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REVIEW ARTICLE

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

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summarizes the regulation and biological function of MCs in OC. The review also highlights the utility of abnormally expressed MCs in the clinical management of OC.

Introduction

Ovarian cancer (OC) is the 7th most common cancer worldwide and is the most lethal type of gynecological malignancies.[1] The GLOBOCAN estimates had reported 313, 959 new victims and 207, 252 fatalities due to OC in 2020.[2] 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.[3] Furthermore, in Europe, approximately 29, 000 deaths were predicted due to OC in 2020.[4] 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.[5] 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.[6] The risk factors associated with OC include family history, ethnicity, genetic syndrome, *BRCA1*/2 (breast cancer 1/2), and *MMR* (mismatch repair) gene mutations, endometriosis, age, obesity, nonsteroidal anti-inflammatory drugs, dietary factors, postmenopausal hormone therapy and smoking.[6–8] The three prominent types of OC include sex-cord-stromal, germ cell and epithelial.[6] Based on the histopathological characters, there are five primary subtypes of epithelial OC, which are low- and high-grade serous carcinoma, endometrioid, mucinous and clear cell.[9] Owing to the vague array of symptoms, OC screening is very challenging.[6] 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.[10] CA125 (cancer antigen 125) is a well-known tumor biomarker that has been used for OC detection.[11] 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.[6,11] 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.[6] Long term use of oral contraceptives has proven to be effective in preventing the risk of OC.[12] On the other hand, the use of oral contraceptives should be equalized to prevent the possible risk of cervical and breast cancer.[13]

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.[14] 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.[15,16] Towards this, expression profiling of miRNAs can be employed for the clinical management of OC.

miRNAs were first discovered in *Caenorhabditis elegans* in 1993 and are single-stranded, non-coding RNAs with an approximate length of 22 nt.[17–19] The mature miRNAs critically modulate target gene expression by translation repression or mRNA cleavage.[20] Adjacently located miRNA genes get transcribed together to result in miRNA clusters (MC).[21] These clusters contain 2 or more miRNA genes transcribed together in the same orientation.[22] Many of the MCs are evolutionarily conserved and regulate diverse biological pathways by controlling the expression of protein-coding genes.[22] 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.[23] 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.[24] 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).[25] 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 *DNMT3A*.[26] Numerous MCs are found colocalized 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[27] (Table 1).

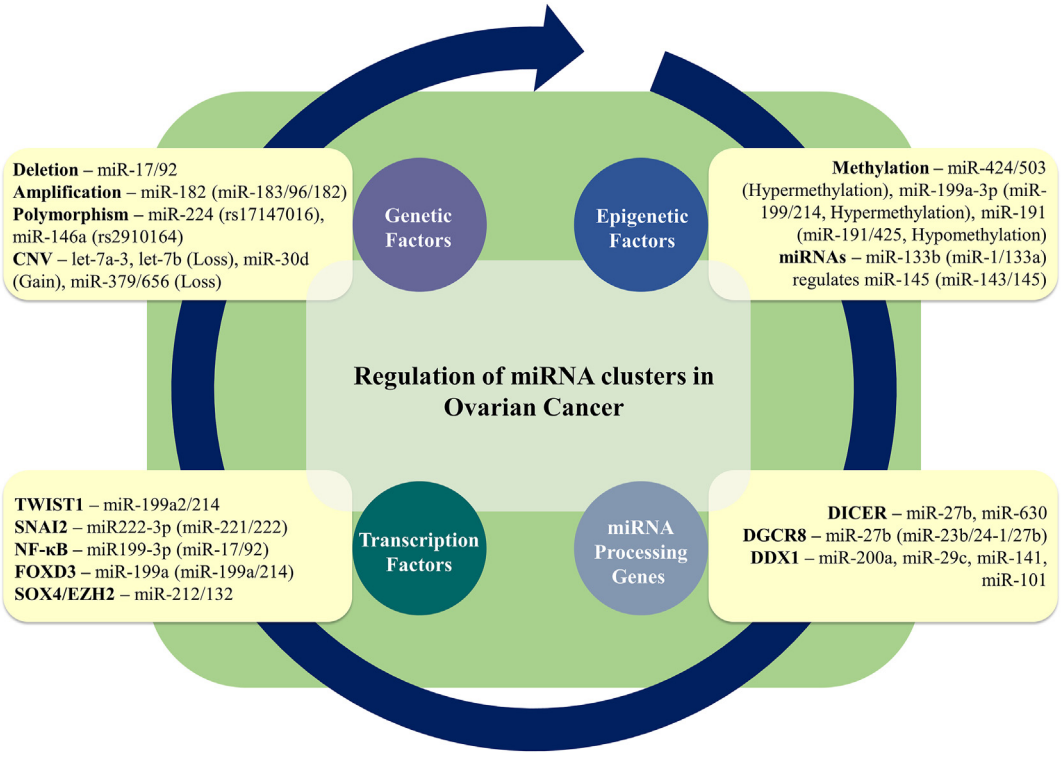


Figure 1 Diagrammatic representation of distinct factors that regulate miRNA cluster expression in OC.

Dysregulation of miR-7a and miR-30c is linked to genomic imbalances in OC.[28] Laddha et al have reported the loss of miR-379/miR-656 cluster in 14% of serous epithelial ovarian cancer (SEOC).[29] On the contrary, miR-182 of miR-183/96/182 cluster was amplified in 28.9% of EOC.[25] Genetic polymorphisms in MCs such as rs17147016 at miR-224, rs10771184 at miR-544, rs2075993 at miR-630 were strongly linked with OC.[30] A strong association between the miR-17/92 cluster expression and rs3814113 polymorphism were linked to familial OC risk.[31] Abnormal expression of TF-miRNA cluster axis participates in OC progression (Table 1). miR-199A2/214-TWIST1 axis critically regulates stemness of EOC cells.[32] In EOC, the suppression of miR-222−3p of miR-221/222 cluster by SNAI2 induced EMT (epithelial−mesenchymal transition) by upregulating PDCD10 (programmed cell death-10).[33] A few reports have described the significance of miRNA processing genes in modulating miRNA expression in OC conditions (Table 1). Guo et al have revealed miR-27b as a highly downregulated miRNA in OC cells lacking DGCR8 expression.[34] *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.[35] 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.[36] 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.[36] Techniques such as immunoprecipitation with AGO2,[37] electrophoresis-based size purification,[38] and crosslinking immunoprecipitation (CLIP)[39] have been employed for the isolation and analysis of miRNAs. Reverse transcription-quantitative PCR (RT-qPCR),[40] microarray,[41] and RNA sequencing (RNA-Seq)[42] 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.[43] Microarray analysis was the commonly used high-throughput technique for parallel examination of large number of miRNAs.[44] This hybridization-based approach is best suited for the analysis of relative abundance of particular miRNAs among different group of samples.[45] However, it does not facilitate absolute quantification and detection of novel miRNAs and isomiRs. Further, microarray-based analysis generally needs high RNA inputs and due to its inadequate specificity, initial findings need to be validated by other methods such as Northern blot or RT-qPCR.[36] The advent of small RNA sequencing platforms has allowed simultaneous identification and quantification of novel miRNAs, isomiRs and other small RNA species.[43] High cost, complex workflow, and the requirement of computational infrastructure for data interpretation are the limitations of this approach.[43] Recent techniques such as single molecule real-time sequencing (SMRT) assures less biased and faster analysis than other approaches.[46] 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.[36]

Table 1 Regulators of miRNA clusters in OC.

miRNA	Cluster Name	No. of miRNAs	Alterations/Regulated by	Reference
Epigenetic Regulation				
miR-382	C14MC	52 miRNAs	Promoter methylation	181
let-7a-3	let-7a-3/let-7b	3 miRNAs (let-7a-3, miR-4763, let-7b)	Hypermethylation	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	184
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	
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-92a)	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)	
miR-17/92	miR-17/92	6 miRNAs (miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-92a)	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			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-92a)	NF-κB	196
miR-92a			STAT3	197
miR-17/92			MYC	87

Table 1 (*continued*)

miRNA	Cluster Name	No. of miRNAs	Alterations/Regulated by	Reference
miRNA Processing Genes				
miR-27b	miR-23b/24—1/27b	3 miRNAs (miR-23b, miR-27b, miR-24-1)	DGCR8	34
23 miRNAs	—	—	DICER	198
miR-200a, —200b, —200c, miR-429, miR-141	miR-200b/200a/429	3 miRNAs (miR-200b, miR-200a, miR-429)	DDX1	35
	miR-200c/141	2 miRNAs (miR-200c, miR-141)		

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.[47] 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.[48] 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).[49] The activation of EMT signaling cascade significantly fosters metastasis[50] 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.[51] Due to its ability to reduce tumorigenicity and invasion of OC cells, miR-200c is proposed as an important therapeutic target.[52] 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.[53] By targeting *SIK1* (salt-inducible kinase 1) and *KEAP1*, miR-141 promotes cell proliferation and cisplatin resistance in OC.[54] 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).[55] 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.[56] 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.[57] The ectopic miR-429 expression upsurges drug sensitivity and results in the induction of MET (mesenchymal to epithelial transition) in metastasizing OC cells.[58] On upregulation, miR-200b-5p targeted *ATAD2* (ATPase family AAA domain containing-2) and inhibited OC cell proliferation via PI3K/AKT pathway.[59] Interestingly, nanoparticle mediated delivery of miR-200a and —200b reduced the metastatic burden with improved organization of the vasculature.[60] 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.[61] The members of the cluster participate in the development of various tissues, notably heart, bone, muscle, pancreatic, nervous system, nephrogenesis, and vascularization.[62] At the cellular level, miR-199a/214 cluster controls proliferative, migratory, invasive ability, and cell cycle progression in OC cells.[63] A study reported 56% and 53% of OC tissues showed upregulation of miR-214 and miR-199a, respectively.[64] 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.[65] 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.[66] In OC, miR-214 displays an oncogenic function by targeting *PTEN* to activate AKT signaling and stimulates cisplatin resistance, cell survival,[67] and radio-resistance.[64,68] On the contrary, by targeting *CTNNB1* (β-catenin), miR-214 acts as a tumor suppressor in OC. Collectively, abnormal expression of miR-199a/

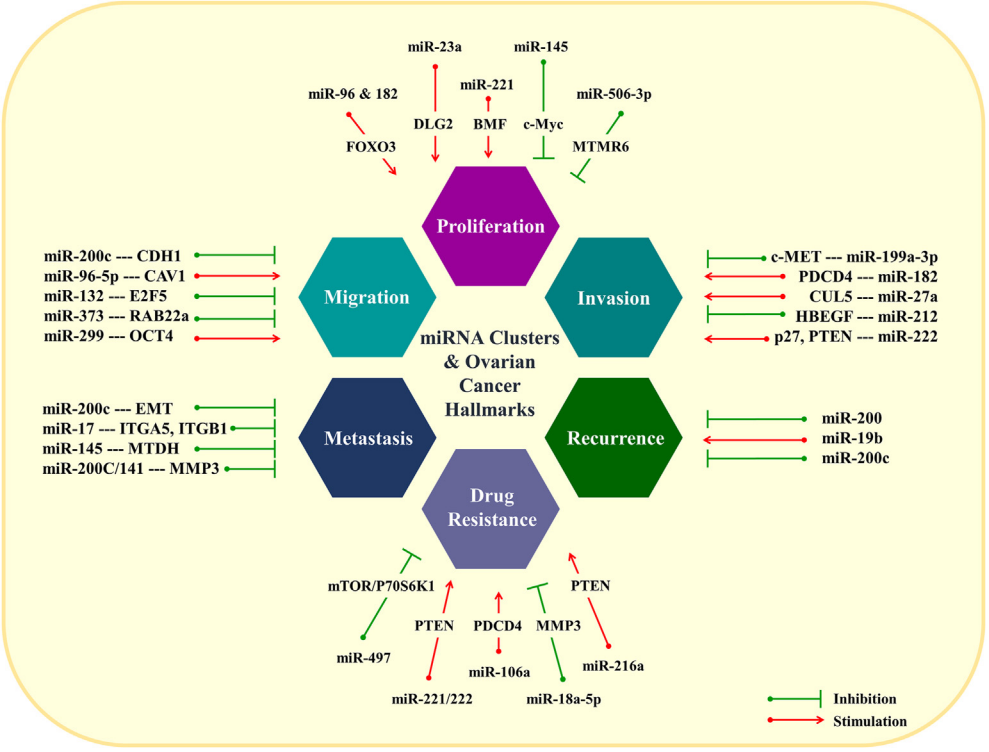


Figure 2 miRNA clusters can control ovarian cancer cell proliferation, growth, migration, invasion, metastasis, drug resistance and recurrence by modulating various molecular targets and accompanied signaling cascades.

214 may promote stemness and therapeutic resistance in OC.[32] 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.[69] miR-183/182/96 is one of the upregulated MCs in OC[70] 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.[71] Importantly, by negatively regulating *PDCD4* (programmed cell death-4), miR-182 induces growth, invasion, resistance to apoptosis, and resistance to cisplatin and taxol.[72] 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.[73] 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.[74] 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.[75] 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.[76] 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).[77] 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).[78] 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.[79] miR-212/132 locus was initially described to target CREB (cAMP-response element

Table 2 Differentially expressed MCs in OC, their chromosomal location, and members of MC.

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	OncomiR	Cell lines (OVCAR, A2780, T80)	[199]
miR-199a/214	1q24	miR-199a-5p, miR-199a-3p and miR-214	Tumor suppressor	Cell lines (SKOV3, A2780) and Human tissue samples	[32]
miR-183/182/96	7q32.2	miR-183, miR-96, miR-182	OncomiR	Cell lines (OVCAR-3, SKOV3) and Human tissue samples	[200]
miR-23a/24—2/27a	19p13.12	miR-23a, miR-24-2, miR-27a	OncomiR	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	OncomiR & Tumor suppressor	Cell lines (OVCAR-3, SKOV3) and Human tissue samples	[201]
miR-106b/25	7q22	miRNA-106b, miR-93, miR-25	OncomiR & Tumor suppressor	Cell lines (OVCAR-3)	[202]
miR-212/132	17p13.3	miR-212, miR-132	Tumor suppressor	Cell lines (SKOV-3, OV2008, A2780)	[79]
miR-221/222	Xp11.3	miR-221, miR-222	OncomiR & 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	Tumor suppressor	Cell lines (SKOV3, A2780) and Human tissue samples	[204]
miR-17/92	13q31.3	miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-92a	OncomiR	Cell lines (SKOV3)	[86]
miR-506/514	Xq27.3	miR-506, -507, —508, —509, —510, —513, miR-514	Tumor suppressor	Cell lines (OVCAR-3, SKOV3, A2780, CAOV3)	[93]
miR-143/145	5q33.1	miR-143, miR-145	Tumor suppressor	Cell lines (A2780, SKOV3, OVCAR-3, ES2 and HO8910) 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 (SKOV3, A2780, OVCAR3 and HO8910) 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	14q32.31	52 miRNAs	OncomiR & Tumor suppressor	Cell lines (OVCAR-3, Caov-3, HO8910, SKOV3, ES2, A2780, SW626) Human tissue samples	[113]
C19MC	19q13.42	46 miRNAs	OncomiR & Tumor suppressor	Cell lines (A2780, CAOV-3, SKOV-3, HO8910, ES-2, OVCAR3) Human tissue samples	[131]

Table 3 miRNAs cluster expression and their target in OC.

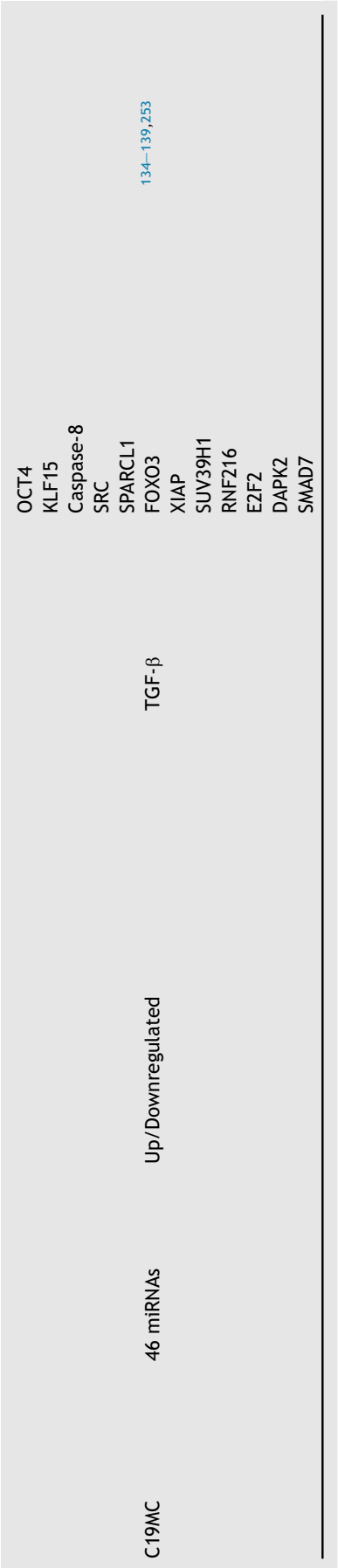
miRNA cluster	miRNAs in cluster	Expression	Regulated by	Signaling pathways	Targets	Reference
miR-200c/141	miR-200c, miR-141	Downregulated	—	EMT NF-κB ZEB1/pSMAD JAK-STAT3	KEAP1 CDH1 SNAI1 ZEB2 KLF12 SIK1 KEAP1	50,52,54,55,208—210
miR-200b/200a/429	miR-200b, miR-200a, miR-429	Upregulated	—	Wnt/β-catenin PI3K/AKT	ING5 PCDH9 PTEN KIAA0101 ZEB1 ATAD2	55—57,59,209—211
miR-199a/214	miR-199a-5p, miR-199a-3p and miR-214	Downregulated	TWIST1 DNMT3 FOXD3	IKKβ/NF-κB PTEN/AKT TGF-β PI3K/AKT CTNNB1	PTEN NF-κB1 DDR1 TGF-β2 ABCG2 Sema 4D	32,66,67,185,195,212,213
miR-183/182/96	miR-183, miR-96, miR-182	Upregulated	DNMT3A Leptin	TGF-β/SMAD4 AKT	SMAD4 PDCD4 BRCA1 MTSS1 HMGA2 FOXO3 CAV1	71—74,214,215
miR-23a/24—2/27a	miR-23a, miR-24-2, miR-27a	Upregulated	—	NF-κB WNT/MAPK WNT/β-catenin	IKKα ST7L DLG2 NANOG OCT4 BCL2 CUL5 FOXO1 HIPK2 BTG1 FBLN5	76—78,216—219
miR-23b/24—1/27b	miR-23b, miR-27b, miR-24-1	Up/Downregulated	—	—	CCNG1 RUNX2 DGCR8 VE- cadherin CXCL1	34,220—223

miR-106b/25	miRNA-106b, miR-93, miR-25	Up/Downregulated	—	PTEN/AKT	RHOC BIM LATS2 PTEN	224—227
miR-212/132	miR-212, miR-132	Downregulated	—	—	SOX4 HBEGF MAP3K3 PEA15 E2F5 BMI1	80—84,228
miR-221/222	miR-221, miR-222	Up/Downregulated	SNAI2	PI3K/AKT Wnt/β-catenin	PTEN BMF APAF1 ARF4 $p27^{Kip1}$ GNAI2 PDCD10	33,153—155,229—232
miR-302/367	miR-367, 302d, 302c-5p, 302c-3p, 302a-5p, 302a-3p, 302b-5p, 302b-3p	Downregulated	—	STAT3 signaling CTNNB1	RUNX1 ATAD2 RAB22A	233,234
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 TRIAP1 IPMK IGFBP-3 YES1 PTEN	88,91,92,196,235,236
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	94—100,237,238
miR-143/145	miR-143, miR-145	Downregulated	—	TGF-β Hippo signaling	SP1 CDK6 MTDH	103—107,239

(*continued on next page*)

Table 3 (*continued*)

miRNA cluster	miRNAs in cluster	Expression	Regulated by	Signaling pathways	Targets	Reference
					TRIM2 TAK1 CSTB	
miR-106a/363	miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2, miR-363	Up/Downregulated	—	Hippo signaling	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 IGFR1 PYGB	243—245
miR-371/373	miR-371, miR-372, miR-373	Up/Downregulated	—	—	LATS2 ATAD2 DKK1 CCNA1 p62 RAB22A	142,156,246,247
miR-379/656	52 miRNAs	Up/Downregulated	—	PI3K/AKT Wnt/β-catenin APK/ERK1/2 NOTCH3 WNT AKT MYC	BAG5 PNAS-105 C16orf72 F-box protein 2 SRM GAPDH RPL41 PRPF6 VIM PAK2 FEN1 TAB1 NOTCH3 PIK3CA PIK3CB ENG CUL4A YY1 NOTCH1 c-MYC FGFR2 CUL4A IGF1R CDCP1 PLAGL2 RAB1A	115—130,248—252



binding protein) in neuronal cells.[79] Subsequently, the expression of miR-212/132 was reported in non-neuronal cells. Abnormal expression of this cluster participates in oncogenesis.[79] 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.[80] In SKOV3 cells, miR-212 by targeting *HBEGF* (heparin binding EGF like growth factor) inhibits cell propagation, migration, and invasion.[81] Forced expression of miR-212 suppressed *PEA15* to inhibit OC cell proliferation via induction of apoptosis.[82] miR-132, when upregulated, halts tumor migration and proliferation via downregulating E2F5.[83] Interestingly, a study reported that the forced expression of miR-132 reversed cisplatin resistance.[84] 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.[85] 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.[86] The members of this cluster participate in pathways, notably cell cycle, tumor cell proliferation, apoptosis, and EMT.[85] 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.[87] 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.[88] 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.[89] miR-20a enhanced tumor development by activating EMT in OVCAR3/DDP cells.[90] 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).[91] 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).[92] Collectively, these data suggest the oncogenic and tumor-suppressive role of miR-17/92 cluster, and the regulation of this cluster could 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.[93] The members of this cluster are usually downregulated and play a tumor-suppressive role in OC. Two studies have shown that the lncRNAs, DQ786243 and MALAT-1 (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.[94,95] Liu and colleagues showed that this miRNA induced senescence and repressed the proliferation of OC cells by targeting CDK4/6-FOXM1 axis.[96] miR-508 suppresses EMT, invasion, and migration through blocking the MAPK1/ERK pathway.[97] This miRNA also targets *CCNA2* (cyclin A2) and *MMP7*, thus inhibiting OC development.[98] 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.[99,100] 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.[101] Members of this MC are reported to regulate genes associated with cell propagation, cell cycle progression, migration, invasion and apoptosis in several cancer types.[102] miR-145 and miR-143 are downregulated in OC tissue samples and cell lines. Downregulation of miR-145 and miR-145/Sp1/CDK6/Pgp/pRb axis is proposed as a key mechanism of chemoresistance in OC.[103] Clinically, low expressions of miR-145 were linked to poor prognosis.[104] Biologically, miR-145 hinders proliferation, migration and cancer dissemination by targeting *MTDH* (metadherin) in HGSOCs (high grade serous ovarian cancer) via p53-miR-145-MTDH axis.[105] 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).[106] Another study proposed that targeting TGF-β/miR-143—3p/CSTB axis can be used for clinical management of OC.[107] 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 intrusion in OC cells by negatively regulating *PTEN*.[108] Increased expression of miR-106a mediated proliferation and differentiation of HGSOC via targeting *p130* (RBL2).[109] This miRNA showed upregulated expression in PTX resistant OC cell lines and reduced *BCL10* and *Caspase-7* expression.[110] Another member of this cluster, miR-18b, whose upregulated expression boosts migratory as well as invasive properties of OC cells by directly targeting *PTEN*.[111] Reduced level of miR-363 was observed in OC cells and tissues. The overexpression of this miRNA resulted in the decreased expression of *NOB1* [NIN1 (RPN12) binding protein-1 homolog], which in turn suppressed tumor growth and proliferation.[112] 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.[113,114] 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.[29] miR-127 is usually downregulated in OC and exerts its tumor-suppressive role by regulating its target gene *BAG5* (BAG cochaperone-5).[115] Many studies have reported the expression of miR-134 to be lower in PTX resistant OC cells.[116—119] A study has reported the role of miR-136 in PTX resistance and identified the oncogene *NOTCH3* as its potential target.[120] miR-370 demonstrates tumor-suppressive nature via regulating *ENG* (endoglin) in endometroid OC.[121] 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.[122] By targeting *c-MYC*, *FGFR2* (fibroblast growth factor receptor 2), *CUL4A* and *IGF1R*, miR-494 impeded OC cell growth, proliferation, and migration.[123—126] 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*.[127] Likewise, miR-376a targets *KLF15* (Kruppel like factor-15) and *Caspase-8* and aids tumor progression.[128] miR-485—5p and miR-539—3p target *SRC* and *SPARCL1* (SPARC like-1) respectively, and promote OC progression.[129,130]

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.[131] C19MC is a primate specific cluster and has been shown to play both oncogenic as well as tumor-suppressive roles.[132] Reduced expression of miR-498 was observed in OC, which in turn is correlated with poor prognosis and OS (overall survival).[133] Ectopic expression of this tumor-suppressive miRNA in OC cells repressed tumor proliferation by targeting *FOXO3* expression.[134] miR-519d targets *XIAP* and suppresses OC cell proliferation and is shown to reduce

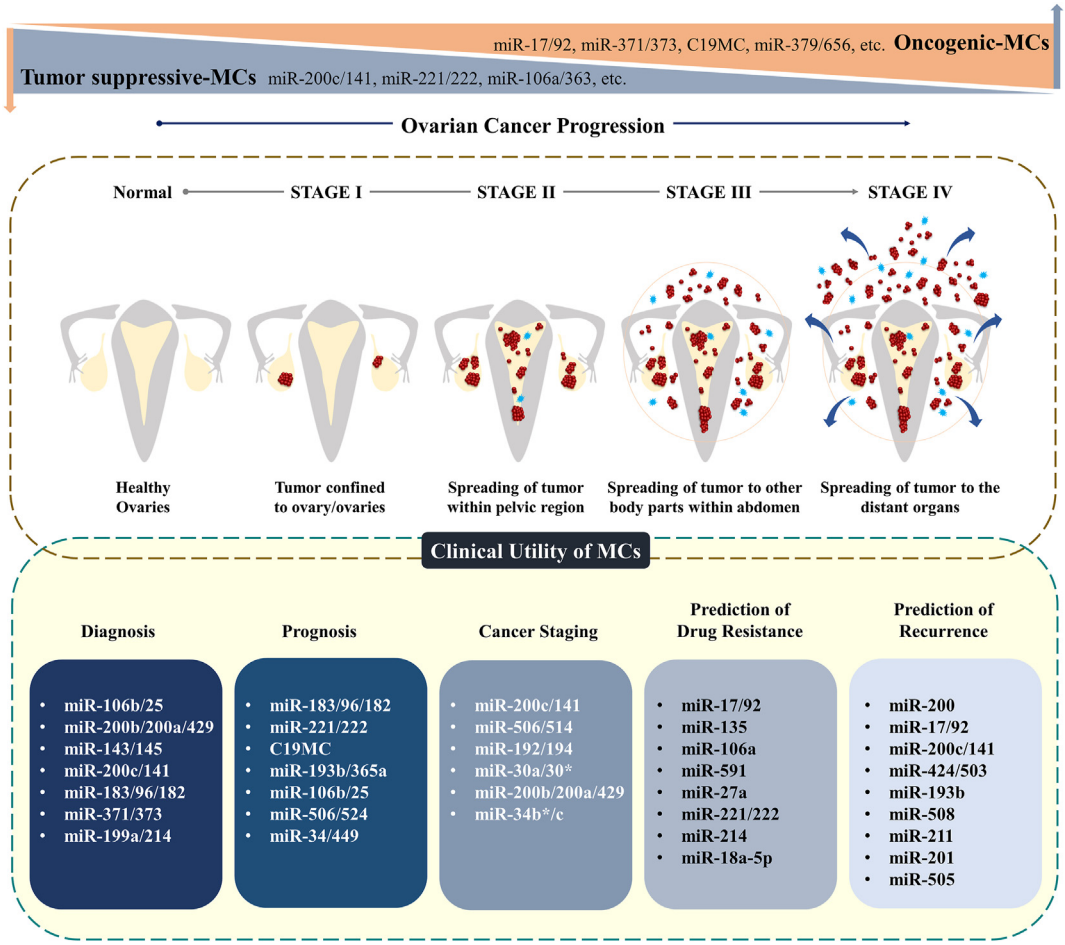


Figure 3 Clinical utility of miRNA cluster expression in OC. Both oncogenic and tumor-suppressive functions of miRNA clusters are reported in OC. Altered expression levels of these miRNA clusters can be used as biomarkers in ovarian cancer diagnosis, prognosis, cancer staging, in the prediction of drug resistance and disease recurrence.

cisplatin resistance.[135] Another miRNA of this cluster, miR-520a-3p, negatively regulates EOC and inhibits tumorigenesis by suppressing *SUV39H1* (suppressor of variegation 39H1).[136] 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.[137] miR-520g and miR-520h were reported to have an oncogenic function in EOC via targeting *DAPK2* (death-associated protein kinase-2) and *SMAD7*.[138,139] 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).[63]

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.[14] 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.[140] 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-200a-c), miR-145 showed a sensitivity of 0.91 [141]. 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.[142] The combination of these miRNAs showed a specificity and sensitivity of 100% and 83%, respectively, to differentiate benign and malignant OCs.[142] 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.[141] 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.[143] 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.[144] Routine diagnostic procedures which include pelvic examination, transvaginal ultrasonography and serum CA125 have failed to detect OC at an early stage.[9] 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.[145] Upregulated miR-30a/30* and miR-192/194 expression was identified as tumor-specific markers for stage I EOC histo-types.[146] The level of miR-200b/200a/429 was elevated in both tissue samples and serum of stage I OC patients.[55] The low chr.Xq27.3 cluster expression in EOC has been reported to be linked with early recurrence in patients with advanced cancer stage.[147] 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.[6,14] 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.[148] The germline mutation in *BRCA1* or *BRCA2* is performed in many countries as a predictive biomarker in OC.[149] 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.[146] 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).[150] 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.[151] 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.[152] 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[63] (Table S1). For instance, Amini-Farsani Z et al suggested that miR-221/222/PTEN/PI3K/AKT axis to have prognostic significance in OC.[153] Increased levels of miR-222 was correlated with good OS,[154] while miR-221 was correlated with poor prognosis[155] 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.[156] 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.[150] 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.[157] 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.[158] 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.[159] The lower miR-422b and miR-34c (miR-34/449) expression levels were concomitant with the reduced disease specific survival in HGSC.[160] 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.[161] 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*.[49] 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.Xq27.3 cluster is linked to early relapse in advanced EOC patients.[147] 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 CD13C3 $^{+}$ 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 (D,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.[175] 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

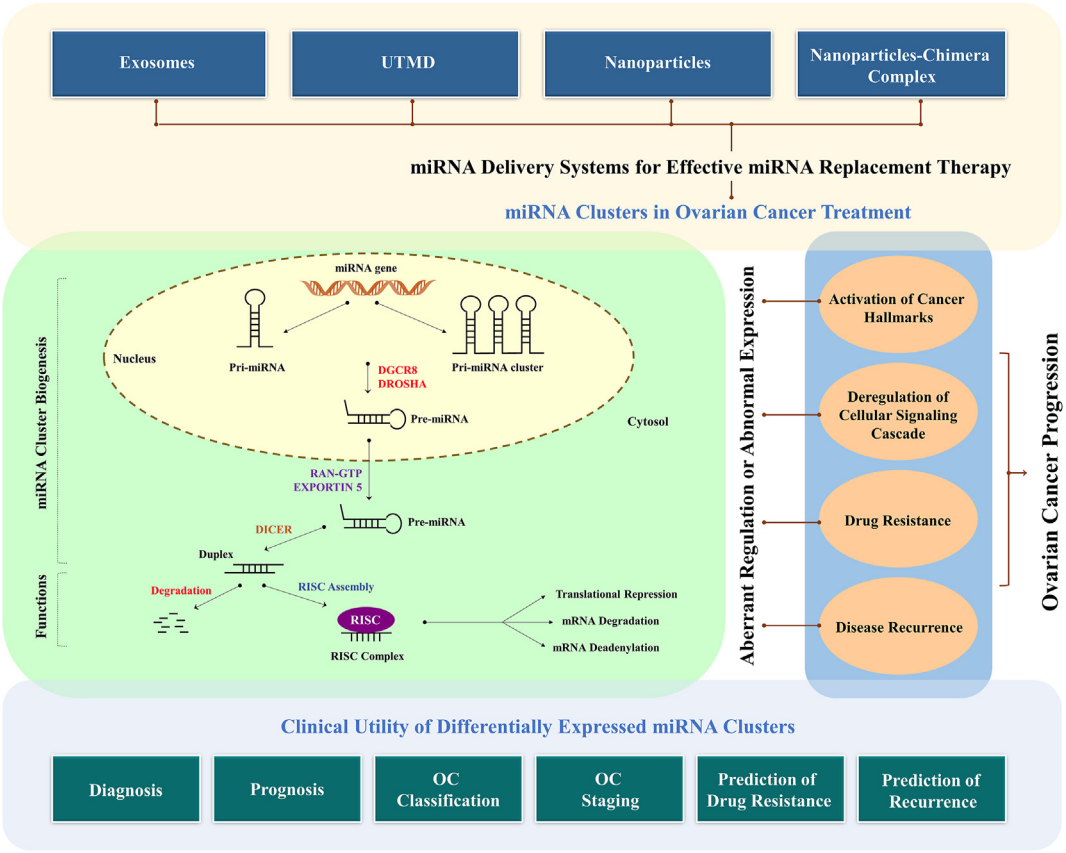


Figure 4 miRNA cluster biogenesis, functions, role in OC progression and their clinical application. Upon getting transcribed from the miRNA gene, pri-miRNAs/pri-miRNA clusters are processed into pre-miRNAs. These pre-miRNAs are then exported to cytosol, wherein they are further processed to form mature 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.

sensitivity suggesting the use of miR-200c restoration along with chemotherapy to improve treatment response in OC subjects.[180] 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

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2021.12.026.

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