting FOXO3 expression. miR-519d targets XIAP and suppresses OC cell proliferation and is shown to reduce...
cisplatin resistance. Another miRNA of this cluster, miR-520a-3p, negatively regulates EOC and inhibits tumorigenesis by suppressing SUV39H1 (suppressor of variegation 39H1). miR-522-3p is associated with PTX resistance in OC cells. Forced expression of this miRNA downregulates the expression of E2F2, in turn mitigating PTX resistance. miR-520g and miR-520h were reported to have an oncogenic function in EOC via targeting DAPK2 (death-associated protein kinase-2) and SMAD7. Based on the various published data, most of the miRNAs of C19MC act as tumor suppressors in OC. However, only a few members of this family have been studied in OC and there is a lack of data pertaining to the majority of the members belonging to this cluster.

Role of miRNA clusters in OC diagnosis, staging, classification, prognosis, therapy resistance, and recurrence

OC is an extremely fatal gynecological cancer and poses significant challenges to its clinical management. Genetic and epigenetic profiling of various histological subtypes of OC has identified specific molecular changes with a potential to be used as a marker for diagnosis, prognosis, and clinical management of OC. Herein, we present a comprehensive overview of the potential applications of miRNA clusters for the clinical management of OC (Fig. 3).

miRNA cluster in OC diagnosis

OC has been described as a heterogenous disease both at the molecular and phenotypical levels that have a significant impact on clinical behavior and therapeutic outcome. OC showcases a varied number of clinicopathological characters across different subtypes. The 5-year survival rate for early-stage and late-stage OC is approximately 92% and 29%, respectively. Unfortunately, only a small percentage (~20%–25%) of OC patients are diagnosed at an early stage. Many studies have shown that accurate and early diagnosis can significantly improve OC patient’s survival. Towards this, molecular studies have proposed miRNA profiling as a promising approach for the early diagnosis of OC (Table S1). A study proposed the expression profiling of miR-145 and miR-200c in serum exosomes could be useful for pre-operative diagnosis of OC. The same study showed that among the seven miRNAs tested (miR-93, miR-21, miR-145, miR-141, miR-145a-c), miR-145 showed a sensitivity of 0.91. Another study...
highlighted the diagnostic significance of elevated serum levels of a panel of 4 miRNAs: miR-200a-b (miR-200b/200a/429), miR-200c (miR-200c/141) and miR-373 (miR-371/373) in OC patients. The combination of these miRNAs showed a specificity and sensitivity of 100% and 83%, respectively, to differentiate benign and malignant OCs. A recent finding has suggested that increased exosomal miR-145 and miR-200c levels can act as effective diagnostic markers to differentiate between the different ovarian masses (normal as well as cancerous) with high sensitivity and specificity. This study has also proposed the combinational effect of miR-145 + miR-200c + CA125 as a significant marker for OC. miR-199a (miR-199a/214 cluster) expression, was identified as a promising biomarker for EOC diagnosis with an area under the curve (AUC) of 0.704 with specificity and sensitivity of 95.7% and 69.1%, respectively. These findings indicate the potential of the miRNA cluster as a highly sensitive and specific marker for early diagnosis of OC. Towards this, more detailed clinical studies are necessitated.

miRNA cluster and OC staging

One of the important factors that determines patient survival in OC is the disease stage at diagnosis. Besides, staging is important for treatment decision in OC. Routine diagnostic procedures which include pelvic examination, transvaginal ultrasonography and serum CA125 have failed to detect OC at an early stage. Studies have proposed that molecular markers have the potential for staging application in OC. Genome wide and gene specific studies have shown that miRNAs expression has the potential for OC staging application (Table S1). The expression of miR-200c seemed to be elevated in the early stages of cancer, where as it showed to descend with tumor advancement. In comparison with stage I, stage III OSC (ovarian serous carcinoma) displayed a downregulation in miR-508-3p, miR-509-5p and miR-510 belonging to miR-506/514 cluster. Uprogulated miR-30a-3p and miR-192/194 expression was identified as tumor-specific markers for stage I EOC histo-types. The level of miR-200b/200a/429 was elevated in both tissue samples and serum of stage I OC patients. The low chrXq27.3 cluster expression in EOC has been reported to be linked with early recurrence in patients with advanced cancer stage. These data suggest that the MCs showed differential expression between different stages of OC. Thus, MCs expression profiling could be used for OC staging.

miRNA cluster and classification of OC

OC is a highly heterogeneous disease with multiple subtypes, each of which are having slightly different histopathologies with varied clinical response and therapeutic outcomes. Technological advancement and the use of molecular tools have shown the molecular complexities among different histological types of OC. Numerous studies have proposed the importance of implementation of molecular characteristics for treatment decisions. The germline mutation in BRCA1 or BRCA2 is performed in many countries as a predictive biomarker in OC. The findings of molecular investigations have suggested the use of new or different treatments with better clinical outcomes. Elevated expression of miR-192/194 cluster and miR-30a/30* was identified as a marker for mucinous histo-type and clear cell histo-type, respectively. miR-510, a member of miR-506/514, showed higher expression in LGSC (low-grade serous carcinoma) and CCC (clear cell carcinoma) when compared to HGSC (high-grade serous carcinoma). miR-371/373 expression was more abundant in malignant OGCTs (ovarian germ cell tumors) when compared with benign OGCTs and SCSTs (sex cord stromal tumors). Very interestingly, the miR-506/514 cluster expression was higher in SCSTs when compared with OGCTs. Since miRNAs show differential expression between different histological types, the expression profiling of miRNAs thus can be useful for the classification of OC (Table S1).

miRNA cluster in OC prognosis

OC has a relatively poor prognosis due to limitations in early detection and screening. Over the past 30 years, 5-year survival of OC patients has significantly improved. Still, the prognosis of OC is poor and is closely linked to the stage at diagnosis. Numerous studies have shown that an accurate prognosis can significantly improve patient survival. Towards this, the studies have proposed use of miRNAs as prognostic indicators in OC. Besides, the MCs along with their target gene axis were also shown to have prognostic utility (Table S1). For instance, Amini-Farsani Z et al suggested that miR-221/222/PTEN/PJ3K/AKT axis to have prognostic significance in OC. Increased levels of miR-222 was correlated with good OS, while miR-221 was correlated with poor prognosis in OC. Exosomal miR-200b (miR-200b/200a/429), miR-373 (miR-371/373), and miR-200c (miR-200c/141) have been reported as independent prognostic factors for OS. Furthermore, the downregulation of these two miRNAs along with lymphatic metastasis and advanced FIGO (International Federation of Gynecology and Obstetrics) stage are related with poor overall disease-specific survival rates in HGSC. miR-25 (miR-106b/25) was stated to aid as a predictive prognostic biomarker of EOC and elevated miR-25 levels were linked to poor prognosis. A study has reported a 6-miRNA signature; miR-193b (miR-193b/365a), miR-211, miR-218, miR-505, miR-508 (miR-506/514) and miR-514 (miR-506/514) to be a significant prognostic biomarker for OC recurrence. Alexandros and co-workers in 2008 demonstrated the involvement of miR-9 and miR-223 in OC recurrence and have described the potential of these miRNAs as prognostic biomarkers for OC clinical outcome. The lower miR-422b and miR-34c (miR-34/449) expression levels were concomitant with the reduced disease specific survival in HGSC. These data suggest the potential of using MC expression for prognostic application in OC. Although many studies have used the expression profiling of individual members of the MCs, the use of members of the MCs together has any advantage over using individual miRNAs requires further investigation.
miRNA clusters for predicting therapy resistance

Therapy resistance is one of the major problems in cancer treatment and its clinical outcome. Surgery coupled with chemotherapy are used for the treatment of advanced OC.143 Similar to many other cancers, a substantial proportion of OC with advanced stage exhibit therapy resistance. Genome-wide studies have shown that both genetic and epigenetic changes contribute significantly to therapy resistance. More recently, studies have shown the role of abnormal miRNA expression in the acquisition of therapy resistant in various cancers, including OC.162 Abnormal expression of MCs has been reported to confer cisplatin and PTX resistance in OC via activation of drug resistance pathway genes.163 Upregulated miR-221/222 cluster displayed cisplatin resistance in OC by targeting PI3K/AKT pathway via PTEN.153 Upregulation of miR-17/92 and reduced expression of miR-134 were observed in cells resistant to PTX.87 miR-141 of miR-141/200c regulates cisplatin resistance of OC cells via modulating its target-KEAP1.154 By targeting PTEN/AKT pathway, miR-214 of the cluster miR-199a/214 participates in the induction of cisplatin resistance.64 Furthermore, the OC cells portraying PTX resistance under hypoxic conditions possess upregulated expression of miR-27a (miR-23a/24-2/27a cluster). This miRNA enhances PTX resistance via blocking APAF1 expression.164 These data suggest a clear association between abnormal miRNA expression with that of acquisition of therapy resistant phenotypes in OC (Table S2). However, detailed investigations are needed to better understand the combined effect of MCs than individual miRNAs in the acquisition of therapeutic resistance.

miRNA clusters for predicting OC recurrence

OC shows a high rate of recurrence which varies with the stage of the disease. OC patients with stage III or IV have shown a recurrence rate of 70–75% within 2 years of initial diagnosis.165 Unfortunately, the high rate of recurrence and resistance to treatment after relapse are the important cause for high mortality rate in OC. Display of new symptoms or a rise in CA125 levels are used to suspect the recurrence of OC. Although measuring the rising levels of CA125 as a marker for determining early recurrence is controversial.166 This suggests the need for more accurate predictive markers for early relapse of OC. Many recent studies have proposed the use of miRNAs as a predictor of early recurrence in OC. Hu et al. by analyzing miR-200 cluster expression in 55 advanced OC patients, proposed that reduced expression of this cluster is linked with disease recurrence and poor survival.167 miR-19b belonging to miR-17/92 cluster was significantly overexpressed in recurrent EOR. Thus, miR-19b expression can be useful for predicting disease recurrence in EOR.168 Another study proposed a 6-miRNA signature (miR-193b, miR-218, miR-211, miR-508, miR-514 and miR-505) for prognostic application in OC, specifically for recurrence prediction.158 Downregulation of members of the chr.6q27.3 cluster is linked to early relapse in advanced EOC patients.142 Besides, forced expression of this cluster inhibited proliferation and increased the sensitivity towards cisplatin treatment.147 Besides, members of miR-424/503 cluster hindered the proliferative, migratory, and invasive capacity of drug-resistant OC cells.169 These findings suggest the significance of abnormal expression of MCs in the development of drug resistance and recurrence (Table S2) and provide an opportunity for reversal of the same for better management of OC patients.

miRNA delivery

In vivo miRNA delivery is a major challenge. Attributing to the complex environment and the instability of miRNAs, they are prone to nuclease degradation in vivo. As a result of which, in recent years the main focus has been on attaining safe and effective miRNA delivery.170 A recent study has described exosomes as potential miRNA delivery systems for effective miRNA replacement therapy. In this study, OC cell lines (OVCAR3, CaOV3 and SKOV3) were treated with miR-199a-3p (miR-199a/214) engineered into exosomes. A dramatic increase in the expression of miR199a-3p was observed in these cell lines. Further, miR-199a-3p-Exo inhibited tumor invasion and proliferation via targeting c-MET.171 The same study also highlighted the inhibition of peritoneal dissemination, ERK phosphorylation, c-MET, and MMP2 expression.171 Yang et al. in their study, transfected miR-let-7b into CD133+ O stem cells via ultrasound-targeted microbubble destruction (UTMD). UTMD significantly increased the transfection efficiency of the miR-let-7b.172 Ascites-derived exosomes (ADEs) promote EMT via delivering miR-6780b-5p into OC cells, thus facilitating cancer progression.173 The co-delivery of miR-7 and PTX in monomethoxy (poly (ethylene glycol))-poly (l,lactide- co-glycolide)-poly (l-lysine) nanoparticles increased the chemotherapeutic efficacy of PTX in OC through the suppression of EGFR/ERK pathway.174 Chi-29b chimera facilitates the active delivery of miR-29b into OVCAR-3 cells, which further induces its antitumorigenic activity via inducing apoptosis and PTEN activation.175 Similarly, another study indicated the use of MUC1/let-7i chimera in the reversal of PTX resistance.176 Bertucci and coworkers, treated mouse xenograft models with pSiNPs (orous silicon nanoparticles) encapsulating an anti-miR-21 LNA (locked nucleic acid) which silenced miR-21.177 Thus, an efficient miRNA delivery system is a key in getting miRNAs to clinic.

miRNA clusters as therapy targets in OC

miRNA based treatment opportunities for OC management involve inhibition or supplementation of miRNAs with the use of complementary nucleic acids.178 Few studies have demonstrated the potential of miRNA-based therapeutics in OC. A study has revealed that targeted delivery of miR-29a (miR-29a/b cluster) chimera to OC cells induced apoptosis by increasing PTEN expression.179 Ohyagi-Hara et al have found that transfection with miR-92a (miR-17/92 cluster) diminished ITGA5 (integrin α5) expression and thus repressed peritoneal metastasis of OC cells.179 Further, recovery of miR-200c (miR-200c/141 cluster) in OC cells significantly reduced tumor burden and enhanced PTX
sensitivity suggesting the use of miR-200c restoration along with chemotherapy to improve treatment response in OC subjects. Additional studies are essential to establish MC-based therapy for OC.

Conclusions and future perspectives

Since the discovery of miRNA clusters, several studies have explored its implications in different cancers. There has been a plethora of evidences suggestive of dysregulation of these miRNA clusters in different cancers including OC. By transcriptional regulation and post-transcriptional repression, miRNAs fine tune the gene regulatory networks to control the function of every cell. OC is one of the fatal gynecological malignancies with high morbidity and mortality rate. The high rate of fatality in OC is mainly due to its diagnosis at a late stage and lack of efficient detection modalities. Both clinical and model system-based studies have proposed that altered expression of miRNA clusters has the potential to be used as a diagnostic and prognostic indicator for better management of OC. Moreover, therapeutic modalities based on the manipulation of these clusters could successfully sensitize the OC cells to these treatment systems. Herein, we have performed a comprehensive review of literature and provided evidences and acuities to the role of miRNA clusters in OC and their possible therapeutic application for better management of OC (Fig. 4). One of the key challenges to develop miRNA cluster-based markers for diagnostic and prognostic application is to recognize the best miRNA cluster as they show significant heterogeneity in their expression. Besides, majority of the studies have analyzed the significance of individual members of the miRNA clusters than looking at the entire cluster. Towards these, comprehensive studies are necessitated to understand the role of complete clusters. Since, members of the miRNA clusters show similar trend of expression and can target multiple genes belonging to the same or different pathways, manipulation of miRNA clusters may show a more significant impact than targeting individual miRNAs. Towards this, more comprehensive mapping of miRNA clusters in OC, manipulation studies and

Figure 4 miRNA cluster biogenesis, functions, role in OC progression and their clinical application. Upon getting transcribed from the miRNA gene, pri-miRNAs/pri-miRNA clusters are processed into pre-miRNAs. These pre-miRNAs are then exported to cytosol, wherein they are further processed to form mature miRNAs. Members of miRNA clusters (MCs) functions to regulate mRNA degradation, deadenylation and gene transcription. Derailed regulation or aberrant expression of these MCs can foster ovarian cancer progression by triggering different cancer hallmarks and by modulating cellular signaling pathways. Differential expression of MC in normal and ovarian cancer tissues can be employed in OC diagnosis, prognosis, cancer staging, classification, in the prediction of therapy resistance and disease relapse. miRNA replacement therapy using different miRNA delivery systems such as exosomes, ultrasound-targeted microbubble destruction (UTMD), nanoparticles, and nanoparticles–chimera complex may serve as a potential strategy in ovarian cancer treatment.
their impact needs to be investigated. Another careful consideration and challenge may be concerning the targets of miRNAs. Since miRNAs can target multiple genes and pathway which can involve both oncogene and tumor suppressor genes. Thus, one should be very careful while selecting the miRNA cluster and target genes for clinical applications in cancer in general and OC in particular. While selecting the miRNA cluster for therapy, one should also consider their target genes, signaling and other interactome. Detection of abnormal expression of miRNA clusters in the blood may provide a unique opportunity to use miRNA profiling as a minimally invasive method for diverse clinical application in OC. In this direction, more detailed and comprehensive studies are required.

Author contributions

AK and DA wrote the manuscript; VD, PS, SC, and RR helped in the critical revision; SPK conceived the study and edited the manuscript.

Conflict of interests

All authors declare no conflict of interests.

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Appendix A. Supplementary data

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References

1. Luo G, Zhang Y, Guo P, Wang L, Huang Y, Li K. Global patterns and trends in stomach cancer incidence: age, period and birth cohort analysis. Int J Cancer. 2017;141(7):1333–1344.

2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2018;68(1):7–30, 2018.

4. Carliol G, Bertuccio P, Boffetta P, et al. European cancer mortality predictions for the year 2020 with a focus on prostate cancer. Ann Oncol. 2020;31(5):650–658.

5. Bäumler M, Gallant D, Druckmann R, Kuhn W. Ultrasound screening of ovarian cancer. Horm Mol Biol Clin Invest. 2020;41(3):20190022.

6. Stewart C, Ralyea C, Lockwood S. Ovarian cancer: an integrated review. Semin Oncol Nurs. 2019;35(2):151–156.

7. Roett MA, Evans P. Ovarian cancer: an overview. Am Fam Physician. 2009;80(6):609–616.

8. Doubeni CA, Doubeni AR, Myers AE. Diagnosis and management of ovarian cancer. Am Fam Physician. 2016;93(11):937–944.

9. Motohara T, Masuda K, Morotti M, et al. An evolving story of the metastatic voyage of ovarian cancer cells: cellular and molecular orchestration of the adipose-rich metastatic microenvironment. Oncogene. 2019;38(16):2885–2898.

10. Mathieu KB, Bedi DG, Thrower SL, Qayyum A, Bast Jr RC. Screening for ovarian cancer: imaging challenges and opportunities for improvement. Ultrasound Obstet Gynecol. 2018;51(3):293–303.

11. Scholler N, Urban N. CA125 in ovarian cancer. Biomarkers Med. 2007;1(4):513–523.

12. Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol. 2013;122(1):139–147.

13. Christopher PW, Elisabette W, Bernard WS, eds. World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer; 2020.

14. Kossai M, Leary A, Scoazec JY, Genectic C. Ovarian cancer: a heterogeneous disease. Pathobiology. 2018;85(1–2):41–49.

15. Rein BJD, Gupta S, Dada R, Saij J, Michener C, Agarwal A. Potential markers for detection and monitoring of ovarian cancer. JAMA Oncol. 2011;2011:475983.

16. Kobayashi E, Ueda Y, Matsuzaki S, et al. Biomarkers for screening, diagnosis, and monitoring of ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2012;21(11):1902–1912.

17. Tan W, Liu B, Qu S, Liang G, Luo W, Gong C. microRNAs and cancer: key paradigms in molecular therapy. Oncol Lett. 2018;15(3):2735–2742.

18. Carrington JC, Ambros V. Role of microRNAs in plant and animal development. Science. 2003;301(5631):336–338.

19. Cai Y, Yu X, Hu S, Yu J. A brief review on the mechanisms of miRNA regulation. Dev Reprod Biol. 2009;7(4):147–154.

20. Chen X. microRNA metabolism in plants. Curr Top Microbiol Immunol. 2008;320:117–136.

21. Zhang Y, Zhang R, Su B. Diversity and evolution of microRNA gene clusters. Sci China C Life Sci. 2009;52(3):261–266.

22. Kabekkodu SP, Shukla V, Varghese VK, Souza JD, Chakrabarty S, Satyamoorthy K. Clustered miRNAs and their role in biological functions and diseases. Biol Rev Camb Phil Soc. 2018;93(4):1955–1986.

23. Iorio MV, Croce CM. microRNA involvement in human cancer. Carcinogenesis. 2012;33(6):1126–1133.

24. Barton CA, Hacker NF, Clark SJ, O’Brien PM. DNA methylation changes in ovarian cancer: implications for early diagnosis, prognosis and treatment. Gynecol Oncol. 2008;109(1):129–139.

25. Zhang L, Volinía S, Bonome T, et al. Genomic and epigenetic alterations deregulate microRNA expression in human epithelial ovarian cancer. Proc Natl Acad Sci U S A. 2008;105(19):7004–7009.

26. Li J, Zhang S, Zou Y, Wu L, Pei M, Jiang Y. miR-145 promotes miR-133b expression through c-myc and DNMT3A-mediated methylation in ovarian cancer cells. J Cell Physiol. 2020;235(5):4291–4301.

27. Calin GA, Sevignani C, Dumitru CD, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A. 2004;101(9):2999–3004.
28. Agostini A, Brunetti M, Davidson B, et al. Genomic imbalances are involved in miR-30c and let-7a deregulation in ovarian tumors: implications for HMGA2 expression. Oncotarget. 2017;8(13):21554–21560.

29. Laddha SV, Nayak S, Paul D, et al. Genome-wide analysis reveals downregulation of miR-379/miR-656 cluster in human cancers. Biol Direct. 2013;8:10.

30. Liang D, Meyer L, Chang DW, et al. Genetic variants in microRNA biosynthesis pathways and binding sites modify cancers. Biol Direct. 2017;8:13.

31. Shen J, Wang D, Gregory SR, et al. Evaluation of microRNA expression profiles and their associations with risk alleles in lymphoblastoid cell lines of familial ovarian cancer. Carcinogenesis. 2012;33(3):604–612.

32. Yin G, Chen R, Alvero AB, et al. TWISTing stemness, inflammation and proliferation of epithelial ovarian cancer cells through MiR199A2/214. Oncogene. 2010;29(24):3545–3553.

33. Fan L, Lei H, Zhang S, et al. Non-canonical signaling pathway of SNAI2 induces EMT in ovarian cancer cells by suppressing miR-222-3p transcription and upregulating PDCD10. Theranostics. 2020;10(13):5895–5913.

34. Gao Y, Tian P, Yang C, et al. Silencing the double-stranded RNA binding protein DGCR8 inhibits ovarian cancer cell proliferation, migration, and invasion. Pharm Res (N Y). 2015;32(3):769–778.

35. Han C, Liu Y, Wan G, et al. The RNA-binding protein DDX1 promotes primary microRNA maturation and inhibits ovarian tumor progression. Cell Rep. 2014;8(5):1447–1460.

36. Pritchard CC, Cheng HH, Tewari M. microRNA profiling: approaches and considerations. Nat Rev Genet. 2012;13(5):358–369.

37. Panshin DD, Kondratov KA. The efficiency of immunoprecipitation of microRNA/Ago2 complexes from human blood plasma is protocol dependent. Mol Biol. 2020;54(2):213–219.

38. van Wynsberghe PM, Chan SP, Slack FJ, Pasquiniell AE. Analysis of microRNA expression and function. Methods Cell Biol. 2011;106:219–252.

39. Jaskiewicz L, Bilen B, Hausser J, Zavolan M. Argonaute CLIP: a

40. Agostini A, Brunetti M, Davidson B, et al. Genomic imbalances are involved in miR-30c and let-7a deregulation in ovarian tumors: implications for HMGA2 expression. Oncotarget. 2017;8(13):21554–21560.

41. Liu CG, Calin GA, Volinia S, Croce CM. microRNA expression patterns in primary microRNA maturation and inhibits ovarian cancer development by targeting ING5. JAMA Oncol. 2020;6(5):751–762.

42. Yin G, Chen R, Alvero AB, et al. TWISTing stemness, inflammation and proliferation of epithelial ovarian cancer cells through MiR199A2/214. Oncogene. 2010;29(24):3545–3553.

43. Fan L, Lei H, Zhang S, et al. Non-canonical signaling pathway of SNAI2 induces EMT in ovarian cancer cells by suppressing miR-222-3p transcription and upregulating PDCD10. Theranostics. 2020;10(13):5895–5913.

44. Gao Y, Tian P, Yang C, et al. Silencing the double-stranded RNA binding protein DGCR8 inhibits ovarian cancer cell proliferation, migration, and invasion. Pharm Res (N Y). 2015;32(3):769–778.

45. Han C, Liu Y, Wan G, et al. The RNA-binding protein DDX1 promotes primary microRNA maturation and inhibits ovarian tumor progression. Cell Rep. 2014;8(5):1447–1460.

46. Pritchard CC, Cheng HH, Tewari M. microRNA profiling: approaches and considerations. Nat Rev Genet. 2012;13(5):358–369.

47. Panshin DD, Kondratov KA. The efficiency of immunoprecipitation of microRNA/Ago2 complexes from human blood plasma is protocol dependent. Mol Biol. 2020;54(2):213–219.

48. van Wynsberghe PM, Chan SP, Slack FJ, Pasquiniell AE. Analysis of microRNA expression and function. Methods Cell Biol. 2011;106:219–252.

49. Jaskiewicz L, Bilen B, Hausser J, Zavolan M. Argonaute CLIP: a
miRNA clusters in ovarian cancer

69. Peskova L, Jurcikova D, Vanova T, et al. miR-183/96/182 cluster is an important morphogenic factor targeting PAX6 expression in differentiating human retinal organoids. Stem Cell. 2020.

70. Wang L, Zhu MJ, Ren AM, et al. A ten-microRNA signature identified from a genome-wide microRNA expression profiling in human epithelial ovarian cancer. PLoS One. 2014;9(5):e96472.

71. Zhou J, Zhang C, Zhou B, Jiang D. miR-183 modulated cell proliferation and apoptosis in ovarian cancer through the TGF-β/Smad4 signaling pathway. Int J Mol Med. 2019;43(4):1734–1746.

72. Wang YQ, Guo RD, Guo RM, Sheng W, Yin LR. MicroRNA-182 promotes cell growth, invasion, and chemoresistance by targeting programmed cell death 4 (PDCD4) in human ovarian carcinomas. J Cell Biochem. 2013;114(7):1464–1473.

73. Lu W, Lu T, Wei X. Downregulation of DNMT3a expression increases miR-182-induced apoptosis of ovarian cancer through caspase-3 and caspase-9-mediated apoptosis and DNA damage response. Oncol Rep. 2016;36(6):3597–3604.

74. Liu B, Zhang J, Yang D. miR-96-5p promotes the proliferation and migration of ovarian cancer cells by suppressing Cav-1. J Ovarian Res. 2019;12(1):57.

75. Quan J, Liu S, Dai K, et al. microRNA-23a/24-2/27a as a potential diagnostic biomarker for cancer: a systematic review and meta-analysis. Mol Clin Oncol. 2018;8(1):159–169.

76. Yang Z, Wang XL, Bai R, et al. miR-23a promotes IKK expression but suppresses STLE expression to contribute to the malignancy of epithelial ovarian cancer cells. Br J Cancer. 2016;115(6):731–740.

77. Zhuang RJ, Bai XX, Liu W. MicroRNA-23a depletion promotes the malignancy of epithelial ovarian cancer cells. Int J Oncol. 2010;37(1):125–130.

78. Wang L, Zhu MJ, Ren AM, et al. A ten-microRNA signature regulates cell proliferation, invasion, migration by targeting DLG2. Cancer Biol Ther. 2019;20(6):897–911.

79. Wei LQ, Li H, Zeng W, et al. microRNA-27a modulates MDR1/P-glycoprotein expression by targeting HIPK2 in human ovarian cancer cells. Tumor Biol. 2016;37:15719–15727.

80. Wei LQ, Li H, Zeng W, et al. microRNA-27a modulates MDR1/P-glycoprotein expression by targeting HIPK2 in human ovarian cancer cells. Tumor Biol. 2016;37:15719–15727.

81. Wei LQ, Li H, Zeng W, et al. microRNA-27a modulates MDR1/P-glycoprotein expression by targeting HIPK2 in human ovarian cancer cells. Tumor Biol. 2016;37:15719–15727.

82. Luo Y, Fang C, Jin L, Ding H, Lyu Y, Ni G. The microRNA212 regulator PEAS1 promotes ovarian cancer progression by inhibiting of apoptosis. J Cancer. 2020;11(6):1424–1435.

83. Tian H, Hou L, Xiong YM, et al. miR-132 targeting E2F5 suppresses cell proliferation, invasion, migration in ovarian cancer cells. Am J Transl Res. 2016;8(3):1492–1501.

84. Zhang XL, Sun BL, Tian SX, Li L, Zhaoyang C, Shi PP. microRNA-132 reverses cisplatin resistance and metastasis in ovarian cancer by the targeted regulation on Bmi-1. Eur Rev Med Pharmacol Sci. 2019;23(9):3635–3644.

85. Mogilansky E, Rigoutsos I. The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. Cell Death Differ. 2013;20(2):1603–1614.

86. Fuziwaras, Kimura M. Insights into regulation of the miR-17-92 cluster using miRNAs in cancer. Front Med. 2015;2:64.

87. Zhu H, Yang SY, Wang J, Wang L, Lan SY. Evidence for miR-17-92 and miR-134 gene cluster regulation of ovarian cancer drug resistance. Eur Rev Med Pharmacol Sci. 2016;20(12):2526–2531.

88. Feng S, Sun H, Zhu W. miR-92 overexpression suppresses immune cell function in ovarian cancer via LAT52/YAP1/PD-L1 pathway. Clin Transl Oncol. 2021;23(3):450–458.

89. Liu DT, Yao HR, Li Y, Song Y, Su MY. microRNA-19b promotes the migration and invasion of ovarian cancer cells by inhibiting the PTEN/PI3K/AKT signaling pathway. Oncol Lett. 2018;16(1):559–565.

90. Liu Y, Han S, Li Y, et al. microRNA-20a contributes to cisplatin-resistance and migration of OVCAR3 ovarian cancer cell line. Oncol Lett. 2017;14(2):1780–1786.

91. Gong C, Yang Z, Wu F, Han L, Liu Y, Gong W. miR-17 inhibits ovarian cancer cell perilactone metastasis by targeting ITGA5 and ITGB1. Oncol Rep. 2016;36(4):2177–2183.

92. Liu P, Qi X, Bian C, et al. microRNA-18a inhibits ovarian cancer growth via directly targeting TRIPA1 and IPMK. Oncol Lett. 2017;13(6):4039–4046.

93. Li J, Ju J, Ni B, Wang H. The emerging role of miR-506 in cancer. Oncotarget. 2016;7(38):62778–62788.

94. Han Y, Silva MA, Li H, et al. Long noncoding RNA DQ786243 interacts with miR-506 and promotes progression of ovarian cancer through targeting CAMP responsive element binding protein 1. J Cell Biochem. 2018;119(12):9764–9780.

95. Ouyang R, Xue M, Zhang L, Lin Z. Long noncoding RNA MALAT1-regulated microRNA 506 modulates ovarian cancer growth by targeting iASPP. Oncotargets Ther. 2016;10:35–46.

96. Liu G, Sun Y, Ji P, et al. miR-506 suppresses proliferation and induces senescence by directly targeting the CDK4/6/FOXM1 axis in ovarian cancer. J Pathol. 2014;233(3):308–318.

97. Hong L, Wang Y, Chen W, Yang S. microRNA-508 suppresses epithelial-mesenchymal transition, migration, and invasion of ovarian cancer cells through the MAPK/ERK signaling pathway. J Cell Biochem. 2018;119(9):7431–7440.

98. Guo F, Zhang K, Li M, et al. miR-508-3p suppresses the development of ovarian carcinoma by targeting CCNA2 and MMP7. Int J Oncol. 2020;57(1):264–276.

99. Chen W, Du J, Li X, et al. miR-509-3p promotes cisplatin-induced apoptosis in ovarian cancer cells through the regulation of anti-apoptotic genes. Pharmacogenomics. 2017;18(18):1671–1682.

100. Chen W, Zeng W, Li X, et al. microRNA-509-3p increases the sensitivity of epithelial ovarian cancer cells to cisplatin-induced apoptosis. Pharmacogenomics. 2016;17(3):187–197.

101. Yamakuchi M, Panta S, Hashiguchi T. p53 and vascular dysfunction: microRNA in endothelial cells. In: Vascularis in Practice - an Update on Special Situations - Clinical and Therapeutic Considerations. London: InTech; 2018.

102. Almeida MI, Calin GA. The miR-143/miR-145 cluster and the tumor microenvironment: unexpected roles. Genome Med. 2016;8(1):29.

103. Zhu X, Li Y, Xie C, et al. miR-154 sensitizes ovarian cancer cells to paclitaxel by targeting Sp1 and Cdk6. Int J Cancer. 2014;135(6):1286–1296.

104. Hang W, Feng Y, Sang Z, et al. Downregulation of miR-145-5p in cancer cells and their derived exosomes may contribute to the development of ovarian cancer by targeting CT. Int J Mol Med. 2018;43(1):256–266.

105. Dong R, Liu X, Zhang Q, et al. miR-145 inhibits tumor growth and metastasis by targeting metadherin in high-grade serous ovarian carcinoma. Oncotarget. 2014;5(21):10816–10829.

106. Shi H, Shen H, Xu J, Zhao S, Yao S, Jiang N. miR-143-3p suppresses the progression of ovarian cancer. Am J Transl Res. 2018;10(3):866–874.

107. Guan W, Wang X, Lin Q, Zhang Q, Ren W, Wu G. Transforming growth factor-β/miR-143-3p/cystatin B axis is a therapeutic target in human ovarian cancer. Int J Oncol. 2019;55(1):267–276.

108. Chen L, Zhang F, Sheng XG, Zhang SQ, Chen YT, Liu BW. microRNA-106a regulates phosphatase and tensin homologue
expression and promotes the proliferation and invasion of ovarian cancer cells. *Oncof. Rep.* 2016;36(4):2135–2141.

109. Liu Z, Gersbach E, Zhang X, et al. miR-106a represses the Rb tumor suppressor p130 to regulate cellular proliferation and differentiation in high-grade serous ovarian carcinoma. *Mol Cancer Res.* 2013;11(11):1314–1325.

110. Huh JH, Kim TH, Kim K, et al. Dysregulation of miR-106a and miR-591 confers paclitaxel resistance to ovarian cancer. *Br J Cancer.* 2013;109(2):452–461.

111. Han X, Zhang Y, Wang D, Fu X, Li M, Wang A. Upregulation of microRNA-18b induces phosphatase and tensin homolog to accelerate the migration and invasion abilities of ovarian cancer. *Oncof. Lett.* 2017;14(5):5631–5637.

112. Lin Y, Xu T, Zhou S, Cui M. microRNA-363 inhibits ovarian cancer progression by inhibiting NOB1. *Oncotarget.* 2017;8(60):101649–101658.

113. Kumar A, Nayak S, Pathak P, et al. Identification of miR-379/miR-656 (C14MC) cluster downregulation and associated epigenetic and transcription regulatory mechanism in oligodendrogliomas. *J Neuro Oncol.* 2018;139(1):23–31.

114. Dini P, El-Sheikh Ali H, Carossino M, et al. Expression profile of the chromosome 14 microRNA cluster (C14MC) ortholog in equine mammary circulation throughout pregnancy and its potential implications. *Int J Mol Sci.* 2019;20(24):E6285.

115. Bi L, Yang Q, Yuan J, et al. microRNA-127-3p acts as a tumor suppressor in epithelial ovarian cancer by regulating the BAG5 gene. *Oncof. Rep.* 2016;36(5):2563–2570.

116. Shuang T, Wang M, Chang S. Hybrid-polymerase chain reaction to identify novel target genes of miR-134 in paclitaxel resistant human ovarian carcinoma cells. *Oncof. Lett.* 2015;9(6):2910–2916.

117. Shuang T, Wang M, Shi C, Zhou Y, Wang D. Down-regulated expression of miR-134 contributes to paclitaxel resistance in human ovarian cancer cells. *FEBS Lett.* 2015;589(20 Pt B):3154–3164.

118. Zhao M, Ji H, Fu Q, Cheng Q, Zhang Y, Yang Y. microRNA-134-3p inhibits ovarian cancer progression by targeting flap structure-specific endonuclease 1 in vitro. *Oncof. Rep.* 2021;45(1):119–128.

119. Shuang T, Wang M, Zhou Y, Shi C, Wang D, NF-κB, c-Rel, and ELK1 inhibit miR-134 expression leading to TAB1 upregulation in paclitaxel-resistant human ovarian cancer. *Oncotarget.* 2017;8(15):24853–24868.

120. Jeong JY, Kang H, Kim TH, et al. microRNA-136 inhibits cancer stem cell activity and enhances the anti-tumor effect of paclitaxel against chemoresistant ovarian cancer cells by targeting Notch3. *Cancer Lett.* 2017;386:168–178.

121. Chen XP, Chen YG, Lan JY, Shen ZJ. microRNA-370 suppresses proliferation and promotes endometrioid ovarian cancer chemosensitivity to CDDP by negatively regulating ENO1. *Cancer Lett.* 2014;353(2):201–210.

122. Yu R, Cai L, Chi Y, Ding X, Wu K. miR-377 targets CUL4A and regulates metastatic capability in ovarian cancer. *Int J Mol Med.* 2018;41(6):3147–3156.

123. Yuan J, Wang K, Xi M. miR-494 inhibits epithelial ovarian cancer growth by targeting c-myc. *Med Sci Mon Int Med J Exp Clin Res.* 2016;22:617–624.

124. Zhao X, Zhou Y, Chen YU, Yu F. miR-494 inhibits ovarian cancer cell proliferation and promotes apoptosis by targeting FGFR2. *Oncof. Lett.* 2016;11(6):4245–4251.

125. Han X, Fang Z, Wang H, Jiao R, Zhou J, Fang N. CUL4A functions as an oncogene in ovarian cancer and is directly regulated by miR-494. *Biochem Biophys Res Commun.* 2016;480(4):675–681.

126. Li N, Zhao X, Wang L, Zhang S, Cui M, He J. miR-494 suppresses tumor growth of epithelial ovarian carcinoma by targeting IGFR1. *Tumour Biol.* 2016;37(6):7767–7776.

127. Zhao R, Liu Q, Lou C. microRNA-299-3p regulates proliferation, migration and invasion of human ovarian cancer cells by modulating the expression of OCT4. *Arch Biochem Biophys.* 2018;651:21–27.

128. Yang L, Wei QM, Zhang XW, Sheng Q, Yan XT. miR-376a promotes proliferation and metastases in ovarian cancer: potential role as a biomarker. *Life Sci.* 2017;173:62–67.

129. Yang Y, Liu J, Qian X, Li Y, Wang Y, Xu X. miR-485-5p improves the progression of ovarian cancer by targeting SRC in vitro and in vivo. *Neoplasma.* 2020;67(5):1022–1031.

130. Gong Y, Fan XH, miR-539-3p promotes the progression of epithelial ovarian cancer by targeting SPARC/1. *Eur Rev Med Pharmacol Sci.* 2019;23(6):2366–2373.

131. Jinesh GG, Flores ER, Brohl AS. Chromosome 19 miRNA cluster and CEBPB expression specifically mark and potentially drive triple negative breast cancers. *PLoS One.* 2018;13(10):e0206008.

132. Flor I, Bullerdiek J. The dark side of a success story: micro-RNAs of the C19MC cluster in human tumours. *J Pathol.* 2012;227(3):270–274.

133. Cong J, Liu R, Wang X, Wang J, Wang H, Hou J. Low miR-498 expression levels are associated with poor prognosis in ovarian cancer. *Eur Rev Med Pharmacol Sci.* 2015;19(24):4762–4765.

134. Liu R, Liu F, Li L, Sun M, Chen K. miR-498 regulates FOXO3 expression and inhibited the proliferation of human ovarian cancer cells. *Biomed Pharmacother.* 2015;72:52–57.

135. Pang Y, Mao H, Shen L, Zhao Z, Liu R, Liu P. miR-519d represses ovarian cancer cell proliferation and enhances cisplatin-mediated cytotoxicity in vitro by targeting XIAP. *Oncotargets Ther.* 2014;7:587–597.

136. Li J, Shao W, Zhao J. miR-520a-3p inhibits malignant progression of epithelial ovarian cancer by targeting SV39H1 expression. *Hum Cell.* 2021;34(2):570–578.

137. Miyamoto M, Sawada K, Nakamura K, et al. Paclitaxel exposure downregulates miR-522 expression and its downregulation induces paclitaxel resistance in ovarian cancer cells. *Sci Rep.* 2020;10(1):16755.

138. Zhang J, Liu L, Sun Y, et al. microRNA-520g promotes epithelial ovarian cancer progression and chemoresistance via DAPK2 repression. *Oncotarget.* 2016;7(18):26516–26534.

139. Zhang J, Liu W, Shen F, et al. The activation of microRNA-520h-associated TGF-β1/c-Myc/Smad7 axis promotes epithelial ovarian cancer progression. *Cell Death Dis.* 2018;9(9):884.

140. Susynska M, Ratajewska M, Kozlowski P, BRIP1, RAD51C, and RAD51D mutations are associated with high susceptibility to ovarian cancer: mutation prevalence and precise risk estimates based on a pooled analysis of ~30, 000 cases. *J Ovarian Res.* 2020;13(1):50.

141. Kim S, Choi WC, Jeong JY, et al. Serum exosomal miRNA-145 and miRNA-200c as promising biomarkers for preoperative diagnosis of ovarian carcinomas. *J Cancer.* 2019;10(9):1958–1967.

142. Meng X, Muller V, Milde-Langosch K, Trillas F, Pantel K, Schwarzenbach H. Circulating cell-free miR-373, miR-200a, miR-200b and miR-200c in patients with epithelial ovarian cancer: expression potential. *Adv Exp Med Biol.* 2016;892:3–8.

143. Zuberi M, Khan I, Gandhi G, Ray PC, Saxena A. The conglomerate of diagnostic, prognostic and therapeutic potential of serum miR-199a and its association with clinicopathological features in epithelial ovarian cancer. *Tumour Biol.* 2016;37(8):11259–11266.

144. Javadi S, Ganeshan DM, Qayyum A, Iyer RB, Bhosale P. Ovarian cancer, the revised FIGO staging system, and the role of imaging. *AJR Am J Roentgenol.* 2016;206(6):1351–1360.

145. Yu X, Zhang X, Bi T, et al. miRNA expression signature for potentially predicting the prognosis of ovarian serous carcinoma. *Tumour Biol.* 2013;34(6):3501–3508.

146. Calura E, Fruscio R, Paracchini L, et al. miRNA landscape in stage I epithelial ovarian cancer defines the histotype specificities. *Clin Cancer Res.* 2013;19(15):4114–4123.
147. Bagnoli M, de Cecco L, Granata A, et al. Identification of a chrx27.3 microRNA cluster associated with early relapse in advanced stage ovarian cancer patients. Oncotarget. 2011;2(12):1265–1278.

148. Lalwani N, Prasad SR, Vikram R, Shanbhogue AK, Huettner PC, Fasih N. Histologic, molecular, and cytogenetic features of ovarian cancers: implications for diagnosis and treatment. Radiographics. 2011;31(3):625–646.

149. Fazzite A, Jouhadi H, Nadin D, et al. BRCA1 and BRCA2 germline mutations in Moroccan breast/ovarian cancer families: novel mutations and unclassified variants. Gynecol Oncol. 2012;125(3):687–692.

150. Zhang X, Guo G, Wang G, et al. Profile of differentially expressed miRNAs in high-grade serous carcinoma and clear cell ovarian carcinoma, and the expression of mir-510 in ovarian carcinoma. Mol Med Rep. 2015;12(6):8021–8031.

151. Chang RK, Li X, Mu N, et al. microRNA expression profiles in non-epithelial ovarian tumors. Int J Oncol. 2018;52(6):55–66.

152. Wright JD, Chen L, Tergas AI, et al. Trends in relative survival for ovarian cancer from 1975 to 2011. Obstet Gynecol. 2015;125(6):1345–1352.

153. Amini-Farsani Z, Sangtarash MH, Shamsara M, Teimori H. mir-221/222 promote chemoresistance to cisplatin in ovarian cancer cells by targeting PTEN/P13K/akt signaling pathway. Cytotechnology. 2018;70(1):203–213.

154. Fu X, Li Y, Alvera A, et al. microRNA-222-3p/GNA12/akt axis inhibits epithelial ovarian cancer cell growth and associates with good overall survival. Oncotarget. 2016;7(49):80633–80654.

155. Li J, Li Q, Huang H, et al. Overexpression of miRNA-221 promotes cell proliferation by targeting the apoptotic protease activating factor-1 and indicates a poor prognosis in ovarian cancer. Int J Oncol. 2017;50(4):1087–1096.

156. Meng X, Müller V, Milde-Langosch K, Trillsch F, Pantel K, Schwarzenbach H. Diagnostic and prognostic relevance of circulating exosomal miR-373, miR-200a, miR-200b and miR-200c in ovarian cancer patients. Oncotarget. 2016;7(13):16923–16935.

157. Wang X, Meng X, Li H, Liu W, Shen S, Gao Z. microRNA-25 expression level is an independent prognostic factor in epithelial ovarian cancer. Clin Transl Oncol. 2014;16(11):954–958.

158. Dong J, Xu M. A 19-miRNA Support Vector Machine classifier and a 6-miRNA risk score system designed for ovarian cancer patients. Oncol Rep. 2019;41(6):3233–3243.

159. Lalios A, O’Toole S, Flavin R, et al. Potential role of miR-9 and miR-223 in recurrent ovarian cancer. Mol Cancer. 2008;7:35.

160. Lee CH, Subramanian S, Beck AH, et al. BRCA1 and BRCA2 germline mutations in Moroccan breast/ovarian cancer families: novel mutations and unclassified variants. Gynecol Oncol. 2012;125(3):687–692.

161. Sato S, Itamochi H. Neoadjuvant chemotherapy in advanced stage ovarian cancer: latest results and place in therapy. Ther Adv Med Oncol. 2014;6(6):293–304.

162. Si W, Shen J, Zheng H, Fan W. The role and mechanisms of action of microRNAs in cancer drug resistance. Clin Epigenet. 2019;11(1):25.

163. Kazmierczak D, Jopek K, Sterzymska K, et al. The significance of microRNAs expression in regulation of extracellular matrix and other drug resistant genes in drug resistant ovarian cancer cell lines. Int J Mol Sci. 2020;21(7):E2619.

164. Feng L, Shen F, Zhou J, Li Y, Jiang R, Chen Y. Hypoxia-induced up-regulation of miR-27a promotes paclitaxel resistance in ovarian cancer. Biosci Rep. 2020;40(4):BSR20192497.

165. Gogineni V, Morand S, Staats H, et al. Current ovarian cancer maintenance strategies and promising new developments. J Cancer. 2021;12(1):38–53.

166. Bast Jr RC. CA 125 and the detection of recurrent ovarian cancer. Cancer. 2010;116(12):2850–2853.

167. Hu X, MacDonald DM, Huettner PC, et al. A miR-200 microRNA cluster as prognostic marker in advanced ovarian cancer. Gynecol Oncol. 2009;114(3):457–464.

168. Chong GO, Jeon HS, Han HS, et al. Differential microRNA expression profiles in primary and recurrent epithelial ovarian cancer. Anticancer Res. 2015;35(5):2611–2617.

169. Wu Y, Wang W, Yang AG, Zhang R. The microRNA-424/503 cluster: a master regulator of tumorigenesis and tumor progression with paradoxical roles in cancer. Cancer Lett. 2020;494:58–72.

170. Fu Y, Chen J, Huang Z. Recent progress in microRNA-based delivery systems for the treatment of human disease. ExRNA. 2019;1:24.

171. Kobayashi M, Sawada K, Miyamoto M, et al. Exploring the potential of engineered exosomes as delivery systems for tumor-suppressor microRNA replacement therapy in ovarian cancer. Biochem Biophys Res Commun. 2020;527(1):153–161.

172. Yang C, Li B, Yu J, Yang F, Cai K, Chen Z. Ultrasound micro-bubbles mediated miR-let-7b delivery into CD133 + ovarian cancer stem cells. Biosci Rep. 2018;38(5):BSR20180922.

173. Cai J, Gong L, Li G, Guo J, Yi X, Wang Z. Exosomes in ovarian cancer asctes promote epithelial-mesenchymal transition of ovarian cancer cells by delivery of miR-6780b-5p. Cell Death Dis. 2021;12(2):210.

174. Cui X, Sun Y, Shen M, et al. Enhanced chemotherapeutic efficacy of paclitaxel nanoparticles co-delivered with microRNA-7 by inhibiting paclitaxel-induced EGFR/ERK pathway activation for ovarian cancer therapy. ACS Appl Mater Interfaces. 2018;10(9):7821–7831.

175. Dai F, Zhang Y, Zhu X, Shan N, Chen Y. Anticancer role of MUC1 aptamer-miR-29b chimera in epithelial ovarian carcinoma cells through regulation of PTEN methylation. Targeted Oncol. 2012;7(4):217–225.

176. Liu N, Zhou C, Zhao J, Chen Y. Reversal of paclitaxel resistance in epithelial ovarian carcinoma cells by a MUC1 aptamer-let-7i chimera. Cancer Invest. 2012;30(8):577–582.

177. Bertucci A, Kim KH, Kang J, et al. Tumor-targeting, microRNA-silencing porous silicon nanoparticles for ovarian cancer therapy. ACS Appl Mater Interfaces. 2019;11(27):23926–23937.

178. Ishida M, Selaru FM. microRNA-based therapeutic strategies. Curr Anesthesiol Rep. 2013;1(1):63–70.

179. Ohyagi-Hara C, Sawada K, Kamiura S, et al. miR-92a inhibits integrin alphavbeta3 expression through miR-34a and miR-34b/c by CpG methylation in ovarian cancer. Anticancer Res. 2012;32(9):3577–3582.

180. Vogt M, Mundinger J, Gruner M, et al. Frequent concomitant inactivation of miR-34a and miR-34b/c by CpG methylation in colorectal, pancreatic, mammary, ovarian, urethelial, and renal cell carcinomas and soft tissue sarcomas. Virchows Arch. 2011;458(3):313–322.

181. Li T, Li Y, Gan Y, et al. Methylation-mediated repression of miR-424/503 cluster promotes proliferation and migration of ovarian cancer cells through targeting the hub gene KIF23. Cell Cycle. 2019;18(14):1601–1618.
Deng Y, Zhao F, Hui L, et al. Suppressing miR-199a-3p by promoter methylation contributes to tumor aggressiveness and cisplatin resistance of ovarian cancer through promoting DDR1 expression. J Ovarian Res. 2017;10(1):50.

Loginov VI, Burdennyy AM, Filippova EA, et al. Hypermethylation of miR-107, miR-130b, miR-203a, miR-1258 genes associated with ovarian cancer development and metastasis. Mol Biol (Mosk). 2018;52(5):801–809.

Loginov VI, Pronina IV, Burdennyy AM, et al. Novel miRNA genes deregulated by aberrant methylation in ovarian carcinoma are involved in metastasis. Gene. 2018;662:28–36.

Teng Y, Zuo X, Hou M, et al. A double-negative feedback interaction between microRNA-29b and DNM3TA3B contributes to ovarian cancer progression. Cell Physiol Biochem. 2016;39(6):2341–2352.

Zuberi M, Khan I, MiR R, Gandhi G, Ray PC, Saxena A. Utility of serum miR-125b as a diagnostic and prognostic indicator and its alliance with a panel of tumor suppressor genes in epithelial ovarian cancer. PloS One. 2016;11(4):e0153902.

Xu S, Fu Z, Tao Z, et al. miR-497 decreases cisplatin resistance in ovarian cancer cells by targeting mTOR/P70S6K1. Oncotarget. 2015;6(28):26457–26471.

Liu MX, Shi LW, Liu SS, Yen JWP, Ngn HYS, Chan DW. Epigenetic silencing of microRNA-199b-5p is associated with acquired chemoresistance via activation of JAG1-Notch1 signaling in ovarian cancer. Oncotarget. 2014;5(5):944–958.

Kan CWS, Howell VW, Hahn MA, Marshall DJ. Genomic alterations as mediators of miRNA dysregulation in ovarian cancer. Genes Chromosomes Cancer. 2015;54(1):1–19.

Das AV, Pillai RM. Implications of miR cluster 143/145 as universal anti-oncomirs and their dysregulation during tumorigenesis. Cancer Cell Int. 2015;15:92.

Zhang L, Huang J, Yang N, et al. microRNAs exhibit high frequency genomic alterations in human cancer. Proc Natl Acad Sci USA. 2006;103(24):9136–9141.

Song K, Lv T, Chen Y, Diao Y, Yao Q, Wang Y. Emodin inhibits TGF-β2 by activating the FOXO3/miR-199a axis in ovarian cancer cells in vitro. Oncol Rep. 2018;39(5):2063–2070.

Bai R, Cui Z, Ma Y, et al. The NF-κB-modulated miR-19a-3p target, BTG1 mediates the proliferation in human ovarian cancer cells through inhibition of IGFBP-3 expression. Mol Carcinog. 2019;58(12):2254–2265.

Chen MW, Yang ST, Chien MH, et al. The STAT3-miRNA-92-wnt signaling pathway regulates spheroid formation and malignant progression in ovarian cancer. Cancer Res. 2017;77(8):1955–1967.

Faggad A, Budczies J, Tchermitza O, et al. Prognostic significance of Dicer expression in ovarian cancer-link to global microRNA changes and oestrogen receptor expression. J Pathol. 2010;220(3):382–391.

Muralidhar G5, Barbolina MV. The miR-200 family: versatile players in epithelial ovarian cancer. Int J Mol Sci. 2015;16(8):16833–16847.

Song C, Zhang L, Wang J, et al. High expression of microRNA-183/182/96 cluster as a prognostic biomarker for breast cancer. Sci Rep. 2016;6:24502.

Goto Y, Kojima S, Nishikawa R, et al. The microRNA-23b/27b/24-1 cluster is a disease progression marker and tumor suppressor in prostate cancer. Oncotarget. 2014;5(17):7748–7759.

Mehlich D, Garbicz F, Wlodarski PK. The emerging roles of the polycistrionic miR-106b~25 cluster in cancer - a comprehensive review. Biomed Pharmacother. 2018;107:1183–1195.

Song Q, An Q, Niu B, Lu X, Zhang N, Cao X. Role of miR-221/222 in tumour development and the underlying mechanism. JAMA Oncol. 2019;7:252013.

Gao Z, Zhu X, Dou Y. The miR-302/367 cluster: a comprehensive update on its evolution and functions. Open Biol. 2015;5(12):150138.

Khoo C, Utuhe TP, Senth A. The three paralogous microRNA clusters in development and disease, miR-17-92, miR-106a-363, and miR-106b-25. Sci Tech Rep. 2016;2016:1379643.

Nohata N, Hanazawa T, Enokida H, Seki N. microRNA-1/133a and microRNA-206/133b clusters: dysregulation and functional roles in human cancers. Oncotarget. 2012;3(11):9–21.

Ghasemi M, Samaei NM, Mowlwaj SJ, Shafiee M, Vasei M, Ghasemian N. Upregulation of miR-371-373 cluster, a human embryonic stem cell specific microRNA cluster, in esophageal squamous cell carcinoma. J Cancer Res Therapeut. 2018;14(1Supplement):S132–S137.

Ye Q, Lei L, Shao L, Shi J, Jia J, Tong X. microRNA-141 inhibits epithelial-mesenchymal transition, and ovarian cancer cell migration and invasion. Mol Med Rep. 2017;16(5):6743–6749.

Shi C, Yang Y, Zhang L, et al. miR-200a-3p promoted the malignant behaviors of ovarian cancer cells through regulating PCDH9. Onco Targets Ther. 2019;12:8329–8338.

Suo HB, Zhang KC, Zhao J. miR-200a promotes cell invasion and migration of ovarian carcinoma by targeting PTEN. Eur Rev Med Pharmacol Sci. 2018;22(13):4080–4089.

Zou J, Liu L, Wang Q, et al. Downregulation of miR-429 contributes to the development of drug resistance in epithelial ovarian cancer by targeting ZEB1. Am J Transl Res. 2017;9(3):1357–1368.

Liu X, Yao B, Wu Z. miRNA-199a-5p suppresses proliferation and invasion by directly targeting NF-kB1 in human ovarian cancer cells. Oncol Lett. 2018;16(4):4543–4550.

Liu Y, Zhou H, Ma L, et al. miR-214 suppressed ovarian cancer and negatively regulated semaphorin 4D. Tumor Biol. 2016;37(6):8239–8248.

Liu Z, Liu J, Segura MF, et al. miR-182 overexpression in tumourigenesis of high-grade serous ovarian carcinoma. J Pathol. 2012;228(2):204–215.

Xu X, Dong Z, Li Y, et al. The upregulation of signal transducer and activator of transcription 5-dependent microRNA-182 and microRNA-96 promotes ovarian cancer cell proliferation by targeting forkhead box O1 upon leptin stimulation. Int J Biochem Cell Biol. 2013;45(3):536–545.

Li R, Wu H, Jiang H, et al. FBLN5 is targeted by microRNA-27a-3p and suppresses tumorigenesis and progression in high-grade serous ovarian carcinoma. Oncol Rep. 2020;44(5):2143–2151.

Si L, Jia Y, Lin R, Jian W, Yu Q, Yang S. microRNA-27a regulates the proliferation, chemosensitivity and invasion of human ovarian cancer cells by targeting Cullin 5. Arch Biochem Biophys. 2019;668:9–15.

Zhang LY, Chen Y, Jia J, Zhu X, He Y, Wu LM. miR-27a promotes EMT in ovarian cancer through active Wnt/β-catenin signalling by targeting FOXO1. Cancer Biomark. 2019;24(1):31–42.

Li E, Han K, Zhou X. microRNA-27a-3p down-regulation inhibits malignant biological behaviors of ovarian cancer by targeting BTG1. Open Med. 2019;14:577–585.

Yan J, Jiang JY, Meng XN, Xiu YL, Zong ZH. miR-23b targets cyclin G1 and suppresses ovarian cancer tumorigenesis and progression. J Exp Clin Cancer Res. 2016;35:31.

Li W, Liu Z, Chen L, Zou L, Yao Y. microRNA-23b is an independent prognostic marker and suppresses ovarian cancer progression by targeting runt-related transcription factor-2. FEBS Lett. 2014;588(9):1608–1615.

Liu W, Lv C, Zhang B, Zhou Q, Cao Z. microRNA-27b functions as a new inhibitor of ovarian cancer-mediated vasculogenic mimicry through suppression of VE-cadherin expression. RNA. 2017;23(7):1019–1027.

Liu CH, Jing XN, Liu XL, Qin SY, Liu MW, Hou CH. Tumor-suppressor miRNA-27b-5p regulates the growth and metastatic behaviors of ovarian carcinoma cells by targeting CXCL1. J Ovarian Res. 2020;13(1):92.
miRNA clusters in ovarian cancer

224. Feng S, Pan W, Jin Y, Zheng J. miR-25 promotes ovarian cancer proliferation and motility by targeting LAT52. *Tumour Biol.* 2014;35(12):12339–12344.

225. Chen S, Chen X, Xiu YL, Sun KK, Zhao Y. Inhibition of ovarian epithelial carcinoma tumorigenesis and progression by microRNA 106b mediated through the RhoC pathway. *PLoS One.* 2015;10(5):e0125714.

226. Zhang H, Zuo Z, Lu X, Wang L, Wang H, Zhu Z. miR-25 regulates apoptosis by targeting Bim in human ovarian cancer. *Oncol Rep.* 2012;27(2):594–598.

227. Fu X, Tian J, Zhang L, Chen Y, Hao Q. Involvement of microRNA-93, a new regulator of PTEN/Akt signaling pathway, in regulation of chemotherapeutic drug cisplatin chemosensitivity in ovarian cancer cells. *FEBS Lett.* 2012;586(9):1279–1286.

228. Zhang L, Zhang Y, Wang S, et al. miR-212-3p suppresses high-grade serous ovarian cancer progression by directly targeting MAP3K3. *Am J Transl Res.* 2020;12(3):875–888.

229. Xie X, Huang Y, Chen L, Wang J. miR-221 regulates proliferation of ovarian cancer cells by targeting BIM. *Oncol Lett.* 2018;16(5):6697–6704.

230. Wu Q, Ren X, Zhang Y, et al. miR-221-3p targets ARF4 and inhibits the proliferation and migration of epithelial ovarian cancer cells. *Biochem Biophys Res Commun.* 2018;497(4):1162–1170.

231. Sun C, Li N, Zhou B, et al. miR-222 is upregulated in epithelial-mesenchymal transition and cisplatin resistance by microRNA-302 represses the expression of PTEN and promotes the growth of ovarian cancer cells. *FEBS Lett.* 2013;586(9):1279–1286.

232. Gong L, Zhang W, Yuan Y, Xing X, Li H, Zhao G. miR-222 regulates apoptosis by targeting Bim in human ovarian cancer cell lines. *PLoS One.* 2015;10(5):e0125714.

233. Chen S, Chen X, Xiu YL, Sun KX, Zhao Y. Inhibition of ovarian epithelial carcinoma tumorigenesis and progression by microRNA 106b mediated through the RhoC pathway. *PLoS One.* 2015;10(5):e0125714.

234. Ge T, Liu T, Guo L, Chen Z, Lou G. microRNA-302 represses epithelial-mesenchymal transition and cisplatin resistance by regulating ATAD2 in ovarian carcinoma. *Exp Cell Res.* 2020;396(1):112241.

235. Li L, He L, Zhao JL, et al. miR-17-5p up-regulates YES1 to modulate the cell cycle progression and apoptosis in ovarian cancer cell lines. *J Cell Biochem.* 2015;116(6):1050–1059.

236. Wang Y, Zhao S, Zhu L, Zhang Q, Ren Y. miR-19a negatively regulated the expression of PTEN and promoted the growth of ovarian cancer cells. *Gene.* 2018;670:166–173.

237. Wang Y, Lei X, Gao C, et al. miR-506-3p suppresses the proliferation of ovarian cancer cells by negatively regulating the expression of MTMR6. *J Biostoch.* 2019;44(6):126.

238. Xie XY, Yu YJ, Ye F, Peng GY, Li YJ, Zhou XM. microRNA-506-3p inhibits proliferation and promotes apoptosis in ovarian cancer cell via targeting SIRT1/AKT/FOXO3a signaling pathway. *Neoplasma.* 2020;67(2):344–353.

239. Chen X, Dong C, Law PTY, et al. microRNA-145 targets TRIM2 and exerts tumor-suppressing functions in epithelial ovarian cancer. *Gynecol Oncol.* 2015;139(3):513–519.

240. Rao YM, Shi HR, Ji M, Chen CH. miR-106a targets Mcl-1 to suppress cisplatin resistance of ovarian cancer A2780 cells. *J Huazhong Univ Sci Technolog Med Sci.* 2013;33(4):567–572.

241. Li H, Xu H, Shen H, Li H. microRNA-106a modulates cisplatin sensitivity by targeting PDCD4 in human ovarian cancer cells. *Oncol Lett.* 2014;7(1):183–188.

242. Mohamed Z, Hassan MK, Okasha S, et al. miR-363 confers taxane resistance in ovarian cancer by targeting the Hippo pathway member. *LAT52. Oncotarget.* 2018;9(53):30053–30065.

243. Qu W, Chen X, Wang J, Lv J, Yan D. microRNA-1 inhibits ovarian cancer cell proliferation and migration through c-Met pathway. *Clin Chim Acta.* 2017;473:237–244.

244. Guo J, Xia B, Meng F, Lou G. miR-133a suppresses ovarian cancer cell proliferation by directly targeting insulin-like growth factor 1 receptor. *Tumour Biol.* 2014;35(2):1557–1564.

245. Zhou Y, Jin Z, Wang C. Glycogen phosphorylase B promotes ovarian cancer progression via Wnt/b-catenin signaling and is regulated by miR-133a-3p. *Biomed Pharmacother.* 2019;120:109449.

246. Zhang Y, Zhao FJ, Chen LL, et al. miR-373 targeting of the Rab22a oncogene suppresses tumor invasion and metastasis in ovarian cancer. *Oncotarget.* 2014;5(23):12291–12303.

247. Guan X, Zong ZH, Chen S, et al. The role of miR-372 in ovarian carcinoma cell proliferation. *Gene.* 2017;624:14–20.

248. Zhang Z, Zhang L, Wang B, et al. miR-337-3p suppresses proliferation of ovarian epithelial ovarian cancer by targeting PIK3CA and PIK3CB. *Cancer Lett.* 2020;469:54–67.

249. Xia B, Li H, Yang S, Liu T, Lou G. miR-381 inhibits epithelial ovarian cancer malignancy via YY1 suppression. *Tumour Biol.* 2016;37(7):9157–9167.

250. Liang T, Guo Q, Li L, Cheng Y, Lou G. miR-133a suppresses ovarian cancer proliferation by targeting PIK3CA and PIK3CB. *Oncogene.* 2017;36(5):696–704.

251. Majem B, Parrilla A, Jiménez C, et al. microRNA-654-5p suppresses ovarian cancer development impacting on MYC, WNT and AKT pathways. *Oncogene.* 2019;38(32):6035–6050.

252. Zha JF, Chen DX. miR-655-3p inhibited proliferation and migration of ovarian cancer cells by targeting RAB1A. *Experientia.* 2019;75(8):888.

253. Guo J, Xia B, Meng F, Lou G. miR-133a suppresses ovarian cancer cell proliferation by directly targeting insulin-like growth factor 1 receptor. *Tumour Biol.* 2014;35(2):1557–1564.

254. Mohamed Z, Hassan MK, Okasha S, et al. miR-363 confers taxane resistance in ovarian cancer by targeting the Hippo pathway member. *LAT52. Oncotarget.* 2018;9(53):30053–30065.

255. Qu W, Chen X, Wang J, Lv J, Yan D. microRNA-1 inhibits ovarian cancer cell proliferation and migration through c-Met pathway. *Clin Chim Acta.* 2017;473:237–244.

256. Guo J, Xia B, Meng F, Lou G. miR-133a suppresses ovarian cancer cell proliferation by directly targeting insulin-like growth factor 1 receptor. *Tumour Biol.* 2014;35(2):1557–1564.