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Clinically Relevant microRNAs in Ovarian Cancer

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Abstract

MicroRNAs (miRNAs/miRs) belong to a class of small non-coding RNAs that can negatively regulate messenger RNA (mRNA) expression of target genes. miRNAs are involved in multiple aspects of ovarian cancer cell dysfunction and the phenotype of ovarian cancer cells can be modified by targeting miRNA expression. miRNA profiling has detected a number of candidate miRNAs with the potential to regulate many important biological functions in ovarian cancer, but their role still needs to be clarified, given the remarkable heterogeneity among ovarian cancers and the context dependent role of miRNAs. This review summarizes the data collected from The Cancer Genome Atlas (TCGA) and several other genome-wide projects to identify dysregulated miRNAs in ovarian cancers. Copy number variations (CNVs), epigenetic alterations, and oncogenic mutations are also discussed that impact miRNA levels in ovarian disease. Emphasis is given to the role of particular miRNAs in altering expression of genes in human ovarian cancers with the potential to provide diagnostic, prognostic and therapeutic targets. Particular attention has been given to TP53, BRCA1/2, CA125 (MUC16), HE4 (WFDC2), and imprinted genes such as ARHI (DIRAS3). Better understanding of the abnormalities in miRNA expression and downstream transcriptional and biological consequences will provide leads for more effective biomarkers and translational approaches in the management of ovarian cancer.

Keywords

microRNA; ovarian cancer; biomarker

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CONFLICT OF INTEREST DISCLOSURES

The authors declare no conflict of interest.

INTRODUCTION

In the United States, ovarian cancer is the most lethal gynecologic malignancy in women with 22,240 estimated new cases and 14,030 estimated deaths in 2013 (1). With advances in diagnosis and treatment, 5-year survival has improved significantly over the last three decades, but the overall cure rate remains at 30% (2). Poor outcomes relate to late diagnosis and persistence of dormant, drug resistant cancer cells (2). If we are to improve clinical outcomes, we must take advantage of contemporary technologies to identify the molecular alterations that occur in ovarian cancer and to define the heterogeneity that is observed within and between cancers from different patients. Having identified these changes, we can better develop strategies for earlier diagnosis or more effective therapy.

MicroRNAs (miRNAs) are small non-coding RNAs of 19–25 nucleotides that can modulate gene expression by hybridizing to complementary target mRNAs, resulting in either mRNA degradation or direct inhibition of translation. miRNA can also activate gene expression by interacting with complementary regions found in the promoter and coding region, as well as the 3'UTR of mRNA targets (3). Expressed miRNAs provide a novel layer of regulation for human gene expression and play important roles in diverse biological processes (4) including carcinogenesis (5). Alterations in miRNAs have been detected in human ovarian cancers (6). The Cancer Genome Atlas (TCGA) project has recently published an integrated analysis of nearly 500 high-grade serous ovarian cancers that clearly documents multiple changes in miRNA levels (7). In this review, we focus on changes in miRNA expression in ovarian cancers and their potential application for earlier detection, more accurate prognostication and more effective treatment of the disease. Several miRNAs are predicted to regulate a number of clinically relevant genes in ovarian cancer such as *MUC16* (CA125), *WFDC2* (HE4), and several imprinted tumor suppressor genes such as *DIRAS3* (ARHI) that are downregulated in ovarian cancer.

Dysregulation of miRNAs has been detected by miRNA profiling of ovarian cancers

Several studies have compared expression of miRNAs in ovarian cancers to whole normal ovaries, primary ovarian surface epithelial cells (OSE) and immortalized OSE (8–11). Among these reports, 310 dysregulated miRNAs in ovarian cancers have been reported. Of these 310 miRNAs, 34 miRNAs were found to be consistently dysregulated in ovarian cancers from at least three independent studies (Table 1.1 and Table 1.2) (8, 9, 12–15). Several miRNAs that regulate growth in other cancer types are downregulated in ovarian cancers (Table 1.1 and Table 1.2), including let-7a/b/d/f, miR-31, miR-34abc, miR-125b, and miR-127. Other oncogenic miRNAs such as miR-20a, miR-23a/b, and miR-200b/c are up-regulated in ovarian cancers (Table 1.1 and Table 1.2).

High grade serous ovarian cancers exhibit distinctive changes in miRNA expression

Ovarian cancers are remarkably heterogeneous at the cellular and molecular level and can be divided into type I low-grade and type II high-grade cancers based on histologic appearance and molecular profile. More than 70% of ovarian cancer related deaths occur in patients with advanced stage, high grade serous ovarian cancer (7). High grade cancers are characterized by multiple copy number abnormalities, *TP53* mutation and epigenetic changes. When

alterations in BRCA1 and BRCA2 occur, they are most frequently associated with high grade serous ovarian cancers.

Mining the TCGA data, Miles et al identified seventeen miRNAs that were dysregulated in high grade serous cancers when compared to normal ovarian samples, including eight up-regulated miRNAs (miR-183-3P, miR-15b-3p, miR-15b, miR-590-5p, miR-18a, miR-16, miR-96, and miR-18b) and nine down-regulated miRNAs (miR-140-3p, miR-145-3p, miR-143-5p, miR-34b-5p, miR-145, miR-139-5p, miR-34c-3p, miR-133a and miR-34c-5p) (16). In other reports that compared miRNA expression in ovarian cancers and normal ovarian tissues (17–19), five miRNAs were down-regulated (miR-140-3p, miR-143-5p, miR-34b-5p, miR-34c-5p and miR-145) and three were up-regulated (miR-96, miR-15b and miR-16) and these were among the top ten miRNAs from TCGA data listed in Table 1.1 and Table 1.2. These miRs could well contribute the pathogenesis of high-grade serous ovarian cancers, but their dysregulation needs to be confirmed in larger data sets and their functional roles need to be elucidated. Use of whole normal ovaries as a control in profiling is problematic. As epithelial cells comprise the majority of cells within a cancer but only a small subpopulation among cells within the normal ovary, apparent differences in miRNA expression could reflect differences in miRNA profiles between normal epithelial cells, granulosa-theca cells and germ cells. Epithelial cells that cover the ovary or that line the fallopian tube would provide more relevant as a control.

Copy number alterations regulate miRNAs

One of the characteristics of ovarian cancer is genomic instability (7). Chromosomal abnormalities are common in high grade serous ovarian cancers, as are alterations in DNA copy number (8). Overall, about 50% of miRNAs are found at fragile sites of chromosomes, as well as at the minimal regions of deletion, amplification or common chromosome breakpoints associated with different cancers (20). Chromosome abnormalities that involve miRNAs are not random events (4). Alterations of DNA copy number could account for much of the miRNA dysregulation in ovarian cancers (21). Through a high-resolution array-based genomic hybridization study of 227 human cancer samples, Zhang et al found that certain genomic loci containing miRNA genes were frequently altered in human ovarian cancers, breast cancers and melanomas (22). There were 26 miRNAs consistently associated with copy number gains and 15 miRNAs consistently associated with copy number losses in all three-cancer types (22). Down-regulation of eight potential tumor suppressor miRNAs (miR337, mir376a, miR376b, miR432, miR368, miR495, miR377 and miR410) mapped to a deletion in chromosome 14 (Dlk1-Gtl2 domain) and correlated with poor survival in epithelial ovarian cancer (23). Furthermore, the positive correlation between copy number and dysregulation of five miRNAs has been repeatedly confirmed by a number of studies involving miR-31 in 9p21; miR-93 in 7q22.1; miR-182 in 7q32.2; and miR-200b/429 in 1p36 (Fig. 1) (10, 21, 22, 24).

In the TCGA data, several miRNAs are located in amplified or deleted genomic regions (25). Downregulation of let-7b is related to recurrent hemizygous genomic loss (86% of samples) and homozygous deletion (7% of samples). miR-31 is another frequently deleted miRNA. By contrast, miR-30 family members, located at two different focally amplified

loci (8q24 and 1p34), are the most frequently amplified miRNAs, and copy number correlates with the expression of mature miRNA (25). Creighton et al computed the correlation between miRNA and its host gene expression and indicated that miRNA-host gene pairs tended to be highly correlated with each other, with 52% of the miRNA-host gene pairs showing significant positive correlation (25). *Cyclin E1 (CCNE1), Notch3, HBXAP/Rsf-1, AKT2* and *PIK3CA* are among the most frequently amplified genes in high grade serous ovarian cancer (26). No known miRNA is found within 2Mb downstream of *CCNE1, HBXAP/Rsf-1* or *PIK3CA*. Downstream of *Notch3*, however, miR-23a (19p13, negative strand, −13947483:−13947389) has been shown to be consistently up-regulated in ovarian cancers in different studies (11). MiRNA-641 (19q13.2, negative strand, −40788533: −40788510) is located near the amplicon that contains *AKT2*, but miRNA-641 is not overexpressed in high grade serous ovarian cancers.

Epigenetic alterations regulate miRNAs

In addition to copy number changes, Iorio et al found that miR-21, miR-203, and miR-205 were overexpressed in ovarian cancers and that levels could be further increased in the ovarian cancer cell line OVCAR3 by incubation with the demethylating agent 5-aza-2-deoxycytidine (5-AZA), suggesting that these miRNAs might be regulated by methylation (18). Zhang and colleagues treated five ovarian cancer cell lines with 5-AZA and a histone deacetylase inhibitor 4-phenylbutyric acid and found that 16 of 44 (36.4%) miRNAs down-regulated in advanced stage ovarian cancer could be restored using these drugs (21). Recently, the hypermethylation of tumor suppressor mir-34a and mir-34bc has also been confirmed in ovarian cancer patients with decreased mir-34 (19, 24). Thus, epigenetic alteration is also an important mechanism for miRNA dysregulation.

TP53 regulates miRNAs

TP53 mutation is found in at least 96% of high grade serous ovarian cancers and can regulate miRNAs. As the miRNA-34 family is upregulated by wild type TP53, expression of miRNA 34a was decreased in 100% and 34b and 34c in 72% of cancers with *TP53* mutation (17). In addition to genomic deletion, *TP53* mutation may also be responsible for the underexpression of miR-31 (10).

miRNAs can downregulate BRCA1 and BRCA2 expression

Approximately 15% of ovarian cancer patients have a strong family history associated with germ line mutations of *BRCA1, BRCA2*, mismatch repair genes or, on rare occasions, *TP53* (27). While mutations of *BRCA1* and *BRCA2* can affect gene expression profiles, at least one study found that a fraction of high grade serous ovarian cancers exhibited *BRCA1/2* associated abnormalities in the absence of mutation (17). miRNAs can downregulate wild-type BRCA1 expression. A G to C polymorphism (rs2910164) in the miR-146a precursor leads to mismatch in its stem region. This variant allele can increase miR-146a expression as well as the binding capacity between miR-146a and the 3'-untranslated region (UTR) of *BRCA1*. Thus, miR-146a can bind to the 3'-UTRs of *BRCA1* and *BRCA2* mRNAs and potentially modulate their expression. The rs2910164 polymorphism of miR-146a may

affect the age of cancer onset. Patients who had at least one miR-146a variant allele were diagnosed at a younger age than women without a variant allele (28).

Low grade serous ovarian cancers exhibit distinctive changes in miRNA expression

Only 10% of ovarian cancers are low grade. Clinically, these cancers grow slowly and present in early stage, but are not as responsive as high grade cancers to platinum and taxane based therapy (29). More than half of low grade serous ovarian cancers are associated with mutations of *KRAS*, and smaller fractions exhibit mutations of *BRAF*, *PTEN* and *PIK3CA* (2). Less than 20 miRNAs differ in expression between low grade and high grade serous ovarian cancers (17). By analyzing the miRNA profiles of the NCI-60 panel of 60 human cancer cell lines, Patnaik et al found that mutation of *BRAF* and *PTEN* affects miRNA expression, but mutation of *KRAS* did not (30). Among the miRNAs related with mutant *BRAF*, 4 miRNAs (miR-509-3p, miR-30d, miR-30b-3p, miR-30b) have been reported to be upregulated in low grade serous ovarian cancers, when compared to normal fallopian tube (17). The $BRAF^{V600E}$ mutation can increase MAPK signaling, lead to higher levels of mature miRNAs and enhance miRNA processing in undifferentiated pleomorphic sarcoma (31), but its role in low grade serous cancer still needs to be explored. *PTEN* mutation is responsible for downregulation of miR-29b and miR-769-3p in cancer cell lines, *PIK3CA* mutation has not yet been linked to any change in miRNA expression.

Dysregulation of miRNAs and predicted targets tend to be anti-correlated in ovarian cancer gene expression

The function of miRNAs is determined by the genes and signaling pathways regulated by each miRNA. Having assembled the published transcriptome profiling data in ovarian cancer, we have integrated the results from both miRNA and transcriptome profiling to identify genes that are regulated by miRNAs. A number of differentially expressed genes in ovarian cancers have been reported (32). Approximately 200 miRNAs were anti-correlated with the 186 most differentially expressed genes using the miRNA algorithm Targetscan (http://www.targetscan.org/ Release 5.1 Apr 2009) (Table S1 and Table S2). Among these 186 genes, ten differentially expressed genes have been reported in at least two independent studies (33, 34). These ten gene changes are thought to associate with ovarian cancers and are summarized in Table 2 along with their potential regulating miRNAs. Three pairs of miRNA/mRNA association are of particular interest: 1) downregulation of tumor suppressor gene *ID4* and miR-203 upregulation in ovarian cancers; 2) *BCAT1* upregulation and downregulation of let-7, miR-125b & miR-155; and 3) *SERPINE1* upregulation and miR-152 downregulation (Fig. 2). ID4 has a regulatory loop with another tumor suppressor *BRCA1*, which enables appropriate normal cycling during cell division. There is a modestly correlated downregulation between *BRCA1* and *ID4* (35). The BRCA1–ID4 regulatory loop might be disrupted in many breast and ovarian cancers (35). Upregulation of miR-203 may be responsible for this disruption. Since downregulation of *ID4* has been indicated as a potential biomarker of recurrence in breast cancer (36), both *ID4* and miR-203 might serve as disease biomarkers in ovarian cancers as well.

BCAT1 is a direct target of *c-myc*, which is important in oncogenesis and amplified in a fraction of ovarian cancers (37). The let-7 family also performs a tumor suppressor role in

many cancer types including ovarian cancers. MiR-125b is a putative tumor suppressor in ovarian cancers and can suppress cancer proliferation by targeting *BCL3* (15). Although miR-155 levels are increased in B cell lymphoma (38), miR-155 has been consistently down-regulated in ovarian cancers with a potential tumor suppressor role in targeting *BCAT1*. *SERPINE1* (also known as *PIA-1*) is an inhibitor of fibrinolysis and involved in tumor cell invasion and metastasis. MiR-152 is down-regulated in hepatocellular and gastric carcinomas, and acts as a tumor suppressor by targeting *DNMT1* (39). In ovarian cancers, miR-152 might serve as a tumor suppressor by targeting *SERPINE1* based on predictions of the Targetscan algorithm.

miRNAs regulate ovarian cancer-associated imprinted genes

Genomic imprinting represents another level of regulation in gene expression where one allele of each autosomal gene pair is preferentially silenced depending upon its parent-of-origin, leaving only a single functional allele. Disruption of imprinted gene expression is linked to the initiation of malignancy (40). Of the candidate imprinted genes identified to date, four tumor suppressor genes including *ARHI* (*DIRAS3*), *LOT1* (also known as *PLAGL1/ZAC1*), *PEG3*, and *NDN* are consistently down-regulated in ovarian cancers (2, 41). A Targetscan algorithm predicted that there are 53 miRNAs with poorly conserved binding sites in the 3' UTR of *ARHI*, 2 conserved sites in *PEG3*, 15 conserved sites in *PLAGL1*, and 4 conserved sites in *NDN*. As shown in Fig. 3, ARHI-targeting miR-203 and miR-194, PLAGL1-targeting miR-15a/16 and miR-23a/b, and NDN-targeting miR200b/c/429 have been reported to be overexpressed in ovarian cancers (9–11, 17, 18, 42, 43). Among these miRNAs, miR-194 and miR-23a/b are overexpressed in a number of human cancers (44, 45). *NDN*-targeting miR200b/c/429 is associated with decreased progression-free survival and overall survival in ovarian cancer patients (43). ARHI-targeting miR-203 and *PLAGL1*-targeting miR-15a/16 have been reported as putative tumor suppressors in other cancer types (46). MiRNA-221 and 222 are also predicted to target *ARHI* and their negative regulation effects on *ARHI* gene has been confirmed in prostate cancer cells (47). However, dysregulation of miR-221 and 222 in ovarian cancers has not been observed in all studies (8, 10, 11, 18, 21, 42, 43). In addition, *ARHI*-targeting miR-371 and miR-181b/c are reported to be overexpressed in chemo-resistant biopsies and cell lines (48). MiRNA can be imprinted in normal physiological development and in oncogenesis (49).

miRNAs may serve as biomarkers and also regulate levels of protein biomarkers

Detection of altered levels of miRNA dysregulation in blood, serum and tumor-derived exosomes of cancer patients might provide biomarkers for early detection (50). Among the consistently dysregulated miRNAs in ovarian cancers listed in Table 1.1 and Table 1.2, two down-regulated miRNAs, let-7 family and miR-155, and five up-regulated miRNAs, miR-15/16 cluster, miR-20a, miR-92, miR-203 and miR-205 are found in the peripheral circulation of patients with ovarian cancers and represent promising biomarkers for early diagnosis (50). The miR-15/16 cluster, miR-20a, and miR-205 were also identified as the top ten up-regulated miRNAs in the TCGA data set (Table 1.1 and Table 1.2) (7).

CA125, also known as *MUC16*, is a well-characterized biomarker that is used to monitor the progression and regression of epithelial ovarian cancer (51). The complete sequence of the cDNA-encoding *MUC16* has been determined (52). Based on our *in silico* analysis of the TCGA data base and literature reports, a number of miRNAs could potentially regulate the *MUC16* gene (Table 3). Several miRNAs in this list have already been shown to be low in cancers. For example, miR-9 and miR-584 are downregulated in ovarian cancers when compared to normal ovary (18, 42, 53). miR-124 and miR-637 were also downregulated in ovarian cancer cell lines compared to IOSE (18, 21). If miRNAs in Table 3 are true regulators of *CA125*, down-regulation of these miRNAs could be one of mechanisms that lead to abnormal CA125 levels in ovarian cancers and could be potential biomarkers along with CA125 for patients with ovarian cancers.

Additionally, the *Notch3* amplicon is located upstream of the *CA125 (MUC16)* gene on Chromosome 19, in high grade serous ovarian cancer.(26) In addition to miR-23a mentioned above, several miRNAs, including miR-27a (−13947342:−13947241), miR-24-2(−13947183:−13947089), miR-199a-1 (−10928182:−10928090) and miR-1181 (−10514225:−10514121) map between *Notch 3* and the *CA125 (MUC16)* gene (Fig. 3). miR-1181 increased serially in blood samples from patients diagnosed with relapsed ovarian cancers (22 serous and 2 endometrioid) when compared to age- and sex-matched volunteers without a history of cancer. So far, there is no report that links these miRNAs with CA125 levels.

Human epididymis secretory protein 4 (HE4) is a member of a family of whey acidic four-disulfide core proteins (*WFCD2*) that are secreted at high levels by normal endometrium and by endometrial and epithelial ovarian cancers. HE4 overexpression in ovarian cancers has been confirmed through microarray studies (54). Gene therapy targeting the promoter of *HE4* can reduce the xenograft growth, block primary and metastatic tumors and prolong life span of mice with ovarian cancer (55). The HE4 ELISA assay has been shown to have a potential advantage over the CA125 assay in that it is less frequently positive in pre-menopausal women with non-malignant gynecologic conditions.(56) HE4 protein can also provide a useful biomarker in a small fraction of ovarian cancers that have little or no CA125 expression (57). A predictive model - ROMA (Risk of Ovarian Malignancy Algorithm) - utilizes the combination of HE4 and CA125 to triage patients with pelvic masses to gynecologic oncologists (58). The *HE4* gene is located at 20q12-q13.2 without any known miRNAs that map within or near this region. After analysis with the Targetscan algorithm, seven miRNA binding sites were found in the 3'-UTR of the *HE4* gene. Among these miRNAs, miR-140-5p and miR-409-5p are downregulated in ovarian cancers (Fig. 3) (9, 11). These two miRNAs that regulate the HE4 gene might serve as candidate miRNA biomarkers for detecting or monitoring ovarian cancers.

miRNAs might serve as potential prognostic biomarkers

Based on currently available data, some miRNAs have the potential to be prognostic biomarkers for ovarian cancer. Overexpression of miR-200 family members and miR-519a, under-expression of let-7 family members and miR-153 have been linked to a poor prognosis of patients with ovarian cancers (42, 43, 59). Under-expression of a tumor

suppressor miR-9 in recurrent ovarian cancers is reported as a signature for recurrence (42). Low expression of miR-31 in ovarian cancers could also be an indicator for earlier disease recurrence and metastasis. Upregulation of miR-15a, miR-21 and miR-92 has been reported to signal recurrent disease. Let-7 family members have also served as prognostic biomarkers in ovarian cancer (43). Downregulation of miR-34a/b/c, miR449b, miR-503 and miR-507 has been observed in late stage and high grade ovarian cancers (17, 21, 24). However, at the present time the mechanism that underlies the change in the expression of miRNA in ovarian cancer recurrence and metastasis remains elusive.

miRNAs can provide predictive biomarkers for response or lack of response to treatment

miRNAs have been implicated in the initiation, progression, metastasis and chemoresistance of cancers at different sites. In theory, targeting miRNAs could provide a therapeutic strategy. Transfection of paclitaxel-resistant A2780 ovarian cancer cells with miR-27a inhibitors has been reported to reduce the expression of MDR1 mRNA and P-gp protein, to increase HIPK2 protein expression, and to enhance paclitaxel sensitivity (60). Exogenous expression of miR-31 has been shown to inhibit proliferation and induce significant p53-independent apoptosis in ovarian cancers (10). Considering that virtually all high-grade serous ovarian cancers exhibit p53 deficiency, miR-31-based therapy might be particularly effective in this subset of ovarian cancers (10). miR-152 and miR-185 can increase cisplatin sensitivity ovarian cancer in vitro and in vivo by targeting *DNMT1* (61).

miRNAs could provide targets for therapy

miRNA mimics, adenovirus-associated vectors that express miRNAs, miRNA masks and miRNA sponges, are being developed to modulate the gain or loss of miRNA function (62). Many miRNA targets have been identified. Among the most consistently deregulated miRNAs in ovarian cancers are listed in Table 1.1, Table 1.2 and in Fig. 2 & 3. Targeting miR-203 may restore both the *BRCA1–ID4* regulatory loop and expression of ARHI in ovarian cancers. Delivery of let-7, miR-125b, miR-155 and miR-152 might suppress tumorgenesis and metastasis by targeting *BCAT1* and *SERPINE1* (Table 1.1, Table 1.2 and Fig. 2). Additionally, about 50 dysregulated miRNAs have been linked to chemo-resistance or chemo-sensitivity to taxanes or platinum compounds (48). Overexpression of miR-27a and miR-514 and downregulation of let-7e have been related to development of resistance to taxanes and/or platinum. MiR-214 expression can induce platinum resistance by affecting PTEN function (63). Conversely, the upregulation of miR-378 and miR-625 has correlated with sensitivity to platinum based therapy.

Conclusions

Epithelial ovarian cancers are remarkably heterogeneous and this heterogeneity is reflected in dysregulation of multiple miRNAs. Different miRNA profiles are observed in high grade and in low grade cancers. miRNAs can be regulated by abnormalities in DNA copy number, methylation, histone acetylation and mutation in *TP53*. In turn, miRNAs can regulate *BRCA1, BRCA2* and imprinted tumor suppressor genes such as ARHI (DIRAS3), Loss of certain miRNAs may upregulate ovarian cancer biomarkers such as CA125 (MUC16) and HE4 (WFCD2). Altered levels of miRNAs may also serve as potential biomarkers for

detecting, monitoring, estimating resectability, determining prognosis and predicting response to conventional therapy. As methods are developed to manipulate miRNAs in the clinic certain miRs may also serve as targets for therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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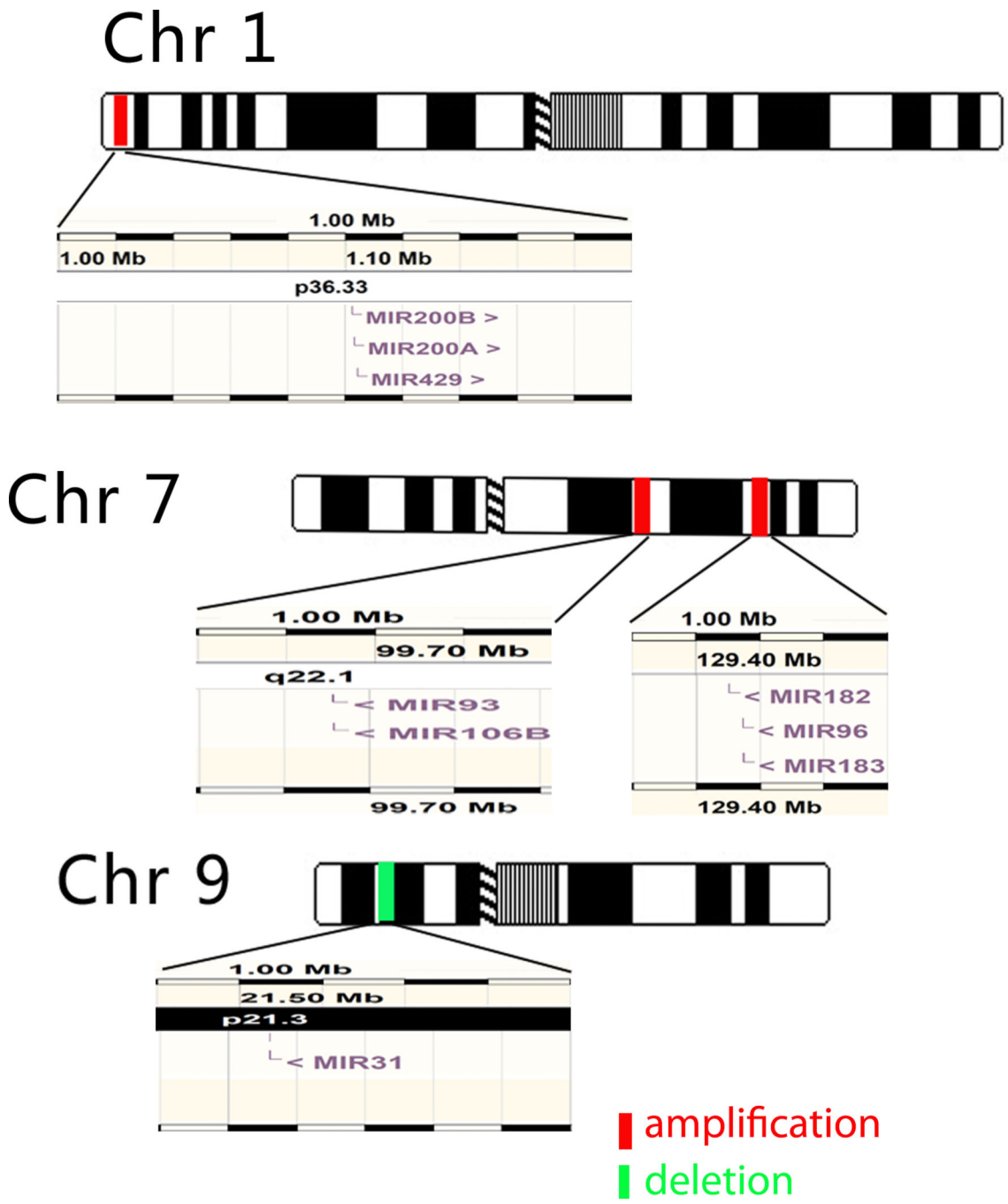

Fig 1.

Positive correlation between DNA copy number and dysregulation of miRNAs. The up-regulated miRNAs mir-200b/429, mir-93 and mir-182 are located on 1p36, 7q22.1, in 7q32.2, respectively. These regions are amplified in some ovarian cancers. mir-31 is located in a deleted region 9p21.3. A positive correlation between the alteration of copy number and the miRNAs listed above has been confirmed. The diagrams for miRNA genomic location come from http://www.ensembl.org.

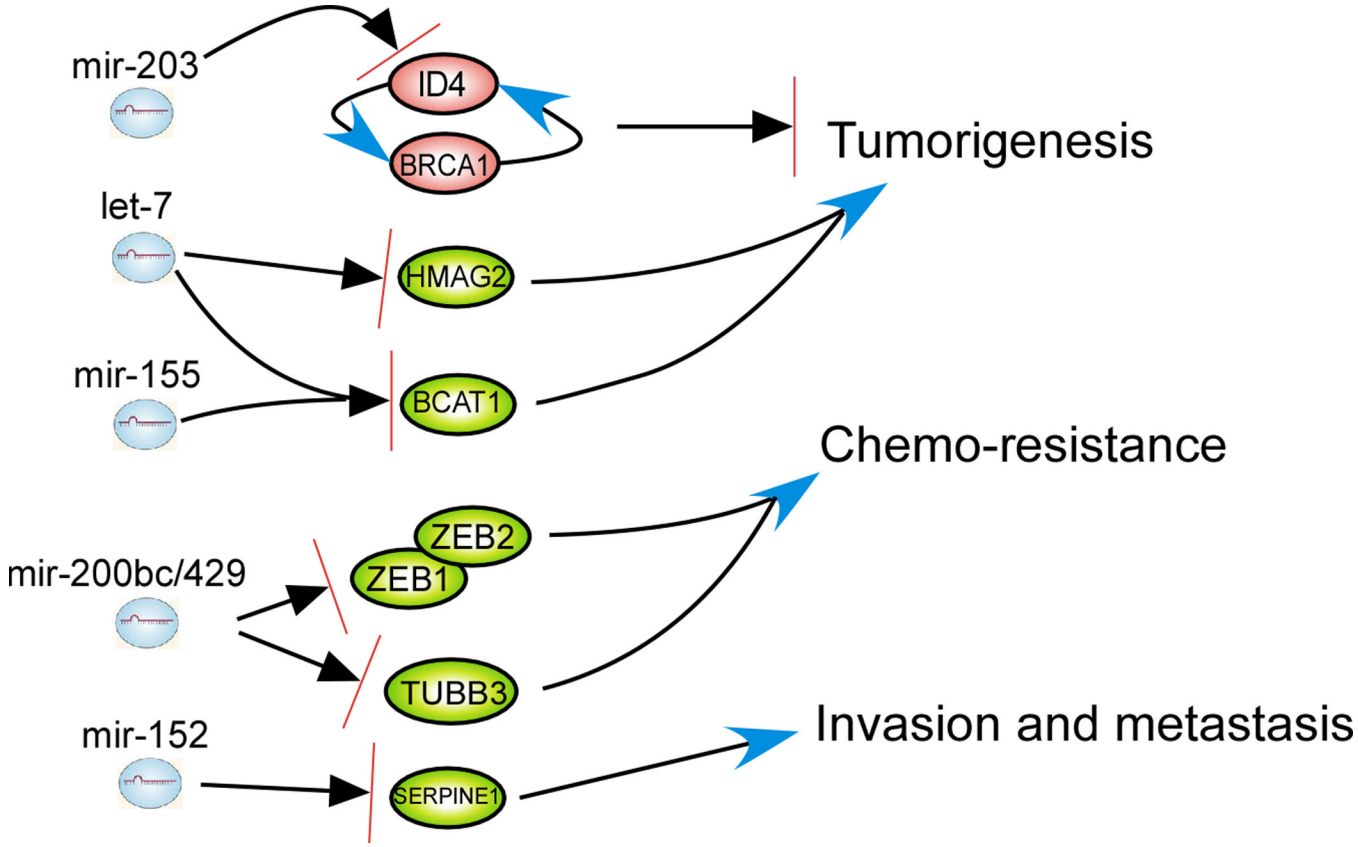

Fig 2.

Potential function of dysregulated miRNA in ovarian cancers. Upregulation of mir-203 can inhibit the expression of ID4, disrupting the BRCA1–ID4 regulatory loop, which assures appropriate cycling of expression for both genes during normal cell division. Down-regulated let-7 family and mir-155 expression may be responsible for the overexpression of the oncogene BCAT1, a direct target of c-Myc. Low levels of let-7 also induce upregulation of embryonic genes such as HMAG2. These are also important in oncogenesis. Downregulation of ZEB1/2 and TUBB3 by mir-200b/c and 429 can increase sensitivity to paclitaxel of ovarian cancer cells. mir-152 may play a potential tumor suppressor role by targeting SERPINE1, an inhibitor of fibrinolysis, involved in tumor cell invasion and metastasis. An arrow indicates activation and an arrow with bar indicates inhibition.

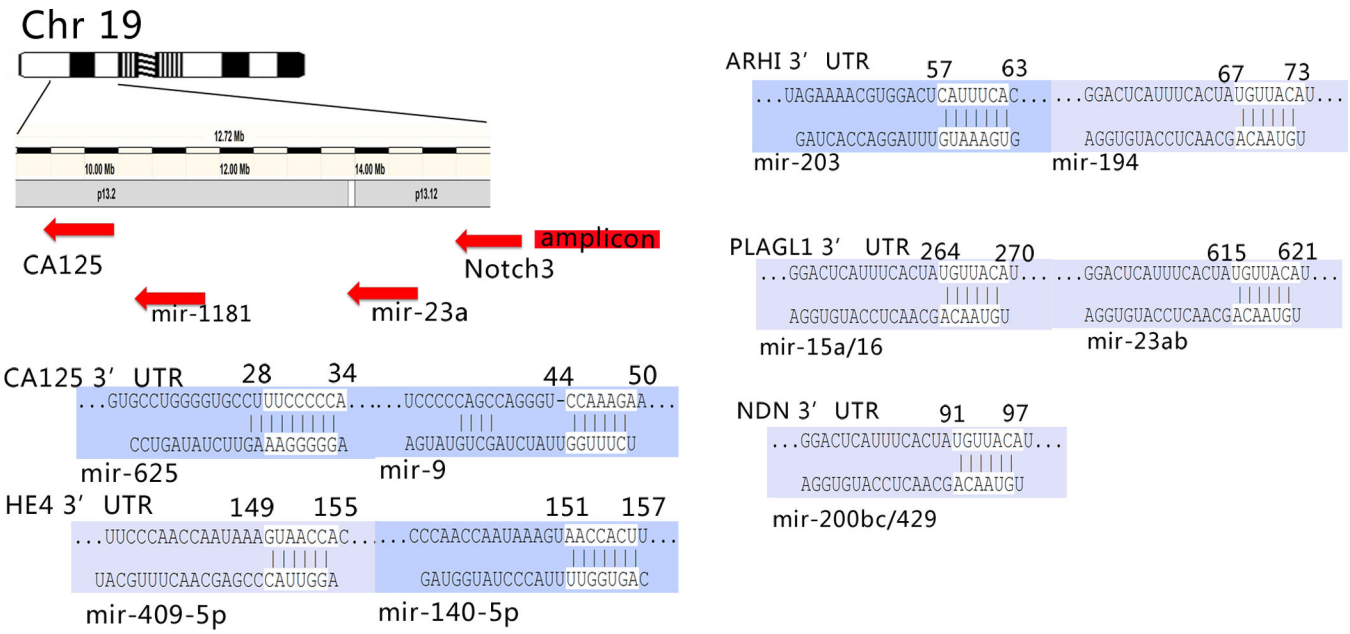

Fig 3.

Predicted interaction of dysregulated miRNA and protein coding genes. CA-125 and HE4 are well characterized ovarian cancer biomarkers. An amplicon upstream of CA125 in Chr19 is responsible for the overexpression of the oncogene Notch3. mir-23a, mir-27a, mir-24-2, mir-199a-1 and mir-1181 are located between Notch 3 and CA-125, mir-23a has been reported to be up-regulated in different studies. Also shown are the predicted binding sites of dysregulated miRNAs in the 3' UTR of imprinted tumor suppressor genes. The annotation for the binding sites is taken from www.tagetscan.org.

Table 1.1

Consistently deregulated miRNAs in ovarian cancers.

miRNAs	Alteration	Counterpart	Effect	Mechanism of Deregulation	Targets	Associated References
Let-7a/b/d/f	Down-regulated	HOSE, IOSE, ovary, fallopian tube from fimbriated end	tumor suppressor	promoter methylation, copy number variations	*KLK10*, HMAG2	10,11,16,17,20,42,62,63
miR-22		HOSE	tumor suppressor		*ARRB1*, *CLIP2*, *EVI1*,*FRAT2*, *EDC3*	8–10, 17, 20
miR-31		HOSE	tumor suppressor	copy number variations	*E2F2*, *STK40*, *CEBPA*	9, 10
miR-34a/b/c		IOSE, ovary, fallopian tube from fimbriated end	tumor suppressor	promoter methylation, copy number variations and p53 mutation	*MET*, *CDK4*	16, 17, 20, 23, 63
miR-125b		HOSE, IOSE, ovary, fallopian tube from fimbriated end	putative tumor suppressor		*BCL3*, *VEGF*, *HIF-1a*, *HER3*	10, 14, 16, 17, 41, 42, 62, 65
miR-127-3p		HOSE, NOSE, ovary, serum	related to drug-resistant	imprinting, copy number variations, promoter methylation		8, 10, 17, 20
miR-152		HOSE, IOSE, fallopian tube from fimbriated end	putative tumor suppressor	promoter methylation		9, 10, 16, 20
miR-155		IOSE, blood, serum	putative tumor suppressor			20, 63
miR-181a-3p		HOSE, ovary, blood		copy number variations, promoter methylation		10, 17
miR-382		HOSE		copy number variations, promoter methylation		8–10

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Table 1.2

Consistently deregulated miRNAs in ovarian cancers.

miRNAs	Alteration	Counterpart	Effect	Mechanism of Deregulation	Targets	Associated References
miR-15a/16	Up-regulated	HOSE, fallopian tube from fimbriated end		promoter methylation	*Bmi-1*	7–10, 13, 16, 41, 42
miR-20a		HOSE, fallopian tube from fimbriated end	oncogenic miRNA		*APP*	8, 9, 16, 42, 66
miR-23a/b		ovary		copy number variationspromoter methylation		7, 41, 42
miR-30a/b/c		HOSE, IOSE, fallopian tube from fimbriated end	related to drug-resistant	copy number variations	*AVEN*, *GALNT1*	8–10, 16–17, 41
miR-92		HOSE, fallopian tube from fimbriated end	putative oncogenic miRNA			8–10, 16, 41
miR-93		ovary	putative oncogenic miRNA	copy number variations, promoter methylation		41, 42
miR-106a		HOSE, fallopian tube from fimbriated end	putative oncogenic miRNA			7, 10, 16, 41
miR-146b		HOSE, IOSE, fallopian tube from fimbriated end	putative oncogenic miRNA	copy number variations		16, 63
miR-182		HOSE, IOSE, ovary fallopian tube from fimbriated end	putative oncogenic miRNA(67)	copy number variations, promoter methylation	*PDCD4*	7–8, 16–17, 20, 68
miR-200		HOSE, ovary fallopian tube from fimbriated end	oncogenic miRNA	copy number variations	*ZEB*, *c-Myc*, *TUBBIII*, *FN1*, *NTRK2*, *QKI*	7, 10, 12, 16, 17, 42, 62, 69

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miRNAs	Alteration	Counterpart	Effect	Mechanism of Deregulation	Targets	Associated References
miR-203		HOSE, ovary fallopian tube from fimbriated end		promoter methylation		9–10, 16–17
miR205		HOSE, ovary fallopian tube from fimbriated end	putative oncogenic miRNA	promoter methylation		10, 16–17
miR-223		HOSE	putative oncogenic miRNA		*SEPTIN6, MMP9, USF2*	9–10, 41

Table 2

Ten consistently deregulated genes and their regulating miRNAs in ovarian cancers

Genes	Gene ID	Alteration	Description	Effect	Regulating miRNAs	Associated References
CLU	1191		clusterin	chemoresistance, prognosis		70, 71
ID4	3400	down	inhibitor of DNA binding 4, dominant negative helix-loop-helix protein	oncogenesis	miR-203	72
BCAT1	586		branched chain amino-acid transaminase 1, cytosolic	chemo-resistance, oncogenesis	let-7, miR-125b, miR-155	36, 73
FN1	2335		fibronectin 1	chemoresistance, prognosis		74
MAL	4118		mal, T-cell differentiation protein	chemoresistance, prognosis		31–32
SERPINE1	5054	up	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	invasion and metastasis	miR-152	33
SERPINA5	5104		serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5	putative tumor suppressor		75
SOX17	64321		SRY (sex determining region Y)-box 17			
TOP2A	7153		topoisomerase (DNA) II alpha 170kDa	chemoresistance		73
THBS2	7058		thrombospondin 2	metastasis		33

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Table 3

Putative CA125-targeting miRNAs in ovarian cancers

miRNAs	Chromosome Location	Targets	Deregulation in cancers	Potential link with chromosome abnormality in ovarian cancer
miR-9-2	5q14.3	*CA125, NFkB*	Down-regulated	Yes, deletion of 5q14 tumor suppressor loci
miR-9-3	15q26.1	*CA125, NFkB*	Down-regulated	Yes, deletion of 15q26 region
miR-124-1	8p23.1	*CA125, EZH2*	Down-regulated	Yes, deletion of 8p23 region
miR-324-3p	17p13.1	*CA125*	NA	Yes, LOH of 17p13 region
miR-544	14	*CA125, cMYC*	NA	Yes, loss of 14q region
miR-584	5q32	*CA125, Rock1*	Down-regulated	Yes, loss of 5q32 region
miR-625	14q23.3	*CA125*	NA	Yes, loss of 14q region
miR-637	19p13.3	*CA125, LIF*	Down-regulated	Yes, LOH of 19p13 region