

Role of DNA methylation and non-coding RNAs expression in pathogenesis, detection, prognosis, and therapy-resistant ovarian carcinoma (Review)

VICTOR M. DEL CASTILLO FALCONI¹, JENNY A. GODINEZ RODRIGUEZ²,
VERÓNICA FRAGOSO-ONTIVEROS¹, LAURA CONTRERAS-ESPINOSA^{1,3},
ABRAHAM PEDROZA-TORRES⁴, JOSÉ DÍAZ-CHÁVEZ^{1,5} and LUIS A. HERRERA^{1,5}

¹Carcinogenesis Laboratory, Biomedical Cancer Research Unit of Biomedicine - National Autonomous University of Mexico (UNAM), National Cancer Institute (INCan), Mexico City 14080, Mexico; ²Celular Biology Department of Science Faculty, UNAM, Mexico City 04510, Mexico; ³Biological Sciences Postgrade, UNAM, Mexico City 04510, Mexico; ⁴Investigadores por México Program - SECIHTI, Hereditary Cancer Clinic, INCan, Mexico City 14080, Mexico; ⁵School of Medicine and Health Sciences, Mexico-Monterrey Institute of Technology, Mexico City 14380, Mexico

Received July 4, 2024; Accepted December 17, 2024

DOI: 10.3892/mmr.2025.13509

Abstract. Ovarian cancer is the deadliest gynecological cancer globally, with epithelial ovarian cancer (EOC) comprising up to 90% of cases. A molecular characterization linking the histological subtypes with tumor grade in EOC has been suggested. Variations in genetic biomarkers such as BRCA1/2, MSH2, MLH1/6, BRIP1, and RAD51C/D have been studied in EOC. In addition, molecular characteristics, including DNA methylation and RNA transcription, are being explored as potential new biomarkers for the diagnosis and prognosis of this type of neoplasia. The present review focused on the role of DNA methylation and non-coding RNA expression in the development of ovarian carcinomas and their association with diagnosis, prognosis, and the resistance of cancer cells to radiotherapy and chemotherapy. The present review considered the transition from the DNA structure to the RNA expression in ovarian carcinoma.

Contents

1. Introduction
2. DNA methylation in the diagnoses of ovarian carcinomas
3. Discussion and conclusions

1. Introduction

Ovary cancer (OC) is considered the most lethal malignancy among gynecological cancers. In 2020 worldwide, OC caused 1.6% of all new cancer-related deaths (1). Epithelial ovarian cancer (EOC) is a clinical type of OC that is already diagnosed in 90% of women patients with OC; patients with this OC type are typically diagnosed in the advanced stages of the disease (75%) when cancer has disseminated to a different abdominal tissue or metastases are present. The majority of patients (>70%) with advanced-stage OC do not respond to standard therapies, resulting in a resistant, fatal disease (2). Due to this, the identification and understanding of the molecular characteristics associated with early disease progression, prediction and clinical responses are necessary to improve survival and clinical treatment in women with EOC.

In this regard, differential cancer DNA methylation, compared with the origin tissue cells, is an early event during carcinogenesis. That is, DNA methylation is composed of concomitant global unmethylated DNA and local locus-methylated DNA. Methylated DNA consists of the addition of a methyl group in the fifth carbon of cytosine residues, forming a CpG; this addition forms 5-methylcytosine. Typical examples of DNA-methylation phenotypes have been characterized in certain types of cancer, such as colorectal carcinoma, breast carcinoma and glioma (3-8). Methylated DNA molecules are more compact than unmethylated DNA molecules (3). It has been proposed that unmethylated DNA is a characteristic of cancer while methylated DNA presents only a variable consequence depending on the locus and on the specific part of the locus in cancer cells (9,10). RNA transcription is strongly

Correspondence to: Dr Luis A. Herrera, Carcinogenesis Laboratory, Biomedical Cancer Research Unit of Biomedicine - National Autonomous University of Mexico (UNAM), National Cancer Institute (INCan), Mexico, 22 Av. San Fernando, Mexico City 14080, Mexico
E-mail: lherrera@inmegen.gob.mx

Dr José Díaz-Chavez, School of Medicine and Health Sciences, Mexico-Monterrey Institute of Technology, 222 Avenue Puente, Mexico City 14380, Mexico
E-mail: jdiazchavez03@gmail.com

Key words: ovarian carcinomas, DNA methylation, miRNAs, lncRNAs, biomarkers

influenced by DNA methylation. Methylated loci are silenced and unmethylated loci are transcriptionally activated in ovarian carcinoma tumors. The diagnosis of patients is made by transvaginal ultrasound and detection of cancer antigen (CA)-125 levels; however, the state of DNA methylation and RNA expression in the tumors has been currently associated with the diagnosis of the histological subtypes in the different types of ovarian carcinoma, the advanced stages and, importantly, the survival of the patients.

EOC is a heterogeneous carcinoma type and every EOC subtype has its natural history of development. Specifically, cell subtypes are described by histopathological and molecular characteristics of ovarian carcinoma (11-13). However, it is considered that serous ovarian carcinomas are developed as a disease continuum, from low-grade to high-grade serous ovarian carcinomas. Evidence suggests that high-grade and low-grade serous carcinomas develop independently in their natural course of progression and they have different prognoses (12,13).

At the molecular level, the prognosis of spontaneous EOC type I and type II is associated with the EOC sub-type, the age of the patient and the treatment used. Although advances in clinical treatments have increased in the past few decades, the pathology structure remains unaltered (14). Of patients diagnosed with ovarian cancer, ~50% survive five years following diagnosis, including 29% of those with metastases of ovarian carcinoma (1). In ovarian carcinomas, several factors determine survival, including primarily histological subtype, grade, stage, cytoreductive surgery and, secondarily, ethnicity (15,16).

The mortalities associated with ovarian cancer comprise 4% of all cancer-related deaths (1,14). Germinal variations are changes in DNA locus. Germinal variants of ovarian carcinomas are present in 5% of patients with ovarian carcinoma. Ovarian carcinomas are mutated in the following two ways: In germinal DNA (DNA variants of hereditary cancer origin) or in somatic DNA (DNA variants with individual spontaneous tumor cancer origin). Variants in the germ line DNA represent 24% of OC. The majority of the genetic variants are present in BRCA in hereditary breast and ovarian cancer syndrome (HBOC), whereas other DNA repair genes are present in Lynch syndrome (LS), also called hereditary non-polyposis colorectal cancer syndrome (17).

The loci mutations with higher hereditary penetrance to develop ovarian carcinoma are those of *BRCA1* or *BRCA2*. HBOC accounts for ~80% of hereditary ovarian carcinoma and 15% of epithelial OC cases. In HBOC, 65-85% of cancers are due to genomic variants in *BRCA1* and *BRCA2* genes, which are considered high penetrance for OC (18). These genes encode proteins for homologous recombination to repair DNA double-strand breaks and maintain genomic stability. In addition, germinal carcinoma with *BRCA1/2* mutations develops a high-grade serous ovarian carcinoma (HGSOC) subtype (15,16,19). Other loci mutations with moderate familial penetrance involve genes implicated in OC, such as *BARD1*, *BRIPI*, *PALB2*, *RAD50*, *RAD51C*, *NBN* and *MRE11A*; these mutations are encoded in each gene that has been involved in OC as part of the *BRCA2*/Fanconi anemia signaling pathway (20). Epithelial OC deficiency in DNA mismatch repair is the second most common cause of HBOC, accounting for 10-15% of this condition. The lifetime risk of developing OC with LS is ~8-12% and the mean age at presentation is ~43 years. OC-associated

genes in this pathway are the following: *MLH1*, *MSH2*, *MSH6* and *PMS2*. Specifically, *BRIPI*, *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* are moderate penetrance genes in OC (16-19).

It is notable that each mutated locus develops different characteristics in the phenotype of tumor cells present in the patients (19-23). By contrast, EOCs developed from a somatic spontaneous origin are heterogeneous. At the cellular level, ovarian carcinoma tumors are classified into five different types: HGSOC, low-grade serous ovarian carcinoma (LGSOC), mucinous carcinoma (MC), clear cells carcinoma (CCC) and endometrioid carcinoma (EC). Recently, DNA methylation and RNA transcription have been shown to vary in a defined way to develop EOC tumors, such as hypomethylated DNA and variation in RNA expression. It is notable that germinal variation in the DNA locus of the large non-coding RNA (lncRNA) *HOTAIR* is a risk cause of developing ovarian carcinoma. In addition, over-expression of *HOTAIR* has been found in ovarian carcinomas and it has been associated with chemotherapy resistance (24).

Ovarian carcinoma, which is resistant to radiotherapy and chemotherapy is another important problem. For example, in HGSOC, the presence of the *TP53* mutation and chromosome instability (CIN) are associated with resistance to radiotherapy and standard chemotherapy, which is a mix of carboplatin and taxane (25). In addition, it has been observed that DNA methylation loci induce sensitivity to therapies. By contrast, the DNA methylation loci of the nuclear RNA transcripts are associated with resistance to treatment. In this regard, it has been proposed that ovarian carcinoma cells could be sensitized to radiotherapy and chemotherapy by the addition of DNA methylation inhibitors such as decitabine (25).

2. DNA methylation in the diagnoses of ovarian carcinomas

The molecular characteristics validate the natural history of ovarian carcinoma tumors and explain the association between clinical characteristics of ovarian carcinoma, such as mutations in the expression levels of DNA, RNA and proteins with patient survival. The first characterization of ovarian carcinoma is performed by quantifying transvaginal CA-125 levels using ultrasonic waves (26). Subsequently, the characterization of the macroscopic tumors in surgery is required and finally the histological characteristics have to be defined by microscopic observations. Finally, the characterization of the genotype is proposed using nuclear characteristics to improve diagnosis and prognosis, as well as to confirm the natural history of the tumors. This is due to the phenotype of the tumor cells being associated with DNA methylation. Unmethylated DNA has been associated with nuclear size, aneuploidy, carcinoma subtypes and higher proliferation of ovarian carcinoma cells (27,28) [Table I, (29-48)].

Currently, the following examples have been demonstrated that indicate the DNA methylation status of ovarian carcinomas and describe the hypomethylated nuclear locus in the tumors compared with that of ovarian epithelial cells: The global loci markers (satellite sequences and *ALU* repetitive sequences) and the local loci markers. The assays used to discriminate the state of methylation currently available in human tumors are the following: Sodium bisulfite DNA treatment and pyrosequencing, reverse transcription-quantitative PCR (RT-qPCR), or methylation-specific PCR. High-resolution methods to

Table I. Characterization of DNA methylation *loci* in ovarian carcinomas.

First author/s, year	Ovarian carcinoma subtype	Locus chromosome	Gene on the locus	Methods	Status in ovarian carcinoma	(Refs.)
Feng <i>et al</i> , 2008	EOC	3q13.33 and 19q13.43	ARH1 and PEG3	Sodium bisulfite and pyrosequencing	Hypermethylated	(29)
Link <i>et al</i> , 2013	EOC	20q13.31	BORIS/CTCF	Sodium bisulfite and pyrosequencing	Unmethylated	(30)
Wang <i>et al</i> , 2013	EOC	17q21.31	BRCA1	Sodium bisulfite and RT-qPCR	Hypermethylated	(31)
Abou-Zeid <i>et al</i> , 2011; Bhagat <i>et al</i> , 2014	EOC	9p21.3	CDKN2A	Sodium bisulfite and RT-qPCR	Hypermethylated	(32,33)
Yang <i>et al</i> , 2013	EOC	8p21.1	Clusterin	Sodium bisulfite and RT-qPCR	Unmethylated	(34)
Zhang <i>et al</i> , 2015	EOC	Xq26.3	CT45	Sodium bisulfite and pyrosequencing	Unmethylated	(35)
Wang <i>et al</i> , 2017	EOC	11q25	OPCML	Sodium bisulfite and RT-qPCR	Hypermethylated	(36)
Kaur <i>et al</i> , 2016	EOC	9q21.33 and 13q34	DAPK1 and SOX1	Sodium bisulfite and RT-qPCR	Hypermethylated	(37)
Rattanapan <i>et al</i> , 2018	HGSOC	9q34.3	EGFL7	Sodium bisulfite and pyrosequencing	Hypermethylated	(38)
da Conceição Braga <i>et al</i> , 2014	EOC	18q21.33 and 8p21.3	BCL2 and TRAIL2-R2	Sodium bisulfite and RT-qPCR	Hypermethylated	(39)
Bonito <i>et al</i> , 2016	EOC	4p16.2	MSX1	Sodium bisulfite and RT-qPCR	Hypermethylated	(40)
Kardum <i>et al</i> , 2017; Suzuki <i>et al</i> , 2008	EOC	14q23.2	ER-β	Sodium bisulfite and RT-qPCR.	Hypermethylated	(41,42)
Baranova <i>et al</i> , 2018	HGSOC	13q21.1	PCDH17	Sodium bisulfite and pyrosequencing	Hypermethylated	(43)
Ding <i>et al</i> , 2016	EOC	11p14.3	FANCF	Sodium bisulfite and pyrosequencing	Hypermethylated	(44)
Gozzi <i>et al</i> , 2016	EOC	1p12	TBX15	Sodium bisulfite and pyrosequencing	Hypermethylated	(45)
Choi <i>et al</i> , 2006	EOC	3p21.31	RASSF1A	Sodium bisulfite and RT-RT-qPCR	Hypermethylated	(46)
Häfner <i>et al</i> , 2016	EOC	1p36.11 and 1p36.12	RUNX3 and CAMK2N1	Sodium bisulfite and RT-qPCR	Hypermethylated	(47)
Jin <i>et al</i> , 2018	EOC	3p14.3	Wnt5a	Sodium bisulfite and RT-qPCR	Hypermethylated	(48)

EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian carcinoma; RT-qPCR, reverse transcription-quantitative PCR.

determine cell single DNA methylation are currently available, such as droplet and digital PCR (43-50).

DNA methylation and RNA expression are associated with ovarian carcinoma cells. This indicates that RNA transcription could be inhibited due to the DNA methylation status of the locus, except for certain recent paradoxical examples

led by a negative correlation in other types of cancers, where intragenic methylation correlates with gene overexpression (Table II) (51,52). In contrast to these observations, RNA expression is activated in the unmethylated DNA status of the locus (9). Therefore, RNA transcription is differentially present in ovarian carcinoma. MicroRNAs (miRs) are a class of

Table II. Hyper-methylated miRNAs locus in ovarian carcinoma.

Locus chromosome	Non-coding RNA expressed in locus	DNA status methylation in locus	RNA expression of locus
11q24.1	<i>miR-125-1</i>	Hypermethylated	Downregulated
14q32.2	<i>miR-127</i>	Hypermethylated	Downregulated
11p11.2	<i>miR-129-2</i>	Hypermethylated	Downregulated
1p21.3	<i>miR-137</i>	Hypermethylated	Downregulated
17q11.2	<i>miR-193a</i>	Hypermethylated	Downregulated
14q32.2	<i>MEG3</i>	Hypermethylated	Downregulated

miR, microRNA. All dates referenced in this table from (53).

small RNA transcripts (19-22 nucleotides) that decrease gene expression via translational inhibition or degradation of target messenger RNA (mRNA). Various miRs are differentially expressed in cancer, suggesting a link between these molecules and the different expression levels of proteins in cancer tissues (53). By contrast, large non-coding RNAs (lncRNAs) function on affecting the nuclear structure and RNA transcription. It is notable that the hypermethylated DNA of RNA loci decrease the presence of miRs and MEG3 (53-55), which is a lncRNA, so that the RNA transcripts in the normal ovarian tissue, benign epithelial tumors, benign epithelial ovarian cysts, malignant ovarian carcinoma and serous ovarian carcinoma exhibit differential expression of RNA transcripts (56-59).

It remains to be determined why DNA methylation in ovarian carcinomas is heterogeneous. In 2014, the World Health Organization classification guidelines for female reproductive tumors defined the ovarian carcinoma type in cell-level characterized ovarian carcinoma subtypes HGSOC, LGSOC, CCC, MC and EC (11-13,21,60). It was proposed that at the molecular level, the natural history of ovarian carcinomas is HGSOC. A fallopian tube epithelial origin was found when DNA methylation was compared (61,62). HGSOC has locally DNA methylations in 6 loci that differentiate HGSOC from the OSE DNA methylation pattern (*ARMCX1*, *ICAM4*, *LOC134466*, *PEG3*, *PYCARD* and *SGNE1*) (41); HGSOC overexpresses miR-223, miR-551b-3p, miR-30a-5p, miR-9 and miR-30a-5p (63-70). Other studies using miR microarrays have described the different expression patterns of serous ovarian carcinoma (70) and clear cell carcinoma (CCC), specifically the *SFRP1* methylated locus (41,71,72). By contrast, DNA methylation in low-grade serous ovarian carcinoma has not been reported to date compared with other ovarian carcinoma subtypes or epithelial ovarian cells. By contrast, it has been shown that endometrioid carcinoma (EC) has similarities with endometrial and ovarian carcinomas in the promoter hypermethylated locus (73-76). CCC has been characterized by the HNF1 pathway to be unmethylated, whereas the RE alpha pathway is unmethylated, similar to OSE (71). Finally, mucinous carcinomas (MUC) exhibit 81 unmethylated genes that are different from those of HGSOC. It is notable that MUC-DNA methylation is more similar to colorectal and stomach carcinoma than HGSOC, providing additional information on the MUC origins from colorectal metaplasia (12,77). Downregulation of miR-192 and miR-2215 levels is also noted in MUC (78) (Fig. 1).

In conclusion, DNA methylation is a characteristic that varies early in the development of ovarian carcinoma cells. The vestige of a methylated locus in the origin tissues of ovarian carcinomas marks a directional methylation of every ovarian carcinoma subtype. DNA methylation and RNA expression are associated. Finally, DNA methylation and RNA transcripts are associated and differentially presented by the subtype cells.

DNA methylation and ncRNA expression as prognostic biomarkers of ovarian carcinomas. The following factors are associated with the prognosis of patients with ovarian carcinoma: The variations in DNA syndromes, the ethnic origin, the origin of the gynecological pathologies, the subtypes, the advanced stages of the tumors (metastasis to lymph node, or metastasis to distant tissues), the size of residual tumor following cytoreductive surgery and the resistance of cancer cells to radiotherapy and chemotherapy. It is notable that 75% of ovarian carcinomas are of HGSOC sub-type and the patient 5-year survival following diagnosis with ovarian carcinoma is ~47%. In comparison, the survival of the women diagnosed with metastasis of ovarian carcinoma is only 29% (11,15,21-23,79,80).

The RNA expression could be driven by a random accumulation or by a directional and defined development as determined by the stages of International Federation of Gynecology and Obstetrics (FIGO) (81) in every molecular ovarian carcinoma subtype. Several pieces of evidence have concluded that RNA transcripts are overexpressed and down-regulated in a directional way (Tables II and III). First, this has been presented in the diagnosis biomarkers without poor prognosis. Except for the *BRCA1/2* mutation and the DNA methylation locus associated with response to chemotherapy, the RNA transcripts are not related to the prognosis of the patients or the single nucleotide polymorphism in *HOXA11* that protects cells from developing HGSOC (82). This suggests that biologically, hereditary mutations have a higher risk weight than DNA methylation or RNA expression, which are more sensitive to alterations of the phenotype state but not of the patient's outcome. The nuclear characteristics determined of the advanced FIGO stages of ovarian carcinoma are CIN, DNA methylated locus in genes, such as *BRCA1*, *FANCF*, *RASSF1A* and *Wnt5A*, the downregulated levels of *TUBA14B* and the overexpressed RNA transcripts of the following genes and lncRNAs: *MGMT*, *OSMR*, *ESR1* and *FOXL2* and long non-coding (lnc)*BRM*, *HOTAIR*, *HOXDAS-1* and *lncSOX4* and *CPS1-IT1* (83-87) (Table IV).

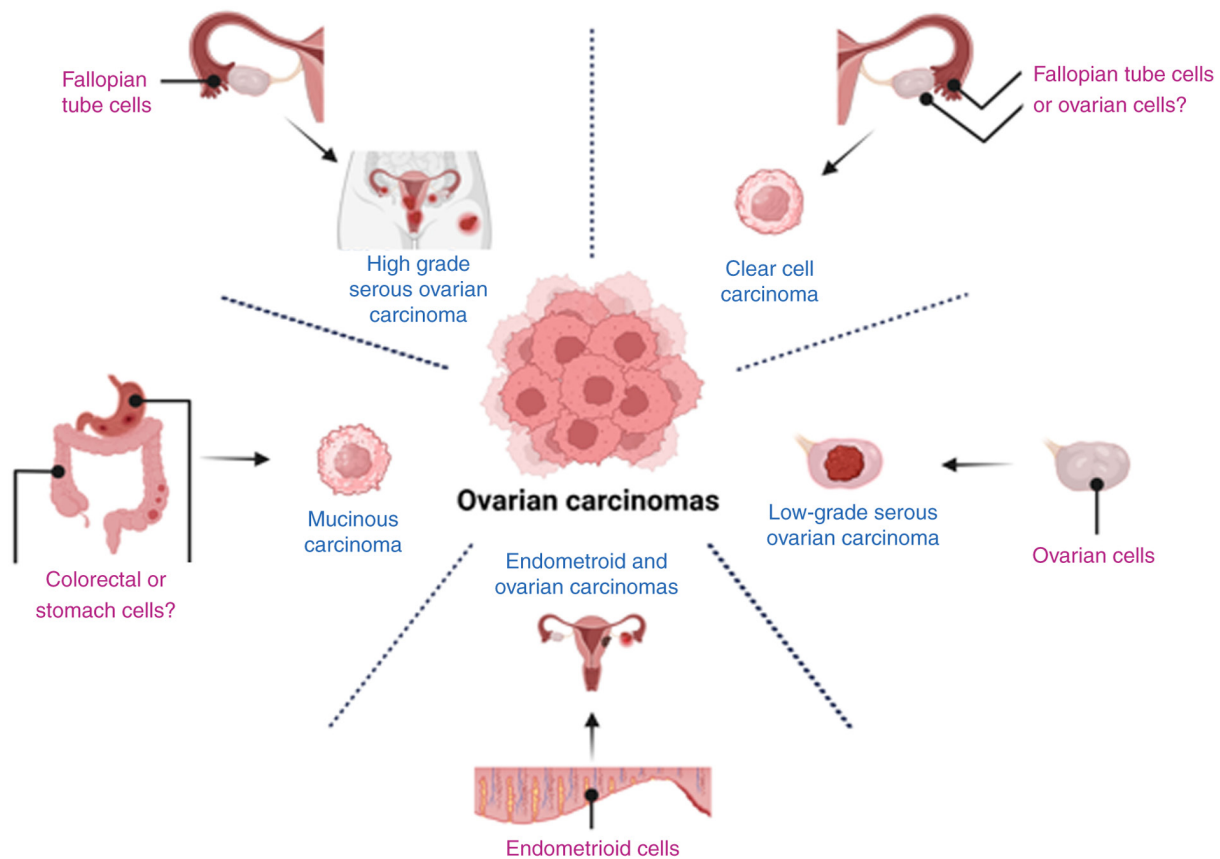


Figure 1. Natural history of ovarian carcinoma. Ovarian carcinoma is a heterogeneous type of cancer. Five subtypes of ovarian carcinomas originate in different forms. Origin tissues are enlisted in the periphery of the image and ovarian carcinomas are enlisted near the image core, similar to the nuclear ovarian carcinoma archetype. The transformation of the cells of the ovarian carcinoma origin can be described as follows: Fallopian tube cells originate HGSOC. Superficial cells of the ovary originate CCC. The origin of colorectal or stomach cells that develop in MC remains to be determined due to their tissue similitudes Endometrial cells originate EC. Fallopian tube cells or ovary cells originate LGSOC. Created by BioRender.com. Accessed on 09/2024. HGSOC, high-grade serous ovarian carcinoma; CCC, clear cell carcinoma; LGSOC, low-grade serous ovarian carcinoma; EC, endometrioid carcinoma; MC, mucinous carcinoma.

The assays used to analyze RNAs are transcriptomics or expression analysis of single locus transcription detected by RT-qPCR (88,89). It is notable that the overexpressed and downregulated transcripts associated with tumor development classified by FIGO stages could probably result in equilibration of their levels in the nuclear structure; in addition, the variation in transcript levels within patients has to be taken into account; for example, the levels of *MLK7-AS1* and *TUG1* were increased 2.5- and 2.2-fold, respectively; the levels of *CASC2* were diminished 0.6-fold compared with the relative expression noted in advanced stage ovarian carcinoma cells (90-98). These types of variation in the RNA expression levels are individual assessments in ovarian carcinoma subtypes derived from a population, which are defined by comparison of the expression levels of their corresponding counterparts. However, in the majority of the studies, the ovarian cancer cells are used as a point of calibration (66,67,98-162).

Patients with advanced stages have methylated loci DNA on *ER-b*, *RUNX3*, and *CAMK2N1*; these alterations have been associated with poor prognosis (41-43). The lncRNAs *SPRY4-IT1* and *HOXA11* are associated with ovarian carcinoma transformation; they are overexpressed in ovarian carcinoma compared with ovarian untransformed cells (107,108,163-184). In addition, overexpression of the

miR-200 family members and MALAT1 have been associated with poor prognosis in advanced stages with a sensitivity of 88%; specifically miR-125b overexpression exhibits a sensitivity of 75.6% (108,172,181-185). In addition, miR-199a exhibits a sensitivity of 72% related to positive lymph node metastasis (154,186-189). Moreover, miR-125b overexpression exhibits a sensitivity of 72%, which is characteristic of ovarian carcinoma, associated with 67% grade, 77% positive lymph node metastasis and 89% metastasis (190). The upregulation of the expression of *CPST1-IT1* is also associated with cancer, stage and lymph node metastasis with a hazard ratio of 3.257 ($P=0.004$) (97). This suggests a variation in the gradual overexpression during the development of ovarian carcinomas. RNA transcripts have a directional variation of expression during the development of the natural history of ovarian carcinomas, which is initiated from the tissues of origin (Fig. 2).

The molecular-resistant ovarian carcinoma. Molecular and cellular biology allows the improved understanding of the microscopic and macroscopic observations of ovarian carcinomas. The selection of the therapeutic methods, such as surgery, radiotherapy and chemotherapy, depends on several factors, such as the carcinoma grade, FIGO stage and patient characteristics, namely age (81). Surgery is performed to obtain

Table III. microRNAs expression associated with cancer functions derived from *locus* and target locus RNAs probed in specific ovarian carcinoma subtypes.

First author/s, year	Ovarian carcinoma subtype	Associated with	Locus of the miRNA	microRNA	RNA regulation	Locus of the target	RNA from the locus target	(Refs.)
Nymoene <i>et al</i> , 2016	EOC	Poor prognosis	<i>7q32.3</i>	29a	Down	<i>2p23.3</i>	DNMT3A	(66)
Arts <i>et al</i> , 2017	HGSOC	HGSOC	<i>Xq12</i>	223	Up	<i>12q13.12</i>	SMARCD1	(67)
Ying <i>et al</i> , 2016	EOC	Poor prognosis, clinical stage III and IV clinical grade	<i>11q24.1</i>	125b	Down	<i>9q34.11</i>	SET	(99)
Zhu <i>et al</i> , 2017	EOC	II and III lymph node metastasis distant metastasis	<i>11q24.1</i>	125b	Up	<i>9q34.11</i>	SET	(100)
Teng <i>et al</i> , 2015	EOC	Poor prognosis	<i>1p36.33</i>	29b	Down	<i>1q21.2, 19q13.2 and 1q43</i>	Mcl-1, AKT2 and AKT3	(101)
Cao <i>et al</i> , 2015; Katepanakis <i>et al</i> , 2015; Meng <i>et al</i> , 2016	EOC	Poor prognosis stage grade	<i>1p36.33</i>	200a/ 200b/ 200c	Up			(102-104)
Du <i>et al</i> , 2017	EOC	EOC	<i>12p13.31</i>	551a	Down	<i>22q11.22/ 14q32.33</i>	MAPK/ AKT	(105)
Chaluvally-Raghavan <i>et al</i> , 2016	EOC	Poor prognosis	<i>1p36.32</i>	551b-3p	Up	<i>17q21.2</i>	STAT3	(68)
Chen <i>et al</i> , 2015	EOC	Advanced stages High grade	<i>3q26.2</i>	490-3p	Up	<i>10q21.2</i>	CDK1	(106)
Shuang <i>et al</i> , 2015	EOC	Chemotherapy resistant	<i>14q32.31</i>	134	Down	<i>3q29</i>	Pak2	(107)
Zou <i>et al</i> , 2015	EOC	Stage histology	<i>15q24.1</i>	630	Down	<i>10q23.31</i>	PTEN	(108)
Zhang <i>et al</i> , 2016	EOC	EOC	<i>5q32</i>	143-3p	Down	<i>18p11.22</i>	RALBP1	(109)
Zhang <i>et al</i> , 2018	EOC	Stage lymph node metastasis	<i>21q21.1</i>	Let-7c	Down	<i>3p21.31</i>	CDC25a	(110)
Liu <i>et al</i> , 2014	EOC	Poor prognosis stage	<i>9q34.11</i>	199b-5p	Down	<i>20p12.2- 9q34.3</i>	JAG1- NOTCH1	(111)
Ma <i>et al</i> , 2016	EOC	EOC	<i>8p11.21</i>	486-5p	Down	<i>13q14.3</i>	OLFM4	(65)
Kobayashi <i>et al</i> , 2018	HGSOC	Advanced stages	<i>1p36.13</i>	1290	Up	-	Serum	(112)
Zhao, <i>et al</i> , 2015.	EOC	Complete response	<i>14q32.2</i>	136	Up	-	DNA repair and apoptosis	(69)
Zhao <i>et al</i> , 2014	EOC	Complete/poor response	<i>Xq25</i>	224-5p	Down	<i>3p21.1</i>	PRKCD	(113)
Wang <i>et al</i> , 2018	HGSOC	EOC	<i>6q13 13p.33</i>	30a-5p 200a-5p	Up	<i>6p21.2</i>	P21	(64)
Chen <i>et al</i> , 2016	EOC	Stage grade relapse	<i>17q23.1</i>	21	Up	<i>20q13.2</i>	HE4	(114)
Li <i>et al</i> , 2014	EOC	Stage III and IV	<i>11p15.5</i>	210	Up	<i>14q23.2</i>	HIF	(115)
Zhu <i>et al</i> , 2017	EOC	Resistance	<i>9p21.12</i>	204	Up	-	-	(116)
Fan <i>et al</i> , 2015	EOC	Poor prognosis stage III and IV tumor size metastasis	<i>17q21.32</i>	196a	Up	<i>21q22.12</i>	RUNX1	(117)

Table III. Continued.

First author/s, year	Ovarian carcinoma subtype	Associated with	Locus of the miRNA	microRNA	RNA regulation	Locus of the target	RNA from the locus target	(Refs.)
Koukorakis <i>et al</i> , 2018	HGSOC	HGSOC	<i>1p36.22</i> <i>1p36.33</i>	34a 200	Down Up	<i>9p24.1</i>	PD-L1	(118)
Liu <i>et al</i> , 2016	EOC	EOC	<i>8p22</i>	383	Up	<i>7q34</i>	Caspase-2	(119)
Dai <i>et al</i> , 2014	EOC	Stages III and IV relapse	<i>7q32.3</i>	29b	Down	<i>4q21.3</i>	MAPK10	(120)
Xiao <i>et al</i> , 2017	EOC	Therapy sensible poor prognosis	<i>19q13.41</i>	Let-7e	Down	<i>17q21.31</i> and <i>15q15.1</i>	BRCA1 and RAD51	(121)
Li <i>et al</i> , 2015	EOC	Therapy sensible poor prognosis metastasis	<i>1q22</i>	9	Down Up	<i>5q34</i> and <i>16q22.1</i>	CCNG1 and E-cadherin	(122)
Paudel <i>et al</i> , 2016	EOC	Stages III and IV	<i>22q11.21</i>	130b	Down	<i>1q36.11</i>	RUNX3	(123)
Duan <i>et al</i> , 2018	EOC	Poor prognosis	<i>3p21.2</i>	135a-3p	Down	<i>3p21.31</i>	CCR2	(124)
Chen <i>et al</i> , 2015	EOC	EOC	<i>5q32</i>	145	Down	<i>4q31.3</i>	TRIM2	(125)
Qin <i>et al</i> , 2015	EOC	Poor prognosis stages III and IV	<i>15q25.1</i>	184	Down	-	-	(126)
Liang <i>et al</i> , 2016	EOC	EOC	<i>1q41</i>	194	Up	<i>7q11.23</i>	PTPN12	(127)
Wei <i>et al</i> , 2017	EOC	EOC	<i>6p21.32</i>	219-5p	Down	<i>7p21.1</i>	Twist	(128)
Fu <i>et al</i> , 2016	EOC	Grades II and III poor prognosis	<i>Xp11.3</i>	222-3p	Down	<i>14q32.33</i> and <i>10q23.31</i>	AKT and PTEN	(129)
Wu <i>et al</i> , 2017	CCC	CCC		424	Down	<i>13q13.3</i>	DCLK1	(130)
Chen <i>et al</i> , 2015	EOC	Advanced stages Grades II and III	<i>Xq26.3</i>	490-3p	Down	<i>10q21.2</i>	CDK1	(106)
Zhang <i>et al</i> , 2016	EOC	Poor prognosis stage III and IV ascites lymph node metastasis grade III tumor size chemoresistance	<i>19q13.42</i>	520g	-	<i>15q22.31</i>	DAPK2	(131)
Zhang <i>et al</i> , 2016	EOC	Stage III and IV lymph node metastasis	<i>1p21.3</i>	137	Down	-	-	(132)
Liu <i>et al</i> , 2017	EOC	EOC	<i>11q13.4</i>	139	Down	<i>1q23.1</i>	HDGF	(133)
Xu <i>et al</i> , 2017	EOC	Stage III and IV tumor size lymph node metastasis	<i>9q32</i>	455	Down	<i>9q34.3</i>	NOTCH1	(134)
Yan <i>et al</i> , 2016	EOC	Age	<i>9q22.32</i>	23b	Down	<i>5q34</i>	CCNG1	(135)
Lin <i>et al</i> , 2015	EOC	Poor prognosis stages III and IV distant metastasis recurrence	<i>2q35</i>	26b	Down	<i>17q24.2</i>	KPNA2	(136)
Xu <i>et al</i> , 2017	EOC	EOC	<i>3q28</i>	28-5p	Up	<i>16q12.1</i>	N4BP1	(137)
Wang <i>et al</i> , 2017	HGSOC	Advanced stages	<i>11q21.1</i>	130a	Down	<i>9q34</i>	TSC1	(138)
Wang <i>et al</i> , 2016	EOC	Stages III and IV Grades II and III lymph node metastasis	<i>5q32</i>	143	Down	<i>6q23.2</i>	CTGF	(139)
Dong <i>et al</i> , 2015	EC	EC	<i>3p21.31</i>	191	Up	<i>9q21.33</i>	DAPK1	(140)
Niu <i>et al</i> , 2015	EOC	Stages III and IV High grade	<i>1q32.2</i>	205	Up	<i>10p11.22</i>	ZEB1	(141)

Table III. Continued.

First author/s, year	Ovarian carcinoma subtype	Associated with	<i>Locus</i> of the miRNA	microRNA	RNA regulation	<i>Locus</i> of the target	RNA from the locus target	(Refs.)
Dai <i>et al</i> , 2018	EOC	EOC	<i>6p12.2</i>	206	Down	<i>1p36.22</i>	mTOR	(142)
Xia <i>et al</i> , 2015	HGSOC, CCC	Tumors	<i>15q13.3</i>	211	Down	<i>11q13.3 and 7q21.2</i>	Cyclin D1 and CDK6	(143)
Wu <i>et al</i> , 2018	EOC	Poor prognosis death	<i>Xp11.3</i>	221-3p	Down	<i>3p14.3</i>	ARF4	(144)
Cao <i>et al</i> , 2018	EOC	Resistant	<i>Xq26.2</i>	363	Down	<i>20q13.3</i>	Snail	(145)
Xia <i>et al</i> , 2016	EOC	Stages III and IV Grades II and III	<i>8p22</i>	383	Down	<i>14q32.2</i>	YY1	(146)
Yuan <i>et al</i> , 2016; Li <i>et al</i> 2016	EOC	Stages III and IV Grades II and III lymph node metastasis	<i>14q32.31</i>	494	Down	<i>8q24.21 and 15q26.3</i>	c-Myc and IGF1R	(147,148)
Zhou <i>et al</i> , 2017	EOC	Stage III and IV Grade II and III distant metastasis	<i>7q36.3</i>	595	Down	-	-	(149)
Zhang <i>et al</i> , 2017	EOC	EOC	<i>15q24.1</i>	630	Up	<i>10p15.2</i>	KLF6	(150)
Shi <i>et al</i> , 2016	EOC	EOC	<i>1p32.3</i>	761	Down	<i>12q24.31</i>	MSI1	(151)
Xie <i>et al</i> , 2018	EOC	EOC	<i>Xp11.3</i>	221	Up	<i>15q15.1</i>	BMF	(152)
Wen <i>et al</i> , 2015	EOC	Stage III and IV Grade II and III lymph node metastasis	<i>17q25.3</i>	338-3p	Down	<i>6p21.1</i>	RUNX2	(153)
Salem <i>et al</i> , 2018	EOC	Grades II and III	<i>7q11.23</i>	590-3p	Up	<i>20p11.21</i>	FOXA2	(154)
Lin <i>et al</i> , 2016	EOC	EOC	<i>17p13.1</i>	497	Down	<i>10q24.31</i>	PAX2	(155)
Lin <i>et al</i> , 2018	EOC	Stage grade lymph node metastasis	<i>19q13.32</i>	330-5p	Up	<i>22q11.22</i>	MAPK	(156)
Chen <i>et al</i> , 2016	EOC	EOC	<i>12p13.31</i>	141	Down	<i>21q22.3</i>	SIK1	(157)
Zuberi <i>et al</i> , 2016	EOC	Stage lymph node metastasis	<i>19p13.2</i>	199a	Down	-	-	(158)
Agostini <i>et al</i> , 2018	MC	MC	<i>11q13.1 and 1q41</i>	192 and 215	Down	-	-	(78)
Guan <i>et al</i> , 2017	EOC	EOC	<i>19q13.42</i>	372	Down	<i>8q24.13, 13q12.11, 5q35.3, 10q21.1 and 13q13.3</i>	ATAD2, LATS2, P62, DKK1 and cyclinA1	(159)
Li <i>et al</i> , 2016	EOC	Advanced stages High grade lymph node metastasis	<i>2p16.1</i>	217	Down	<i>15q26.3</i>	IGF1R	(160)
Zhang <i>et al</i> , 2015	EOC	Poor prognosis	<i>4p15.33</i>	572	Up	<i>16p13.13 and 6p21.2</i>	SOCS1 and P21	(161)
Zhou <i>et al</i> , 2015	SOC	Preoperative	<i>6q13</i>	30a-5p	Up	-	-	(162)

EOC, epithelial ovarian cancer; HGSOC, high grade serous ovarian carcinoma; CCC, clear cells carcinoma; MC, mucinous carcinoma; EC, endometrioid carcinoma. High grade, grades II and III. Advanced stages, III and IV.

the tumor via cytoreduction, which involves extracting carcinoma cells from the patient. Chemotherapy is subsequently

administered following cytoreduction in cases of advanced ovarian carcinoma. By contrast, radiation therapy uses

Table IV. Long non-coding RNAs expression associated to cancer functions derived from locus probed in specific ovarian carcinoma subtypes.

First author/s, year	Ovarian cancer subtype	Associated with	Locus	LncRNA	Regulation	(Refs.)
Xi <i>et al</i> , 2017	EOC	Poor prognosis stage grade lymph node metastasis	5q11.2	<i>lncBRM</i>	Up	(92)
Zhang <i>et al</i> , 2017	EOC	EOC	1p21.2	<i>NR_026689</i>	Up	(163)
Wang <i>et al</i> , 2017	EOC	Favorable prognosis stage Lymph node metastasis	2q34	<i>CPS1-IT1</i>	Down	(97)
Zhu <i>et al</i> , 2018	EOC	Metastasis CA-125 levels	2p25.1	<i>CTD2020K17.1</i>	Up	(164)
Qiu <i>et al</i> , 2017	EOC	EOC	1q32.1	<i>ElncRNA1</i>	Up	(165)
Gao <i>et al</i> , 2015	EOC	EOC	10q23.1	<i>HOST2</i>	Up	(166)
Wang <i>et al</i> , 2015	EOC	Poor prognosis Stage Histological grade Residual tumor Lymph node metastasis	12q13.13	<i>HOTAIR</i>	Up	(167)
Lu <i>et al</i> , 2018	HGSOC	Poor prognosis	7p15.2	<i>HOXA11-AS</i>	Up	(168)
Zhang <i>et al</i> , 2017	EOC	Poor prognostic stage lymph node metastasis	2q31.1	<i>HOXD-AS1</i>	Up	(93)
Du <i>et al</i> , 2018	EOC	Poor prognosis	21q22.3	<i>LINC00319</i>	Up	(169)
Shu <i>et al</i> , 2018	EOC	Poor prognosis stage grade lymph metastasis distant metastasis	9q21.31	<i>ARSR</i>	Up	(170)
Chen <i>et al</i> , 2017	EOC	EOC	6p24.3	<i>HULC</i>	Up	(171)
Liu <i>et al</i> , 2018	EOC	Stage tumor size distant metastasis	6p21	<i>LncSox4</i>	Up	(94)
Qunbo <i>et al</i> , 2018; Lin <i>et al</i> , 2018	EOC	Poor prognostic	11q13.1	<i>MALAT1</i>	Up	(172,173)
Yan <i>et al</i> , 2018	EOC	Poor prognostic stage depth of invasion lymph node metastasis distant metastasis	2q31.1	<i>MLK7-AS1</i>	Up	(95)
Yan <i>et al</i> , 2017	EOC	Favorable prognosis tumor size	6p22.3	<i>NBAT-1</i>	Down	(174)
Liu <i>et al</i> , 2018	EOC	Poor prognostic stage grade residual tumor metastasis	11q13.1	<i>NEAT1</i>	Up	(175)
Chen <i>et al</i> , 2018	EOC	Grade	2q32.3	<i>PCGEM1</i>	Up	(176)
Huang <i>et al</i> , 2018	EOC	Stage grade tumor size	1p13.2	<i>RP11-552M11.4</i>	Up	(177)
Li <i>et al</i> , 2017	EOC	Poor prognosis stage grade lymph node metastasis	5q31.3	<i>SPRY4-IT1</i>	Up	(178)
Zhu <i>et al</i> , 2017	EOC	Favorable prognosis stage grade lymph node metastasis CA-125 levels	2q35	<i>lncRNA-TUBA4B</i>	Down	(98)
Li <i>et al</i> , 2018	EOC	EOC poor prognosis stage grade tumor size	22q12.2	<i>lncRNA-TUG1</i>	Up	(179)
Hong <i>et al</i> , 2016	EOC	Poor prognostic stage lymph node metastasis chemotherapy response	19p13.12	<i>lncRNA-UCA1</i>	Up	(180,181)
Qiu <i>et al</i> , 2016	EOC	Poor prognosis stage grade	9p21.3	<i>ANRIL</i>	Up	(182)
Zhang <i>et al</i> , 2018	EOC	EOC	10q26.11	<i>CASC2</i>	Down	(90)
Cao <i>et al</i> , 2017	EOC	EOC	8q24.21	<i>CCAT1</i>	Up	(183)
Hua <i>et al</i> , 2018	EOC	EOC	8q24.21	<i>CCAT2</i>	Up	(184)

EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian carcinoma.

high-energy particles to destroy tumor cells, either directly or indirectly, to inhibit further cell growth. Concomitantly, radiotherapy has been commonly used as a first-line treatment for ovarian carcinoma until the 1990s. It is now rarely used alone

and is typically used with surgery (191). However, radiotherapy can still be beneficial in certain ways, such as reducing tumor size prior to surgery, treating areas where cancer has spread and providing palliative care (192,193). Ovarian carcinoma

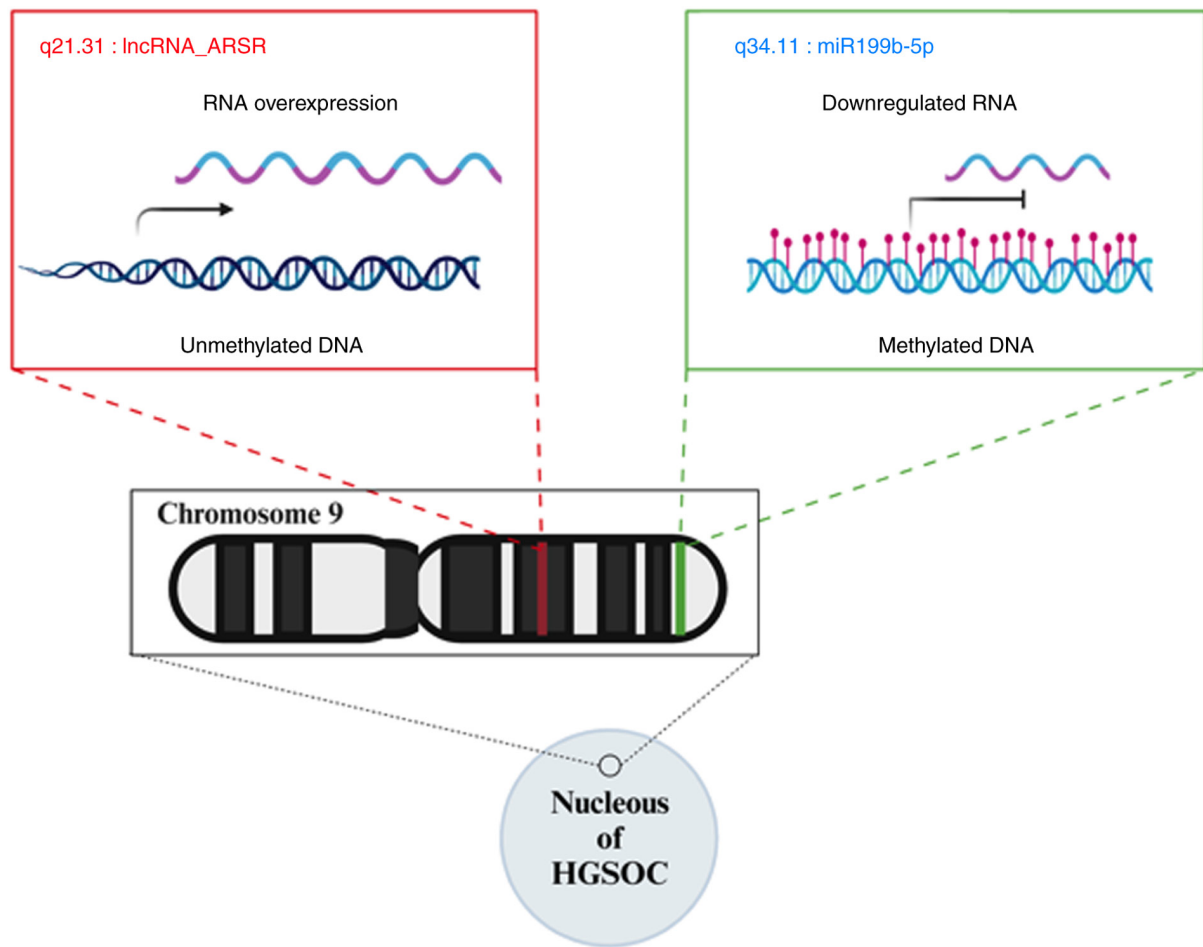


Figure 2. DNA methylation and RNA transcripts in the diagnosis and prognosis of ovarian carcinomas. Heterogeneous DNA methylation corresponds to heterogeneous ovarian carcinomas. RNA expression of the transcripts is associated with DNA methylation. Certain studies have characterized DNA methylation and RNA transcription of specific genes in ovarian carcinoma subtypes. Generally, with a few exceptions, different RNAs are affected by the methylation status of the DNA. For example, molecular diagnosis of HGSOC is performed by chromosome 9 *locus* Chr9q21.31 that contains unmethylated DNA; an overexpression of the large non-coding RNA *ARSR* is noted. By contrast, in the locus Chr9q34.11, which contains a methylated DNA, downregulation of miR199b-59p expression is noted. Created by BioRender.com. Accessed on 09/2024. HGSOC, high-grade serous ovarian carcinoma subtype; miR, microRNA.

cells are radiosensitive at the early stages of development (194), notably in low-grade carcinoma subtypes such as EC (195).

In contrast to these observations, ovarian carcinomas at the late stages are resistant to both radiotherapy and chemotherapy. This resistance is often associated with p53 mutation and CIN (192,196). It is notable that radiotherapy increases global unmethylated DNA levels in cancer cells, while hypomethylated DNA is linked to increased sensitivity to radiotherapy. This explains the ability of DNA methylation inhibitors (such as decitabine) to sensitize ovarian carcinoma cells to radiotherapy (197). By contrast, RNA transcripts can increase resistance to radiotherapy treatment, such as Snail, Slug, NOX4, miR200, miR-299 and MTDH. Conversely, reducing the levels of specific RNA transcripts in ovarian carcinoma cells can increase the sensitivity of the tumor cells to radiotherapy (198-202).

Chemotherapy presents a challenging environment for cells, aiming to eliminate tumor cells and improve the prognosis for patients with cancer. The standard chemotherapy treatment for ovarian carcinoma combines carboplatin and paclitaxel. Chemotherapy can alter the nuclear structure, DNA methylation and RNA expression in ovarian carcinoma cells (203-205). To date, the association of methylation with the incidence of cancer

in patients is not directly known. However, DNA methylation is associated with chromosomal instability of high-grade serous ovarian carcinoma. This is the most aggressive subtype of ovarian cancer. It can be inferred that by understanding the relationship between methylation and CIN, the progression of ovarian cancer can be predicted. For example, it is known that the HGSOC subtype with *TP53* mutation and CIN is associated with DNA hypermethylation in patients with poorer prognosis (206-213). HGSOC is characterized by *TP53* mutation and CIN and is linked to chemotherapy resistance; it is also considered to be the more resistant and heterogeneous subtype of ovarian carcinomas (214). For example, treatment with paclitaxel in specific cell line models induces overexpression of *mdr1* and the lncRNAs *UCA1* and long intergenic non-coding RNA *linc00312* (215).

Paclitaxel is a drug that inhibits depolymerization of microtubules. It arrests cells in the G₂/M phase. It also induces CIN, leading to cell death. However, certain ovarian carcinoma cells are resistant to paclitaxel. Certain miR biomarkers, such as miR-134 and miR-224-5p, are associated with EOC resistance to paclitaxel chemotherapy with 85 and 90% sensitivity, respectively (94,102). Studies in ovarian carcinoma have shown that RNA transcript levels are altered during paclitaxel treatment

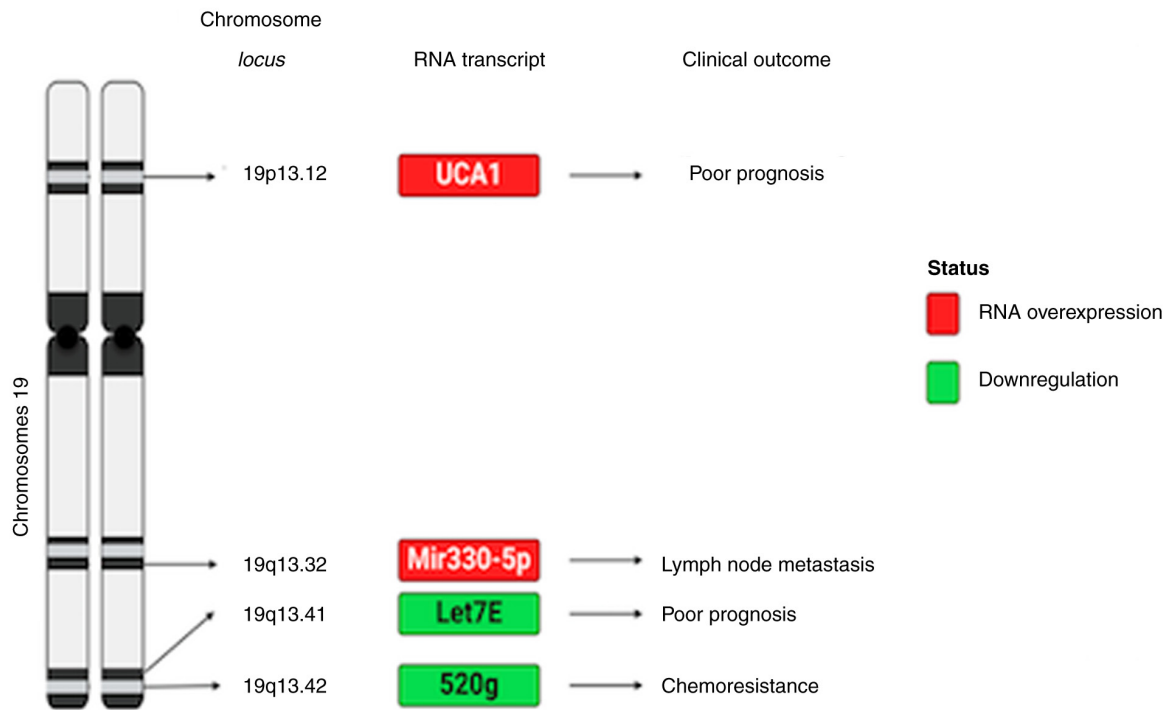


Figure 3. The variability of ncRNAs is related to clinical pathogenesis and resistance in ovarian carcinoma. The differential expression status between ovarian cancer and normal tissue has been associated with clinical outcomes such as ovarian carcinoma subtype, progression, metastases, radioresistance and chemoresistance, and more importantly, in the disease prognosis of the patients. For example, the ncRNA expression levels of the ovarian carcinoma type indicated that the aforementioned genes were located in a specific locus from a unit of chromosome 19. Overexpression of *UCA1*, a large non-coding RNA located in *locus* 19p13.12 and downregulation of the *Let7E* miR levels located in 19q13.41 were associated with poor prognosis. Similarly, overexpression of miR330-5p in 19q13.32 was associated with lymph node invasion and downregulation of miR520g levels was associated with resistance to chemotherapy. ncRNAs overexpressed are shown in red and the downregulated RNA transcript are shown in green. ncRNA, non-coding RNA; miR, microRNA.

in ovarian cancer cells. For example, treatment of A2780, OVCAR3, SKOV3, and SW626 cells with paclitaxel induces overexpression of *mdr1* (215), *UCA1* and *lincRNA00312*.

Previous studies have shown that cisplatin increases the expression of *ZEB1* and *MP63* (216,217). It is notable that the use of array expression and PCR validation in the A2780 cisplatin-resistant cell line revealed that the expression levels of the following six miRs were upregulated: miR-1064, miR-300, miR-193b, miR-642 and miR-1299; however, the expression levels of the following five miRs were downregulated: miR-625, miR-20b, miRPlus-F1147, let-7c, miR-1231 and miR-542-3p (214,215,218,219). This evidence suggests that RNA transcripts are differentially expressed in chemotherapy-resistant cells compared with sensitive cells, providing a solid basis for further research. It also indicates the implications for the survival outcomes of the patients with ovarian cancer (220-225) (Fig. 3).

3. Discussion and conclusions

Ovarian carcinoma is a type of cancer resulting from tissue transformation and can occur both in hereditary (20%) and sporadic (80%) forms. DNA methylations repress RNA transcription differentially in ovarian carcinoma subtypes. This suggests that DNA methylation of ovarian carcinoma subtypes is more similar to their tissue of origin with regard to their nuclear characteristics. Ovarian carcinoma presents a complex molecular landscape where DNA methylation and RNA expression play crucial roles in the disease development, progression and treatment response. DNA methylation serves

as both an early event in carcinogenesis and a key regulator of gene expression, either silencing or activating RNA transcription based on the methylation status of specific loci.

The characteristics of nuclear vestiges vary in a directional range of RNA transcripts. In addition, the directional way of variation of the RNA transcripts is directed by FIGO stages observed in every carcinoma subtype. The molecular ovarian carcinoma subtypes are five and can be classified as follows: High-grade serous, low-grade serous, endometrioid, mucinous and clear cell; however, there are other subtypes to be described since they belong in the five subtypes or other similar subtypes, such as carcinosarcoma (analogous to malignant mixed Mullerian/mesodermal tumors) and malignant Brenner tumors. Other cellular subtypes are currently in discovery. This is particularly relevant in HGSOC, where distinct methylation patterns have been identified, linking them to tumor origin, subtype differentiation and patient prognosis. The heterogeneity of ovarian carcinoma is further exemplified by the differential expression of miRs and lncRNAs, which are involved in gene regulation.

The molecular prognosis of ovarian carcinoma varies. Firstly, hereditary ovarian carcinoma exhibits a greater effect than sporadic ovarian carcinoma. By contrast, the survival of each patient with spontaneous ovarian carcinoma depends on the carcinoma development and the subtype. At a molecular level, deviations in the DNA methylation and RNA transcription have been associated with metastasis stages and the development of therapy-resistant cancer cells. These findings suggest that molecular signatures, including miR and lncRNA profiles, could

serve as valuable biomarkers for diagnosis, prognosis and therapeutic targeting in ovarian carcinomas. Despite the advances in the understanding of the molecular underpinnings of ovarian carcinomas, the disease prognosis for patients, notably those diagnosed with advanced-stage or metastatic disease remains poor, with survival rates being markedly lower among these groups.

Current diagnostic and therapeutic strategies are increasingly incorporating molecular data, including RNA transcriptomics and DNA methylation analysis, to improve the precision of treatment approaches. While hereditary mutations, such as those noted in *BRCA1/2*, confer a significant risk, epigenetic changes, notably in the later stages of the disease, are critical in shaping the tumor phenotype and response to therapy. In clinical practice, evidence leads to the hypothesis that certain genes could be used as a combination to adjust cancer treatments. However, a pair of primers may not provide a clinical solution. Therefore, practical techniques, such as PCR and sequencing, are used for validation of the next biological characterization of chromosomes. In the present review, it was hypothesized that chromosome instability, which is characterized by gain of chromosomes in cancer cells and the loss of specific chromosomes or their translocation, should be the focus of future research. For example, changes in DNA methylation of chromosomes 9 and 19 (Figs. 2 and 3) in high-grade serous ovarian carcinoma are associated with ovarian carcinoma progression and resistance to treatments.

Ultimately, a comprehensive understanding of the molecular heterogeneity in ovarian carcinoma, including the roles of DNA methylation and RNA transcription into the nucleus, is essential to develop a vision for more effective treatments, increase the understanding of disease progression and improve long-term outcomes for patients. The continued exploration of these molecular pathways holds the potential not only to revolutionize but also to reform the clinical management of ovarian carcinomas.

Acknowledgements

This article is part of the productivity of LCE as a PhD student of Biological Sciences Postgrade Program, in the Biomedicine Field.

Funding

This article was supported by the Programa de Posgrado en Ciencias Biológicas, UNAM. This article is part of the productivity work of the Ph.D. student LCE in the Programa de Posgrado en Ciencias Biológicas, UNAM, and received a fellowship from CONACYT Currículum Vitae Único (CVU)- 1003211. National Cancer Institute, México (INCAN) and CONAHCYT supported this project (grant nos. CMIC: 295466 and CBF 2023-2024-4004). The content is solely the authors's responsibility and does not necessarily represent the official views of the National Cancer Institute of México. Institutional Review Board Statement.

Availability of data and materials

Not applicable.

Authors' contributions

Conceptualization and original draft preparation: VMDCF, VFO, JDC, LAH and LCE. Writing and revising the manuscript JAGR, APT, VFO, LAH and VMDCF. Supervision, project administration and funding acquisition: JDC and LAH. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Momenimovahed Z, Tiznobaik A, Taheri S and Salehiniya H: Ovarian cancer in the world: epidemiology and risk factors. *Int J Womens Health* 11: 287-299, 2019.
2. Siegel RL, Miller KD and Jemal A: Cancer Statistics, 2016. *CA Cancer J Clin* 66: 7-30, 2016.
3. Luo Y, Huang J, Tang Y, Luo X, Ge L, Sheng X, Sun X, Chen Y and Zhu D: Regional methylome profiling reveals dynamic epigenetic heterogeneity and convergent hypomethylation of stem cell quiescence-associated genes in breast cancer following neoadjuvant chemotherapy. *Cell Biosci* 9: 16, 2019.
4. Sandhu R, Roll JD, Rivenbark AG and Coleman WB: Dysregulation of the Epigenome in Human Breast Cancer: Contributions of gene-specific DNA hypermethylation to breast cancer pathobiology and targeting the breast cancer methylome for improved therapy. *Am J Pathol* 185: 282-292, 2015.
5. Maire CL, Fuh MM, Kaulich K, Fita KD, Stevic I, Heiland DH, Welsh JA, Jones JC, Görgens A, Ricklefs T, *et al*: Genome-wide methylation profiling of glioblastoma cell-derived extracellular vesicle DNA allows tumor classification. *Neuro Oncol* 23: 1087-1099, 2021.
6. Wang Z, Cui Y, Wang F, Xu L, Yan Y, Tong X and Yan H: DNA methylation-regulated LINC02587 inhibits ferroptosis and promotes the progression of glioma cells through the CoQ-FSP1 pathway. *BMC Cancer* 23: 989, 2023.
7. Wielandt AM, Villarroel C, Hurtado C, Simian D, Zamorano D, Martínez M, Castro M, Vial MT, Kronberg U and López-Kostner F: Characterization of patients with sporadic colorectal cancer following the new Consensus Molecular Subtypes (CMS). *Rev Méd Chile* 145: 419-430, 2017 (In Spanish).
8. Moreno-Ortiz JM, Jiménez-García J, Gutiérrez-Angulo M, Ayala-Madrigal MD, González-Mercado A, González-Villaseñor CO, Flores-López BA, Alvizo-Rodríguez C, Hernández-Sandoval JA, Fernández-Galindo MA, *et al*: High frequency of MLH1 promoter methylation mediated by gender and age in colorectal tumors from Mexican patients. *GMM* 157: 638-644, 2021 (In Spanish).
9. Del Castillo Falconi VM, Torres-Arciga K, Matus-Ortega G, Díaz-Chávez J and Herrera LA: DNA methyltransferases: From evolution to clinical applications. *Int J Mol Sci* 23: 8994, 2022.
10. Li E, Bestor TH and Jaenisch R: Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. *Cell* 69: 915-926, 1992.
11. Shih IeM and Kurman RJ: Ovarian tumorigenesis: A proposed model based on morphological and molecular genetic analysis. *Am J Pathol* 164: 1511-1518, 2004.
12. Kurman RJ and Shih IeM: Pathogenesis of ovarian cancer: Lessons from morphology and molecular biology and their clinical implications. *Int J Gynecol Pathol* 27: 151-160, 2018.
13. Kurman RJ and Shih IeM: The origin and pathogenesis of epithelial ovarian cancer: A proposed unifying theory. *Am J Surg Pathol* 34: 433-443, 2010.

14. Samuel D, Diaz-Barbe A, Pinto A, Schlumbrecht M and George S: Hereditary ovarian carcinoma: Cancer pathogenesis looking beyond BRCA1 and BRCA2. *Cells* 11: 539, 2022.
15. Ramus SJ, Harrington PA, Pye C, DiCioccio RA, Cox MJ, Garlinghouse-Jones K, Oakley-Girvan I, Jacobs IJ, Hardy RM, Whittemore AS, *et al*: Contribution of BRCA1 and BRCA2 mutations to inherited ovarian cancer. *Hum Mutat* 28: 1207-1215, 2007.
16. Menon U, Karpinskyj C and Gentry-Maharaj A: Ovarian cancer prevention and screening. *Obstet Gynecol* 131: 909-927, 2018.
17. Lavoro A, Scalisi A, Candido S, Zanghì GN, Rizzo R, Gattuso G, Caruso G, Libra M and Falzone L: Identification of the most common BRCA alterations through analysis of germline mutation databases: Is droplet digital PCR an additional strategy for the assessment of such alterations in breast and ovarian cancer families? *Int J Oncol* 60: 58, 2022.
18. Kansuttiwat C, Lertwilaiwittaya P, Roothumnong E, Nakthong P, Dungort P, Meesamarnpong C, Tansa-Nga W, Pongsuktavorn K, Wiboonthanasarn S, Titumjariya W, *et al*: Germline mutations of 4567 patients with hereditary breast-ovarian cancer spectrum in Thailand. *NPJ Genom Med* 9: 9, 2024.
19. Andrikopoulou A, Zografos E, Apostolidou K, Kyriazoglou A, Papatheodoridi AM, Kaparelou M, Koutsoukos K, Lontos M, Dimopoulos MA and Zagouri F: Germline and somatic variants in ovarian carcinoma: A next-generation sequencing (NGS) analysis. *Front Oncol* 12: 1030786, 2022.
20. Ghose A, Bolina A, Mahajan I, Raza SA, Clarke M, Pal A, Sanchez E, Rallis KS and Boussios S: Hereditary ovarian cancer: Towards a cost-effective prevention strategy. *Int J Environ Res Public Health* 19: 12057, 2022.
21. McCluggage WG: Morphological subtypes of ovarian carcinoma: A review with emphasis on new developments and pathogenesis. *Pathology* 43: 420-432, 2011.
22. Andrews L and Mutch DG: Hereditary ovarian cancer and risk reduction. *Best Pract Res Clin Obstet Gynaecol* 41: 31-48, 2017.
23. Lynch HT and Lynch JF: Hereditary nonpolyposis colorectal cancer. *Semin Surg Oncol* 18: 305-313, 2000.
24. Wu H, Shang X, Shi Y, Yang Z, Zhao J, Yang M, Li Y and Xu S: Genetic variants of lncRNA HOTAIR and risk of epithelial ovarian cancer among Chinese women. *Oncotarget* 7: 41047-41052, 2016.
25. Bronder D, Tighe A, Wangsa D, Zong D, Meyer TJ, Wardenaar R, Minshall P, Hirsch D, Heselmeyer-Haddad K and Nelson L, *et al*: TP53 loss initiates chromosomal instability in fallopian tube epithelial cells. *Dis Model Mech* 14: dmm049001, 2021.
26. Goff BA, Mandel L, Muntz HG and Melancon CH: Ovarian carcinoma diagnosis. *Cancer* 89: 2068-2075, 2000.
27. Zeimet AG, Fiegl H, Goebel G, Kopp F, Allasia C, Reimer D, Steppan I, Mueller-Holzner E, Ehrlich M and Marth C: DNA ploidy, nuclear size, proliferation index and DNA-hypomethylation in ovarian cancer. *Gynecol Oncol* 121: 24-31, 2011.
28. Widschwendter M, Jiang G, Woods C, Müller HM, Fiegl H, Goebel G, Marth C, Müller-Holzner E, Zeimet AG, Laird PW and Ehrlich M: DNA hypomethylation and ovarian cancer biology. *Cancer Res* 64: 4472-4480, 2004.
29. Feng W, Marquez RT, Lu Z, Liu J, Lu KH, Issa JP, Fishman DM, Yu Y and Bast RC Jr: Imprinted tumor suppressor genes ARHI and PEG3 are the most frequently down-regulated in human ovarian cancers by loss of heterozygosity and promoter methylation. *Cancer* 112: 1489-1502, 2008.
30. Link PA, Zhang W, Odunsi K and Karpf AR: BORIS/CTCF L mRNA isoform expression and epigenetic regulation in epithelial ovarian cancer. *Cancer Immunol* 13: 6, 2013.
31. Wang YQ, Yan Q, Zhang JR, Li SD, Yang YX and Wan XP: Epigenetic inactivation of BRCA1 through promoter hypermethylation in ovarian cancer progression. *J Obstet Gynaecol Res* 39: 549-554, 2013.
32. Abou-Zeid AA, Azzam AZ and Kamel NA: Methylation status of the gene promoter of cyclin-dependent kinase inhibitor 2A (CDKN2A) in ovarian cancer. *Scand J Clin Lab Invest* 71: 542-547, 2011.
33. Bhagat R, Kumar SS, Vaderhobli S, Premalata CS, Pallavi VR, Ramesh G and Krishnamoorthy L: Epigenetic alteration of p16 and retinoic acid receptor beta genes in the development of epithelial ovarian carcinoma. *Tumour Biol* 35: 9069-9078, 2014.
34. Yang G, Zhang H, Liu Y, Zhou J, He W, Quick CM, Xie D, Smoller BR and Fan CY: Epigenetic and immunohistochemical characterization of the Clusterin gene in ovarian tumors. *Arch Gynecol Obstet* 287: 989-995, 2013.
35. Zhang W, Barger CJ, Link PA, Mhaweche-Fauceglia P, Miller A, Akers SN, Odunsi K and Karpf AR: DNA hypomethylation-mediated activation of Cancer/Testis Antigen 45 (CT45) genes is associated with disease progression and reduced survival in epithelial ovarian cancer. *Epigenetics* 10: 736-748, 2015.
36. Wang B, Yu L, Luo X, Huang L, Li QS, Shao XS, Liu Y, Fan Y and Yang GZ: Detection of OPCML methylation, a possible epigenetic marker, from free serum circulating DNA to improve the diagnosis of early-stage ovarian epithelial cancer. *Oncol Lett* 14: 217-223, 2017.
37. Kaur M, Singh A, Singh K, Gupta S and Sachan M: Development of a multiplex MethyLight assay for the detection of DAPK1 and SOX1 methylation in epithelial ovarian cancer in a north Indian population. *Genes Genet Syst* 91: 175-181, 2016.
38. Rattanapan Y, Korkiatasakul V, Kongruang A, Chareonsirithugul T, Rerkamnuaychoke B, Wongkularb A and Wilailak S: EGFL7 and RASSF1 promoter hypermethylation in epithelial ovarian cancer. *Cancer Genet* 224-225: 37-40, 2018.
39. da Conceição Braga C, Silva LM, Piedade JB, Traiman P and da Silva Filho AL: Epigenetic and expression analysis of TRAIL-R2 and BCL2: On the TRAIL to knowledge of apoptosis in ovarian tumors. *Arch Gynecol Obstet* 289: 1061-1069, 2014.
40. Bonito NA, Borley J, Wilhelm-Benartzi CS, Ghaem-Maghami S and Brown R: Epigenetic regulation of the homeobox gene MSX1 associates with platinum-resistant disease in high-grade serous epithelial ovarian cancer. *Clin Cancer Res* 22: 3097-3104, 2016.
41. Kardum V, Karin V, Glibo M, Skrtic A, Martic TN, Ibisevic N, Skenderi F, Vranic S and Serman L: Methylation-associated silencing of SFRP1 gene in high-grade serous ovarian carcinomas. *Ann Diagn Pathol* 31: 45-49, 2017.
42. Suzuki F, Akahira J, Miura I, Suzuki T, Ito K, Hayashi S, Sasano H and Yaegashi N: Loss of estrogen receptor beta isoform expression and its correlation with aberrant DNA methylation of the 5'-untranslated region in human epithelial ovarian carcinoma. *Cancer Sci* 99: 2365-2372, 2008.
43. Baranova I, Kovarikova H, Laco J, Dvorak O, Sedlakova I, Palicka V and Chmelarova M: Aberrant methylation of PCDH17 gene in high-grade serous ovarian carcinoma. *Cancer Biomark* 23: 125-133, 2018.
44. Ding JJ, Wang G, Shi WX, Zhou HH and Zhao EF: Promoter hypermethylation of FANCF and susceptibility and prognosis of epithelial ovarian cancer. *Reprod Sci* 23: 24-30, 2016.
45. Gozzi G, Chelbi ST, Manni P, Alberti L, Fonda S, Saponaro S, Fabbiani L, Rivasi F, Benhattar J and Losi L: Promoter methylation and downregulated expression of the TBX15 gene in ovarian carcinoma. *Oncol Lett* 12: 2811-2819, 2016.
46. Choi YL, Kang SY, Shin YK, Choi JS, Kim SH, Lee SJ, Bae DS and Ahn G: Aberrant hypermethylation of RASSF1A promoter in ovarian borderline tumors and carcinomas. *Virchows Archiv* 448: 331-336, 2006.
47. Häfner N, Steinbach D, Jansen L, Diebolder H, Dürst M and Runnebaum IB: RUNX3 and CAMK2N1 hypermethylation as prognostic marker for epithelial ovarian cancer. *Int J Cancer* 138: 217-228, 2016.
48. Jin P, Song Y and Yu G: The role of abnormal methylation of Wnt5a gene promoter regions in human epithelial ovarian cancer: A clinical and experimental study. *Anal Cell Pathol (Amst)* 2018: 6567081, 2018.
49. Khodadadi E, Fahmideh L, Khodadadi E, Dao S, Yousefi M, Taghizadeh S, Asgharzadeh M, Yousefi B and Kafil HS: Current advances in DNA methylation analysis methods. *Biomed Res Int* 2021: 8827516, 2021.
50. Gattuso G, Lavoro A, Caltabiano R, Madonna G, Capone M, Ascierto PA, Falzone L, Libra M and Candido S: Methylation-sensitive restriction enzyme-droplet digital PCR assay for the one-step highly sensitive analysis of DNA methylation hotspots. *Int J Mol Med* 53: 42, 2024.
51. Falzone L, Salemi R, Travali S, Scalisi A, McCubrey JA, Candido S and Libra M: MMP-9 overexpression is associated with intragenic hypermethylation of MMP9 gene in melanoma. *Aging (Albany NY)* 8: 933-944, 2016.
52. Singer M, Kosti I, Pachter L and Mandel-Gutfreund Y: A diverse epigenetic landscape at human exons with implication for expression. *Nucleic Acids Res* 43: 3498-3508, 2015.
53. Davidson B, Tropé CG and Reich R: The clinical and diagnostic role of microRNAs in ovarian carcinoma. *Gynecol Oncol* 133: 640-646, 2014.
54. Sheng X, Li J, Yang L, Chen Z, Zhao Q, Tan L, Zhou Y and Li J: Promoter hypermethylation influences the suppressive role of maternally expressed 3, a long non-coding RNA, in the development of epithelial ovarian cancer. *Oncol Rep* 32: 277-285, 2014.
55. Loginov VI, Pronina IV, Burdennyy AM, Filippova EA, Kazubskaya TP, Kushlinsky DN, Utkin DO, Khodyrev DS, Kushlinskii NE, Dmitriev AA and Braga EA: Novel miRNA genes deregulated by aberrant methylation in ovarian carcinoma are involved in metastasis. *Gene* 662: 28-36, 2018.

56. Filippov-Levy N, Cohen-Schussheim H, Tropé CG, Hetland Falkenthal TE, Smith Y, Davidson B and Reich R: Expression and clinical role of long non-coding RNA in high-grade serous carcinoma. *Gynecol Oncol* 148: 559-566, 2018.
57. Liu X, Dai C, Jia G, Xu S, Fu Z, Xu J, Li Q, Ruan H and Xu P: Microarray analysis reveals differentially expressed lncRNAs in benign epithelial ovarian cysts and normal ovaries. *Oncol Rep* 38: 799-808, 2017.
58. Lu YM, Wang Y, Liu SQ, Zhou MY and Guo YR: Profile and validation of dysregulated long non-coding RNAs and mRNAs in ovarian cancer. *Oncol Rep* 40: 2964-2976, 2018.
59. Wang H, Fu Z, Dai C, Cao J, Liu X, Xu J, Lv M, Gu Y, Zhang J, Hua X, *et al*: LncRNAs expression profiling in normal ovary, benign ovarian cyst and malignant epithelial ovarian cancer. *Sci Rep* 6: 38983, 2016.
60. Boyd C and McCluggage WG: Low-grade ovarian serous neoplasms (low-grade serous carcinoma and serous borderline tumor) associated with high-grade serous carcinoma or undifferentiated carcinoma: Report of a series of cases of an unusual phenomenon. *Am J Surg Pathol* 36: 368-375, 2012.
61. Pisanic TR II, Cope LM, Lin SF, Yen TT, Athamanolap P, Asaka R, Nakayama K, Fader AN, Wang TH, Shih IM and Wang TL: Methyloic analysis of ovarian cancers identifies tumor-specific alterations readily detectable in early precursor lesions. *Clin Cancer Res* 24: 6536-6547, 2018.
62. Klinkebiel D, Zhang W, Akers SN, Odunsi K and Karpf AR: DNA Methyloic analyses implicate fallopian tube epithelia as the origin for high-grade serous ovarian cancer. *Mol Cancer Res* 14: 787-794, 2016.
63. Givel AM, Kieffer Y, Scholer-Dahirel A, Sirven P, Cardon M, Pelon F, Magagna I, Gentric G, Costa A, Bonneau C, Mieulet V, *et al*: miR200-regulated CXCL12 β promotes fibroblast heterogeneity and immunosuppression in ovarian cancers. *Nat Commun* 9: 1056, 2018.
64. Wang Y, Qiu C, Lu N, Liu Z, Jin C, Sun C, Bu H, Yu H, Dongol S and Kong B: FOXD1 is targeted by miR-30a-5p and miR-200a-5p and suppresses the proliferation of human ovarian carcinoma cells by promoting p21 expression in a p53-independent manner. *Int J Oncol* 52: 2130-2142, 2018.
65. Ma H, Tian T, Liang S, Liu X, Shen H, Xia M, Liu X, Zhang W, Wang L, Chen S and Yu L: Estrogen receptor-mediated miR-486-5p regulation of OLFM4 expression in ovarian cancer. *Oncotarget* 7: 10594-1605, 2016.
66. Nymoen DA, Slipicevic A, Holth A, Emilsen E, Hetland Falkenthal TE, Tropé CG, Reich R, Flørenes VA and Davidson B: MiR-29a is a candidate biomarker of better survival in metastatic high-grade serous carcinoma. *Hum Pathol* 54: 74-81, 2016.
67. Arts FA, Keogh L, Smyth P, O'Toole S, Ta R, Gleeson N, O'Leary JJ, Flavin R and Sheils O: miR-223 potentially targets SWI/SNF complex protein SMARCD1 in atypical proliferative serous tumor and high-grade ovarian serous carcinoma. *Hum Pathol* 70: 98-104, 2017.
68. Chaluvally-Raghavan P, Jeong KJ, Pradeep S, Silva AM, Yu S, Liu W, Moss T, Rodriguez-Aguayo C, Zhang D and Ram P, *et al*: Direct upregulation of STAT3 by MicroRNA-551b-3p deregulates growth and metastasis of ovarian cancer. *Cell Rep* 15: 1493-1504, 2016.
69. Zhao H, Liu S, Wang G, Wu X, Ding Y, Guo G, Jiang J and Cui S: Expression of miR-136 is associated with the primary cisplatin resistance of human epithelial ovarian cancer. *Oncol Rep* 33: 591-598, 2015.
70. Kuznetsov VA, Tang Z and Ivshina AV: Identification of common oncogenic and early developmental pathways in the ovarian carcinomas controlling by distinct prognostically significant microRNA subsets. *BMC Genomics* 18 (Suppl 6): 692, 2017.
71. Zhang X, Guo G, Wang G, Zhao J, Wang B, Yu X and Ding Y: 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* 12: 8021-8031, 2015.
72. Yanaihara N, Noguchi Y, Saito M, Takenaka M, Takakura S, Yamada K and Okamoto A: MicroRNA gene expression signature driven by miR-9 overexpression in ovarian clear cell carcinoma. *PLoS One* 11: e0162584, 2016.
73. Furlan D, Carnevali I, Marcomini B, Cerutti R, Dainese E, Capella C and Riva C: The high frequency of de novo promoter methylation in synchronous primary endometrial and ovarian carcinomas. *Clin Cancer Res* 12: 3329-3336, 2006.
74. Niskakoski A, Pasanen A, Porkka N, Eldfors S, Lassus H, Renkonen-Sinisalo L, Kaur S, Mecklin JP, Büttow R and Peltomäki P: Converging endometrial and ovarian tumorigenesis in Lynch syndrome: Shared origin of synchronous carcinomas. *Gynecol Oncol* 150: 92-98, 2018.
75. Kolbe DL, DeLoia JA, Porter-Gill P, Strange M, Petrykowska HM, Guirguis A, Krivak TC, Brody LC and Elnitski L: Differential analysis of ovarian and endometrial cancers identifies a methylator phenotype. *PLoS One* 7: e32941, 2012.
76. Guo C, Ren F, Wang D, Li Y, Liu K, Liu S and Chen P: RUNX3 is inactivated by promoter hypermethylation in malignant transformation of ovarian endometriosis. *Oncol Rep* 32: 2580-2588, 2014.
77. Liew PL, Huang RL, Weng YC, Fang CL, Hui-Ming Huang T and Lai HC: Distinct methylation profile of mucinous ovarian carcinoma reveals susceptibility to proteasome inhibitors: Methylation profile of MuOC and PSMB8. *Int J Cancer* 143: 355-367, 2018.
78. Agostini A, Brunetti M, Davidson B, Tropé CG, Eriksson AGZ, Heim S, Panagopoulos I and Micci F: The microRNA miR-192/215 family is upregulated in mucinous ovarian carcinomas. *Sci Rep* 8: 11069, 2018.
79. Vang R, Shih IeM and Kurman RJ: Ovarian low-grade and high-grade serous carcinoma: Pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. *Adv Anat Pathol* 16: 267-282, 2009.
80. Bowtell DD: The genesis and evolution of high-grade serous ovarian cancer. *Nat Rev Cancer* 10: 803-808, 2010.
81. O'Shea AS: Clinical staging of ovarian cancer. *Methods Mol Biol* 2424: 3-10, 2022.
82. Richards EJ, Permeth-Wey J, Li Y, Chen YA, Coppola D, Reid BM, Lin HY, Teer JK, Berchuck A and Birrer MJ, *et al*: A functional variant in HOXA11-AS, a novel long non-coding RNA, inhibits the oncogenic phenotype of epithelial ovarian cancer. *Oncotarget* 6: 34745-34757, 2015.
83. Zhang T, Wu D, Deng S, Han R, Liu T, Li J and Xu Y: Integrated analysis reveals that long non-coding RNA TUBA4B can be used as a prognostic biomarker in various cancers. *Cell Physiol Biochem* 49: 530-544, 2018.
84. Meryet-Figüère M, Lambert B, Gauduchon P, Vigneron N, Brotin E, Poulain L and Denoyelle C: An overview of long non-coding RNAs in ovarian cancers. *Oncotarget* 7: 44719-44734, 2016.
85. Zhong Y, Gao D, He S, Shuai C and Peng S: Dysregulated expression of long noncoding RNAs in ovarian cancer. *Int J Gynecol Cancer* 26: 1564-1570, 2016.
86. Ma Y, Lu Y and Lu B: MicroRNA and Long Non-Coding RNA in ovarian carcinoma: Translational insights and potential clinical applications. *Cancer Invest* 34: 465-476, 2016.
87. Lin X, Qiu J and Hua K: Long non-coding RNAs as emerging regulators of epithelial to mesenchymal transition in gynecologic cancers. *Biosci Trends* 12: 342-353, 2018.
88. Micheel J, Safrastyan A and Wolny D: Advances in non-coding RNA sequencing. *Noncoding RNA* 7: 70, 2021.
89. Zhang N, Hu G, Myers TG and Williamson PR: Protocols for the analysis of microRNA expression, biogenesis, and function in immune cells. *Curr Protoc Immunol* 126: e178, 2019.
90. Zhang S, Leng T, Zhang Q, Zhao Q, Nie X and Yang L: Sanguinarine inhibits epithelial ovarian cancer development via regulating long non-coding RNA CASC2-EIF4A3 axis and/or inhibiting NF- κ B signaling or PI3K/AKT/mTOR pathway. *Biomed Pharmacother* 102: 302-308, 2018.
91. Qiu JJ, Lin YY, Ye LC, Ding JX, Feng WW, Jin HY, Zhang Y, Li Q and Hua KQ: Overexpression of long non-coding RNA HOTAIR predicts poor patient prognosis and promotes tumor metastasis in epithelial ovarian cancer. *Gynecol Oncol* 134: 121-128, 2014.
92. Xi J, Feng J and Zeng S: Long noncoding RNA lncBRM facilitates the proliferation, migration and invasion of ovarian cancer cells via upregulation of Sox4. *Am J Cancer Res* 7: 2180-2189, 2017.
93. Zhang Y, Dun Y, Zhou S and Huang XH: LncRNA HOXD-AS1 promotes epithelial ovarian cancer cells proliferation and invasion by targeting miR-133a-3p and activating Wnt/ β -catenin signaling pathway. *Biomed Pharmacother* 96: 1216-1221, 2017.
94. Liu Y, Wang Y, Yao D and Cui D: LncSOX4 serves an oncogenic role in the tumorigenesis of epithelial ovarian cancer by promoting cell proliferation and inhibiting apoptosis. *Mol Med Rep* 17: 8282-8288, 2018.
95. Yan H, Li H, Li P, Li X, Lin J, Zhu L, Silva MA, Wang X, Wang P and Zhang Z: Long noncoding RNA MLK7-AS1 promotes ovarian cancer cells progression by modulating miR-375/YAP1 axis. *J Exp Clin Cancer Res* 37: 237, 2018.
96. Li T, Chen Y, Zhang J and Liu S: LncRNA TUG1 promotes cells proliferation and inhibits cells apoptosis through regulating AURKA in epithelial ovarian cancer cells. *Medicine (Baltimore)* 97: e12131, 2018.
97. Wang YS, Ma LN, Sun JX, Liu N and Wang H: Long non-coding CPS1-IT1 is a positive prognostic factor and inhibits epithelial ovarian cancer tumorigenesis. *Eur Rev Med Pharmacol Sci* 21: 3169-3175, 2017.

98. Zhu FF, Zheng FY, Wang HO, Zheng JJ and Zhang Q: Downregulation of lncRNA TUBA4B is associated with poor prognosis for epithelial ovarian cancer. *Pathol Oncol Res* 24: 419-425, 2018.
99. Ying X, Wei K, Lin Z, Cui Y, Ding J, Chen Y and Xu B: MicroRNA-125b suppresses ovarian cancer progression via suppression of the epithelial-mesenchymal transition pathway by targeting the SET protein. *Cell Physiol Biochem* 39: 501-510, 2016.
100. Zhu T, Gao W, Chen X, Zhang Y, Wu M, Zhang P and Wang S: A pilot study of circulating MicroRNA-125b as a diagnostic and prognostic biomarker for epithelial ovarian cancer. *Int J Gynecol Cancer* 27: 3-10, 2017.
101. Teng Y, Zhang Y, Qu K, Yang X, Fu J, Chen W and Li X: MicroRNA-29B (mir-29b) regulates the Warburg effect in ovarian cancer by targeting AKT2 and AKT3. *Oncotarget* 6: 40799-40814, 2015.
102. Cao Q, Lu K, Dai S, Hu Y and Fan W: Clinicopathological and prognostic implications of the miR-200 family in patients with epithelial ovarian cancer. *Int J Clin Exp Pathol* 7: 2392-2401, 2014.
103. Kapetanakis NI, Uzan C, Jimenez-Pailhes AS, Gouy S, Bentivegna E, Morice P, Caron O, Gourzones-Dmitriev C, Le Teuff G and Bussan P: Plasma miR-200b in ovarian carcinoma patients: Distinct pattern of pre/post-treatment variation compared to CA-125 and potential for prediction of progression-free survival. *Oncotarget* 6: 36815-36824, 2015.
104. Meng X, Müller V, Milde-Langosch K, Trillsch F, Pantel K and Schwarzenbach H: Diagnostic and prognostic relevance of circulating exosomal miR-373, miR-200a, miR-200b and miR-200c in patients with epithelial ovarian cancer. *Oncotarget* 7: 16923-16935, 2016.
105. Du Z and Sha X: Demethoxycurcumin inhibited human epithelial ovarian cancer cells' growth via up-regulating miR-551a. *Tumour Biol* 39: 1010428317694302, 2017.
106. Chen S, Chen X, Xiu YL, Sun KX and Zhao Y: MicroRNA-490-3P targets CDK1 and inhibits ovarian epithelial carcinoma tumorigenesis and progression. *Cancer Lett* 362: 122-130, 2015.
107. Shuang T, Wang M, Shi C, Zhou Y and Wang D: Down-regulated expression of miR-134 contributes to paclitaxel resistance in human ovarian cancer cells. *FEBS Lett* 589: 3154-3164, 2015.
108. Zou YT, Gao JY, Wang HL, Wang Y, Wang H and Li PL: Downregulation of microRNA-630 inhibits cell proliferation and invasion and enhances chemosensitivity in human ovarian carcinoma. *Genet Mol Res* 14: 8766-8777, 2015.
109. Zhang H and Li W: Dysregulation of micro-143-3p and BALBP1 contributes to the pathogenesis of the development of ovarian carcinoma. *Oncol Rep* 36: 3605-3610, 2016.
110. Zhang W, Zeng Q, Ban Z, Cao J, Chu T, Lei D, Liu C, Guo W and Zeng X: Effects of let-7c on the proliferation of ovarian carcinoma cells by targeted regulation of CDC25a gene expression. *Oncol Lett* 16: 5543-5550, 2018.
111. Liu MX, Siu MK, Liu SS, Yam JW, Ngan HY and Chan DW: Epigenetic silencing of microRNA-199b-5p is associated with acquired chemoresistance via activation of JAG1-Notch1 signaling in ovarian cancer. *Oncotarget* 5: 944-958, 2014.
112. Kobayashi M, Sawada K, Nakamura K, Yoshimura A, Miyamoto M, Shimizu A, Ishida K, Nakatsuka E, Kodama M, Hashimoto K, *et al*: Exosomal miR-1290 is a potential biomarker of high-grade serous ovarian carcinoma and can discriminate patients from those with malignancies of other histological types. *J Ovarian Res* 11: 81, 2018.
113. Zhao H, Bi T, Qu Z, Jiang J, Cui S and Wang Y: Expression of miR-224-5p is associated with the original cisplatin resistance of ovarian papillary serous carcinoma. *Oncol Rep* 32: 1003-1012, 2014.
114. Chen Y, Chen Q, Liu Q and Gao F: Human epididymis protein 4 expression positively correlated with miR-21 and served as a prognostic indicator in ovarian cancer. *Tumour Biol* 37: 8359-8365, 2016.
115. Li L, Huang K, You Y, Fu X, Hu L, Song L and Meng Y: Hypoxia-induced miR-210 in epithelial ovarian cancer enhances cancer cell viability via promoting proliferation and inhibiting apoptosis. *Int J Oncol* 44: 2111-2120, 2014.
116. Zhu X, Shen H, Yin X, Long L, Chen X, Feng F, Liu Y, Zhao P, Xu Y, Li M, *et al*: IL-6R/STAT3/miR-204 feedback loop contributes to cisplatin resistance of epithelial ovarian cancer cells. *Oncotarget* 8: 39154-39166, 2017.
117. Fan Y, Fan J, Huang L, Ye M, Huang Z, Wang Y, Li Q and Huang J: Increased expression of microRNA-196a predicts poor prognosis in human ovarian carcinoma. *Int J Clin Exp Pathol* 8: 4132-4137, 2015.
118. Koukourakis MI, Kontomanolis E, Sotiropoulou M, Mittrakas A, Dafa E, Pouliou S, Sivridis E and Giatromanolaki A: Increased soluble PD-L1 levels in the plasma of patients with epithelial ovarian cancer correlate with plasma levels of miR34a and miR200. *Anticancer Res* 38: 5739-5745, 2018.
119. Liu J, Dou Y and Sheng M: Inhibition of microRNA-383 has tumor suppressive effect in human epithelial ovarian cancer through the action on caspase-2 gene. *Biomed Pharmacother* 83: 1286-1294, 2016.
120. Dai F, Zhang Y and Chen Y: Involvement of miR-29b signaling in the sensitivity to chemotherapy in patients with ovarian carcinoma. *Hum Pathol* 45: 1285-1293, 2014.
121. Xiao M, Cai J, Cai L, Jia J, Xie L, Zhu Y, Huang B, Jin D and Wang Z: Let-7e sensitizes epithelial ovarian cancer to cisplatin through repressing DNA double strand break repair. *J Ovarian Res* 10: 24, 2017.
122. Li X, Pan Q, Wan X, Mao Y, Lu W, Xie X and Cheng X: Methylation-associated Has-miR-9 deregulation in paclitaxel-resistant epithelial ovarian carcinoma. *BMC Cancer* 15: 509, 2015.
123. Paudel D, Zhou W, Ouyang Y, Dong S, Huang Q, Giri R, Wang J and Tong X: MicroRNA-130b functions as a tumor suppressor by regulating RUNX3 in epithelial ovarian cancer. *Gene* 586: 48-55, 2016.
124. Duan S, Dong X, Hai J, Jiang J, Wang W, Yang J, Zhang W and Chen C: MicroRNA-135a-3p is downregulated and serves as a tumour suppressor in ovarian cancer by targeting CCR2. *Biomed Pharmacother* 107: 712-720, 2018.
125. Chen X, Dong C, Law PT, Chan MT, Su Z, Wang S, Wu WK and Xu H: MicroRNA-145 targets TRIM2 and exerts tumor-suppressing functions in epithelial ovarian cancer. *Gynecol Oncol* 139: 513-519, 2015.
126. Qin CZ, Lou XY, Lv QL, Cheng L, Wu NY, Hu L and Zhou HH: MicroRNA-184 acts as a potential diagnostic and prognostic marker in epithelial ovarian cancer and regulates cell proliferation, apoptosis and inflammation. *Pharmazie* 70: 668-673, 2015.
127. Liang T, Li L, Cheng Y, Ren C and Zhang G: MicroRNA-194 promotes the growth, migration, and invasion of ovarian carcinoma cells by targeting protein tyrosine phosphatase nonreceptor type 12. *Oncotargets Ther* 9: 4307-4315, 2016.
128. Wei C, Zhang X, He S, Liu B, Han H and Sun X: MicroRNA-219-5p inhibits the proliferation, migration, and invasion of epithelial ovarian cancer cells by targeting the Twist/Wnt/ β -catenin signaling pathway. *Gene* 637: 25-32, 2017.
129. Fu X, Li Y, Alvero A, Li J, Wu Q, Xiao Q, Peng Y, Hu Y, Li X, Yan W, *et al*: MicroRNA-222-3p/GNAI2/AKT axis inhibits epithelial ovarian cancer cell growth and associates with good overall survival. *Oncotarget* 7: 80633-80654, 2016.
130. Wu X, Ruan Y, Jiang H and Xu C: MicroRNA-424 inhibits cell migration, invasion, and epithelial mesenchymal transition by downregulating doublecortin-like kinase 1 in ovarian clear cell carcinoma. *Int J Biochem Cell Biol* 85: 66-74, 2017.
131. Zhang J, Liu L, Sun Y, Xiang J, Zhou D, Wang L, Xu H, Yang X, Du N and Zhang M, *et al*: MicroRNA-520g promotes epithelial ovarian cancer progression and chemoresistance via DAPK2 repression. *Oncotarget* 7: 26516-26534, 2016.
132. Zhang L, Li Z, Gai F and Wang Y: MicroRNA-137 suppresses tumor growth in epithelial ovarian cancer in vitro and in vivo. *Mol Med Rep* 12: 3107-3114, 2015.
133. Liu J, Jin S and Wang R: MicroRNA-139 suppressed tumor cell proliferation, migration and invasion by directly targeting HDGF in epithelial ovarian cancer. *Mol Med Rep* 16: 3379-3386, 2017.
134. Xu L, Li H, Su L, Lu Q and Liu Z: MicroRNA-455 inhibits cell proliferation and invasion of epithelial ovarian cancer by directly targeting Notch1. *Mol Med Rep* 16: 9777-9785, 2017.
135. Yan J, Jiang J, Meng XN, Xiu YL and Zong ZH: MiR-23b targets cyclin G1 and suppresses ovarian cancer tumorigenesis and progression. *J Exp Clin Cancer Res* 35: 31, 2016.
136. Lin J, Zhang L, Huang H, Huang Y, Huang L, Wang J, Huang S, He L, Zhou Y, Jia W, *et al*: MiR-26b/KPNA2 axis inhibits epithelial ovarian carcinoma proliferation and metastasis through downregulating OCT4. *Oncotarget* 6: 23793-23806, 2015.
137. Xu J, Jiang N, Shi H, Zhao S, Yao S and Shen H: miR-28-5p promotes the development and progression of ovarian cancer through inhibition of N4BP1. *Int J Oncol* 50: 1383-1391, 2017.
138. Wang Y, Zhang X, Tang W, Lin Z, Xu L, Dong R, Li Y, Li J, Zhang Z, Li X, *et al*: miR-130a upregulates mTOR pathway by targeting TSC1 and is transactivated by NF- κ B in high-grade serous ovarian carcinoma. *Cell Death Differ* 24: 2089-2100, 2017.
139. Wang L, He J, Xu H, Xu L and Li N: MiR-143 targets CTGF and exerts tumor-suppressing functions in epithelial ovarian cancer. *Am J Transl Res* 8: 2716-2726, 2016.
140. Dong M, Yang P and Hua F: miR-191 modulates malignant transformation of endometriosis through regulating TIMP3. *Med Sci Monit* 21: 915-920, 2015.
141. Niu K, Shen W, Zhang Y, Zhao Y and Lu Y: MiR-205 promotes motility of ovarian cancer cells via targeting ZEB1. *Gene* 574: 330-336, 2015.

142. Dai C, Xie Y, Zhuang X and Yuan Z: MiR-206 inhibits epithelial ovarian cancer cells growth and invasion via blocking c-Met/AKT/mTOR signaling pathway. *Biomed Pharmacother* 104: 763-770, 2018.
143. Xia B, Yang S, Liu T and Lou G: miR-211 suppresses epithelial ovarian cancer proliferation and cell-cycle progression by targeting Cyclin D1 and CDK6. *Mol Cancer* 14: 57, 2015.
144. Wu Q, Ren X, Zhang Y, Fu X, Li Y, Peng Y, Xiao Q, Li T, Ouyang C, Hu Y, *et al*: MiR-221-3p targets ARF4 and inhibits the proliferation and migration of epithelial ovarian cancer cells. *Biochem Biophys Res Commun* 497: 1162-1170, 2018.
145. Cao L, Wan Q, Li F and Tang C: MiR-363 inhibits cisplatin chemoresistance of epithelial ovarian cancer by regulating snail-induced epithelial-mesenchymal transition. *BMB Rep* 51: 456-461, 2018.
146. Xia B, Li H, Yang S, Liu T and Lou G: MiR-381 inhibits epithelial ovarian cancer malignancy via YY1 suppression. *Tumour Biol* 37: 9157-9167, 2016.
147. Yuan J, Wang K and Xi M: MiR-494 inhibits epithelial ovarian cancer growth by targeting c-Myc. *Med Sci Monit* 22: 617-624, 2016.
148. Li N, Zhao X, Wang L, Zhang S, Cui M and He J: miR-494 suppresses tumor growth of epithelial ovarian carcinoma by targeting IGF1R. *Tumour Biol* 37: 7767-7776, 2016.
149. Zhou QH, Zhao YM, JIA LL and Zhang Y: Mir-595 is a significant indicator of poor patient prognosis in epithelial ovarian cancer. *Eur Rev Med Pharmacol Sci* 21: 4278-4282, 2017.
150. Zhang S, Zhang JY, Lu LJ, Wang CH and Wang LH: MiR-630 promotes epithelial ovarian cancer proliferation and invasion via targeting KLF6. *Eur Rev Med Pharmacol Sci* 21: 4542-4547, 217.
151. Shi C and Zhang Z: miR-761 inhibits tumor progression by targeting MSI1 in ovarian carcinoma. *Tumour Biol* 37: 5437-5443, 2016.
152. Xie X, Huang Y, Chen L and Wang J: miR-221 regulates proliferation and apoptosis of ovarian cancer cells by targeting BMF. *Oncol Lett* 16: 6697-6704, 2018.
153. Wen C, Liu X, Ma H, Zhang W and Li H: miR-338-3p suppresses tumor growth of ovarian epithelial carcinoma by targeting Runx2. *Int J Oncol* 46: 2277-2285, 2015.
154. Salem M, O'Brien JA, Bernaud S, Shawer H, Ye G, Brkić J, Amleh A, Vanderhyden BC, Refky B, Yang BB, *et al*: miR-590-3p promotes ovarian cancer growth and metastasis via a Novel FOXA2-versican pathway. *Cancer Res* 78: 4175-4190, 2018.
155. Lin Z, Zhao J, Wang X, Zhu X and Gong L: Overexpression of microRNA-497 suppresses cell proliferation and induces apoptosis through targeting paired box 2 in human ovarian cancer. *Oncol Rep* 36: 2101-2107, 2016.
156. Lin M, Xia B, Qin L, Chen H and Lou G: S100A7 regulates ovarian cancer cell metastasis and chemoresistance through MAPK signaling and is targeted by miR-330-5p. *DNA Cell Biol* 37: 491-500, 2018.
157. Chen JL, Chen F, Zhang TT and Liu NF: Suppression of SIK1 by miR-141 in human ovarian cancer cell lines and tissues. *Int J Mol Med* 37: 1601-1610, 2016.
158. Zuberi M, Khan I, Gandhi G, Ray PC and Saxena A: The conglomeration of diagnostic, prognostic and therapeutic potential of serum miR-199a and its association with clinicopathological features in epithelial ovarian cancer. *Tumour Biol* 37: 11259-11266, 2016.
159. Guan X, Zong ZH, Chen S, Sang XB, Wu DD, Wang LL, Liu Y and Zhao Y: The role of miR-372 in ovarian carcinoma cell proliferation. *Gene* 624: 14-20, 2017.
160. Li J, Li D and Zhang W: Tumor suppressor role of miR-217 in human epithelial ovarian cancer by targeting IGF1R. *Oncol Rep* 35: 1671-1679, 2016.
161. Zhang X, Liu J, Zang D, Wu S, Liu A, Zhu J, Wu G, Li J and Jiang L: Upregulation of miR-572 transcriptionally suppresses SOCS1 and p21 and contributes to human ovarian cancer progression. *Oncotarget* 6: 15180-15193, 2015.
162. Zhou J, Gong G, Tan H, Dai F, Zhu X, Chen Y, Wang J, Liu Y, Chen P, Wu X and Wen J: Urinary microRNA-30a-5p is a potential biomarker for ovarian serous adenocarcinoma. *Oncol Rep* 33: 2915-2923, 2015.
163. Zhang X, Li S, Dong C, Xie X and Zhang Y: Knockdown of long noncoding RNA NR_026689 inhibits proliferation and invasion and increases apoptosis in ovarian carcinoma HO-8910PM cells. *Oncol Res* 25: 259-265, 2017.
164. Zhu L, Guo Q, Lu X, Zhao J, Shi J, Wang Z and Zhou X: CTD-2020K17.1, a novel long non-coding RNA, promotes migration, invasion, and proliferation of serous ovarian cancer cells in vitro. *Med Sci Monit* 24: 1329-1339, 2018.
165. Qiu JJ, Zhang XD, Tang XY, Zheng TT, Zhang Y and Hua KQ: ElncRNA1, a long non-coding RNA that is transcriptionally induced by oestrogen, promotes epithelial ovarian cancer cell proliferation. *Int J Oncol* 51: 507-514, 2017.
166. Gao Y, Meng H, Liu S, Hu J, Zhang Y, Jiao T, Liu Y, Ou J, Wang D, Yao L, *et al*: LncRNA-HOST2 regulates cell biological behaviors in epithelial ovarian cancer through a mechanism involving microRNA let-7b. *Hum Mol Genet* 24: 841-852, 2015.
167. Wang Y, Wang H, Song T, Zou Y, Jiang J, Fang L and Li P: HOTAIR is a potential target for the treatment of cisplatin-resistant ovarian cancer. *Mol Med Rep* 12: 2211-2216, 2015.
168. Lu CW, Zhou DD, Xie T, Hao JL, Pant OP, Lu CB and Liu XF: HOXA11 antisense long noncoding RNA (HOXA11-AS): A promising lncRNA in human cancers. *Cancer Med* 7: 3792-3799, 2018.
169. Du W, Feng Z and Sun Q: LncRNA LINC00319 accelerates ovarian cancer progression through miR-423-5p/NACC1 pathway. *Biochem Biophys Res Commun* 507: 198-202, 2018.
170. Shu C, Yan D, Mo Y, Gu J, Shah N and He J: Long noncoding RNA lncARSR promotes epithelial ovarian cancer cell proliferation and invasion by association with HuR and miR-200 family. *Am J Cancer Res* 8: 981-992, 2018.
171. Chen S, Wu DD, Sang XB, Wang LL, Zong ZH, Sun KX, Liu BL and Zhao Y: The lncRNA HULC functions as an oncogene by targeting ATG7 and ITGB1 in epithelial ovarian carcinoma. *Cell Death Dis* 8: e3118, 2017.
172. Qnbo L, Guan W, Ren W, Zhang L, Zhang J and Xu G: MALAT1 affects ovarian cancer cell behavior and patient survival. *Oncol Rep* 39: 2644-2652, 2018.
173. Lin Q, Guan W, Ren W, Zhang L, Zhang J and Xu G: MALAT1 affects ovarian cancer cell behavior and patient survival. *Oncol Rep* 39: 2644-2652, 2018.
174. Yan C, Jiang Y, Wan Y, Zhang L, Liu J, Zhou S and Cheng W: Long noncoding RNA NBAT-1 suppresses tumorigenesis and predicts favorable prognosis in ovarian cancer. *Oncotargets Ther* 10: 1993-2002, 2017.
175. Liu Y, Wang Y, Fu X and Lu Z: Long non-coding RNA NEAT1 promoted ovarian cancer cells' metastasis through regulation of miR-382-3p/ROCK1 axial. *Cancer Sci* 109: 2188-2198, 2018.
176. Chen S, Wang LL, Sun KX, Liu Y, Guan X, Zong ZH and Zhao Y: LncRNA PCGEM1 induces ovarian carcinoma tumorigenesis and progression through RhoA pathway. *Cell Physiol Biochem* 47: 1578-1588, 2018.
177. Huang K, Geng J and Wang J: Long non-coding RNA RP11-552M11.4 promotes cells proliferation, migration and invasion by targeting BRCA2 in ovarian cancer. *Cancer Sci* 109: 1428-1446, 2018.
178. Li H, Liu C, Lu Z, Chen L, Wang J, Li Y and Ma H: Upregulation of the long non-coding RNA SPRY4-IT1 indicates a poor prognosis and promotes tumorigenesis in ovarian cancer. *Biomed Pharmacother* 88: 529-534, 2017.
179. Li TH, Zhang JJ, Liu SX and Chen Y: Long non-coding RNA taurine-upregulated gene 1 predicts unfavorable prognosis, promotes cells proliferation, and inhibits cells apoptosis in epithelial ovarian cancer: *Medicine (Baltimore)* 97: e0575, 2018.
180. Hong HH, Hou LK, Pan X, Wu CY, Huang H, Li B and Nie W: Long non-coding RNA UCA1 is a predictive biomarker of cancer. *Oncotarget* 7: 44442-44447, 2016.
181. Zhang L, Cao X, Zhang L, Zhang X, Sheng H and Tao K: UCA1 overexpression predicts clinical outcome of patients with ovarian cancer receiving adjuvant chemotherapy. *Cancer Chemother Pharmacol* 77: 629-634, 2016.
182. Qiu JJ, Wang Y, Liu YL, Zhang Y, Ding JX and Hua KQ: The long non-coding RNA ANRIL promotes proliferation and cell cycle progression and inhibits apoptosis and senescence in epithelial ovarian cancer. *Oncotarget* 7: 32478-32492, 2016.
183. Cao Y, Shi H, Ren F, Jia Y and Zhang R: Long non-coding RNA CCAT1 promotes metastasis and poor prognosis in epithelial ovarian cancer. *Exp Cell Res* 359: 185-194, 2017.
184. Hua F, Li CH, Chen XG and Liu XP: Long Noncoding RNA CCAT2 knockdown suppresses tumorous progression by sponging miR-424 in epithelial ovarian cancer. *Oncol Res* 26: 241-247, 2018.
185. Yim GW, Kim HJ, Kim LK, Kim SW, Kim S, Nam EJ and Kim YT: Long Non-coding RNA HOXA11 antisense promotes cell proliferation and invasion and predicts patient prognosis in serous ovarian cancer. *Cancer Res Treat* 49: 656-668, 2017.
186. Koutsaki M, Spandidos DA and Zaravinos A: Epithelial-mesenchymal transition-associated miRNAs in ovarian carcinoma, with highlight on the miR-200 family: Prognostic value and prospective role in ovarian cancer therapeutics. *Cancer Lett* 351: 173-181, 2014.

187. Sulaiman SA, Ab Mutalib NS and Jamal R: miR-200c regulation of metastases in ovarian cancer: Potential role in epithelial and mesenchymal transition. *Front Pharmacol* 7: 271, 2016.
188. Teng Y, Su X, Zhang X, Zhang Y, Li C, Niu W, Liu C and Qu K: miRNA-200a/c as potential biomarker in epithelial ovarian cancer (EOC): Evidence based on miRNA meta-signature and clinical investigations. *Oncotarget* 7: 81621-81633, 2016.
189. Muralidhar G and Barbolina M: The miR-200 Family: Versatile players in epithelial ovarian cancer. *Int J Mol Sci* 16: 16833-16847, 2015.
190. Zuberi M, Khan I, Mir R, Gandhi G, Ray PC and 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* 11: e0153902, 2016.
191. Faul C, Gerszten K, Edwards R, Land S, D'Angelo G, Kelley J III and Price F: A phase I/II study of hypofractionated whole abdominal radiation therapy in patients with chemoresistant ovarian carcinoma: Karnofsky score determines treatment outcome. *Int J Radiat Oncol Biol Phys* 47: 749-754, 2000.
192. Iorio GC, Martini S, Arcadipane F, Ricardi U and Franco P: The role of radiotherapy in epithelial ovarian cancer: A literature overview. *Med Oncol* 36: 64, 2019.
193. Sorbe B: Consolidation treatment of advanced ovarian carcinoma with radiotherapy after induction chemotherapy. *Int J Gynecol Cancer* 13 (Suppl 2): S192-S195, 2003.
194. Pang L and Guo Z: Differences in characteristics and outcomes between large-cell neuroendocrine carcinoma of the ovary and high-grade serous ovarian cancer: A retrospective observational cohort study. *Front Oncol* 12: 891699, 2022.
195. Patel SC, Frandsen J, Bhatia S and Gaffney D: Impact on survival with adjuvant radiotherapy for clear cell, mucinous, and endometrioid ovarian cancer: The SEER experience from 2004 to 2011. *J Gynecol Oncol* 27: e45, 2016.
196. Pestell KE, Medlow CJ, Titley JC, Kelland LR and Walton MI: Characterisation Of The P53 Status, Bcl-2 expression and radiation and platinum drug sensitivity of a panel of human ovarian cancer cell lines. *Int J Cancer* 77: 913-918, 1998.
197. Zielske SP: Epigenetic DNA methylation in radiation biology: On the field or on the sidelines? *J Cell Biochem* 116: 212-217, 2015.
198. Kurrey NK, Jalgaonkar SP, Joglekar AV, Ghanate AD, Chaskar PD, Doiphode RY and Bapat SA: Snail and slug mediate radioresistance and chemoresistance by antagonizing p53-Mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells. *Stem Cells* 27: 2059-2068, 2009.
199. Liu WJ, Huang YX, Wang W, Zhang Y, Liu BJ, Qiu JG, Jiang BH and Liu LZ: NOX4 signaling mediates cancer development and therapeutic resistance through HER3 in ovarian cancer cells. *Cells* 10: 1647, 2021.
200. Chen J, Jia Y, Jia ZH, Zhu Y and Jin YM: Silencing the expression of MTDH increases the radiation sensitivity of SKOV3 ovarian cancer cells and reduces their proliferation and metastasis. *Int J Oncol* 53: 2180-2190, 2018.
201. Zhao Y, Liu S, Wen Y and Zhong L: Effect of MicroRNA-210 on the growth of ovarian cancer cells and the efficacy of radiotherapy. *Gynecol Obstet Invest* 86: 71-80, 2021.
202. Xing Y, Cui D, Wang S, Wang P, Xing X and Li H: Oleuropein represses the radiation resistance of ovarian cancer by inhibiting hypoxia and microRNA-299-targeted heparanase expression. *Food Funct* 8: 2857-2864, 2017.
203. Marques C, Ferreira da Silva F, Sousa I and Nave M: Chemotherapy-free treatment of recurrent advanced ovarian cancer: Myth or reality? *Int J Gynecol Cancer* 33: 607-618, 2023.
204. Marchetti C, De Felice F, Romito A, Iacobelli V, Sassu CM, Corrado G, Ricci C, Scambia G and Fagotti A: Chemotherapy resistance in epithelial ovarian cancer: Mechanisms and emerging treatments. *Semin Cancer Biol* 77: 144-166, 2021.
205. Falzone L, Bordonaro R and Libra M: SnapShot: Cancer chemotherapy. *Cell* 186: 1816-1816.e1, 2023.
206. Raab M, Sanhaji M, Zhou S, Rödel F, El-Balat A, Becker S and Strebhardt K: Blocking mitotic exit of ovarian cancer cells by pharmaceutical inhibition of the anaphase-promoting complex reduces chromosomal instability. *Neoplasia* 21: 363-375, 2019.
207. Swanton C, Nicke B, Schuett M, Eklund AC, Ng C, Li Q, Hardcastle T, Lee A, Roy R, East P and Kschischo M: Chromosomal instability determines taxane response. *Proc Natl Acad Sci USA* 106: 8671-8676, 2009.
208. Pradhan M, Risberg BA, Tropé CG, van de Rijn M, Gilks CB and Lee CH: Gross genomic alterations and gene expression profiles of high-grade serous carcinoma of the ovary with and without BRCA1 inactivation. *BMC Cancer* 10: 493, 2010.
209. Tang Z, Yang J, Wang X, Zeng M, Wang J, Wang A, Zhao M, Guo L, Liu C, Li D and Chen J: Active DNA end processing in micronuclei of ovarian cancer cells. *BMC Cancer* 18: 426, 2018.
210. Morden CR, Farrell AC, Sliwowski M, Lichtensztejn Z, Altman AD, Nachtigal MW and McManus KJ: Chromosome instability is prevalent and dynamic in high-grade serous ovarian cancer patient samples. *Gynecol Oncol* 161: 769-778, 2021.
211. Gorringer KL, Chin SF, Pharoah P, Staines JM, Oliveira C, Edwards PA and Caldas C: Evidence that both genetic instability and selection contribute to the accumulation of chromosome alterations in cancer. *Carcinogenesis* 26: 923-930, 2005.
212. Bayani J, Paderova J, Murphy J, Rosen B, Zielenska M and Squire JA: Distinct patterns of structural and numerical chromosomal instability characterize sporadic ovarian cancer. *Neoplasia* 10: 1057-1065, 2008.
213. Birkbak NJ, Eklund AC, Li Q, McClelland SE, Endesfelder D, Tan P, Tan IB, Richardson AL, Szallasi Z and Swanton C: Paradoxical relationship between chromosomal instability and survival outcome in cancer. *Cancer Res* 71: 3447-3452, 2011.
214. Hille S, Rein DT, Riffelmann M, Neumann R, Sartorius J, Pfützner A, Kurbacher CM, Schöndorf T and Breidenbach M: Anticancer drugs induce mdrl gene expression in recurrent ovarian cancer: Anticancer Drugs 17: 1041-1044, 2006.
215. Zhang C, Wang M, Shi C, Shi F and Pei C: Long non-coding RNA Linc00312 modulates the sensitivity of ovarian cancer to cisplatin via the Bcl-2/Caspase-3 signaling pathway. *Biosci Trends* 12: 309-316, 2018.
216. Cui Y, Qin L, Tian D, Wang T, Fan L, Zhang P and Wang Z: ZEB1 Promotes chemoresistance to cisplatin in ovarian cancer cells by suppressing SLC3A2. *Chemotherapy* 63: 262-271, 2018.
217. Sen T, Sen N, Brait M, Begum S, Chatterjee A, Hoque MO, Ratovitski E and Sidransky D: Np63 confers tumor cell resistance to cisplatin through the AKT1 transcriptional regulation. *Cancer Res* 71: 1167-1176, 2011.
218. Kumar S, Kumar A, Shah PP, Rai SN, Panguluri SK and Kakar SS: MicroRNA signature of cis-platin resistant vs. cis-platin sensitive ovarian cancer cell lines. *J Ovarian Res* 4: 17, 2011.
219. Leung AWY, Veinotte CJ, Melong N, Melong N, Oh MH, Chen K, Enfield KSS, Backstrom I, Warburton C, Yapp D, et al: In vivo validation of PAPSS1 (3'-phosphoadenosine 5'-phosphosulfate synthase 1) as a cisplatin-sensitizing therapeutic target. *Clin Cancer Res* 23: 6555-6566, 2017.
220. Kritsch D, Hoffmann F, Steinbach D, Jansen L, Mary Photini S, Gajda M, Mosig AS, Sonnemann J, Peters S and Melnikova M, et al: Tribbles 2 mediates cisplatin sensitivity and DNA damage response in epithelial ovarian cancer. *Int J Cancer* 141: 1600-1614, 2017.
221. Nam EJ, Kim S, Lee TS, Kim HJ, Lee JY, Kim SW, Kim JH and Kim YT: Primary and recurrent ovarian high-grade serous carcinomas display similar microRNA expression patterns relative to those of normal ovarian tissue. *Oncotarget* 7: 70524-70534, 2016.
222. Chong GO, Jeon HS, Han HS, Son JW, Lee YH, Hong DG, Lee YS and Cho Y: Differential MicroRNA expression profiles in primary and recurrent epithelial ovarian cancer. *Anticancer Res* 7: 2611-2617, 2015.
223. Chong GO, Jeon HS, Han HS, Son JW, Lee YH, Hong DG, Park HJ, Lee YS and Cho YL: Overexpression of microRNA-196b accelerates invasiveness of cancer cells in recurrent epithelial ovarian cancer through regulation of homeobox A9. *Cancer Genomics Proteomics* 14: 137-142, 2017.
224. Zhou Y, Wang M, Wu J, Jie Z, Chang S and Shuang T: The clinicopathological significance of miR-1307 in chemotherapy resistant epithelial ovarian cancer. *J Ovarian Res* 8: 23, 2015.
225. Chen C, Hu Y and Li L: NRP1 is targeted by miR-130a and miR-130b, and is associated with multidrug resistance in epithelial ovarian cancer based on integrated gene network analysis. *Mol Med Rep* 13: 188-196, 2016.

