



# Applications of Multi-omics Approaches for Exploring the Molecular Mechanism of Ovarian Carcinogenesis

Miaomiao Ye<sup>†</sup>, Yibin Lin<sup>†</sup>, Shuya Pan, Zhi-wei Wang\* and Xueqiong Zhu\*

Center of Uterine Cancer Diagnosis & Therapy Research of Zhejiang Province, Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

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### \*Correspondence:

Zhi-wei Wang  
zhiweichina@126.com  
Xueqiong Zhu  
zjwzzxq@163.com

<sup>†</sup>These authors have equally  
contributed to this work

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Ovarian cancer ranks as the fifth most common cause of cancer-related death in females. The molecular mechanisms of ovarian carcinogenesis need to be explored in order to identify effective clinical therapies for ovarian cancer. Recently, multi-omics approaches have been applied to determine the mechanisms of ovarian oncogenesis at genomics (DNA), transcriptomics (RNA), proteomics (proteins), and metabolomics (metabolites) levels. Multi-omics approaches can identify some diagnostic and prognostic biomarkers and therapeutic targets for ovarian cancer, and these molecular signatures are beneficial for clarifying the development and progression of ovarian cancer. Moreover, the discovery of molecular signatures and targeted therapy strategies could noticeably improve the prognosis of ovarian cancer patients.

**Keywords:** ovarian cancer, systems biology, genomics, transcriptomics, proteomics, metabolomics, multi-omics

## INTRODUCTION

Ovarian cancer (OC) ranks as the fifth most common cause of cancer-related death in females, and the American Cancer Society predicts that approximately 21,410 new women will be diagnosed with OC, and that 13,770 women will die from OC in the United States in 2021 (1). OC is generally divided into three major pathological subtypes: epithelial-stromal, germ cell, and sex cord-stromal ovarian cancers; epithelial ovarian cancer (EOC) accounts for 90% of OC cases (2). Unfortunately, OC is generally considered a “silent killer” because of the lack of specific symptoms of OC in patients at the early stage and the lack of effective screening strategies. Therefore, more than 60% of OC patients are diagnosed at an advanced stage with extensive invasion and metastasis (3). The standard clinical treatment of EOC comprises of cytoreductive surgery (whenever possible) followed by chemotherapy (4). Currently, platinum-based chemotherapy followed by surgery is a common treatment strategy for OC patients who are not eligible for surgery at presentation (4, 5). While the initial response rate of patients presenting with OC is 60–80%, 70% of advanced-stage OC patients will relapse within 5 years, and many of them acquire drug-resistance (6, 7). At present, serum cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) are extensively used as circulating biomarkers in OC diagnosis and relapse identification (8). However, the sensitivity and specificity of OC diagnosis should be improved, particularly for early-stage OC patients. The failure of early-stage diagnosis and the development of chemoresistance contribute to the high mortality

rates of OC patients. Thus, it is necessary to further elucidate the molecular mechanisms of ovarian carcinogenesis and chemoresistance in OC, and to identify effective molecular targets for early-stage diagnosis and clinical treatment. Recently, multi-omics approaches have been applied to explore the mechanisms of OC development, and our article aims to review advancements in OC research from genomic (DNA), transcriptomic (RNA), proteomic (protein), and metabolomic (metabolite) perspectives.

## MULTI-OMICS APPROACHES IN OVARIAN CANCER

Systems biology has been conducted to gain deeper insight into the mechanisms of the physiology and pathophysiology of human health and disease (9), which span multiple areas involving biological sciences, mathematics, engineering, physics, and computer science (10). Systems biology belongs to an interdisciplinary research field, which integrates experimental and computational approaches to investigate the complex biological systems (11). Systems biology is mainly benefited from the functional analysis of large-scale/high-throughput data (12). Many strategies have been implemented to exploit the diverse parameters underlying these large-scale/high-throughput data, such as the inference of gene regulatory networks (GRNs) (13), or machine learning algorithms and Random Forest (RF) algorithm (14), or Gaussian process regression (GPR) (15), or Pathway Inspector (PI) (16), or using mass spectrometry platforms (17). Furthermore, systems biology approaches have brought unprecedented abilities to screen many potential factors (e.g. DNA, RNA, protein, metabolite) and their interaction networks (18).

Systems biology must adopt the data from multi-omics approaches to fully understand the biology of development and progression of diseases *via* using computational and bioinformatics methods and tools. Multi-omics technologies obtain huge datasets that must be analyzed by biological scientists to generate the required information regarding biological systems, which are integral part of systems biology. In the last two decades, researchers have applied various multi-omics approaches to search for novel biomarkers for diagnosis and treatment *via* genomics (19), transcriptomics (20), proteomics (21), and metabolomics (22) studies in diverse human cancers. DNA microarrays are extensively applied for genomics analysis, which are comprised of microscopic spots of DNA oligonucleotides, each with a specific DNA sequence (known as probes), are a multiplex technology and can explore the transcriptional and genomic profiles for thousands of genes (23). Transcriptomics are conducted to figure out the variation of ribonucleic acid (RNA) level in a cell, thus providing detailed and useful information at the transcriptional aspects, including messenger RNAs (mRNAs) microarrays and noncoding RNAs (ncRNAs) microarray, such as microRNAs (miRNA) arrays, long noncoding RNAs (lncRNAs) arrays, circular RNAs (circRNAs) arrays (24). Transcriptomics could be captured and analyzed by RNA microarrays and RNA sequencing (25).

The emergence of proteomics techniques has enabled the large-scale analysis of the full protein components of complex organelles, a single cell, a specific tissue, or biological fluids (26, 27). Proteomics systematic study the structure, function, and interaction of proteins, which is crucial in understanding the molecular mechanisms of diseases comprehensively and aiding at the prevention, diagnosis, and treatment of diseases (28). Researchers have performed Reverse Phase Protein Microarrays (29), Multiplexed Antibody-Based Protein Arrays (30), Proteome Chips (31), Mass Spectrometry (MS) (32), and other techniques in proteomic analysis.

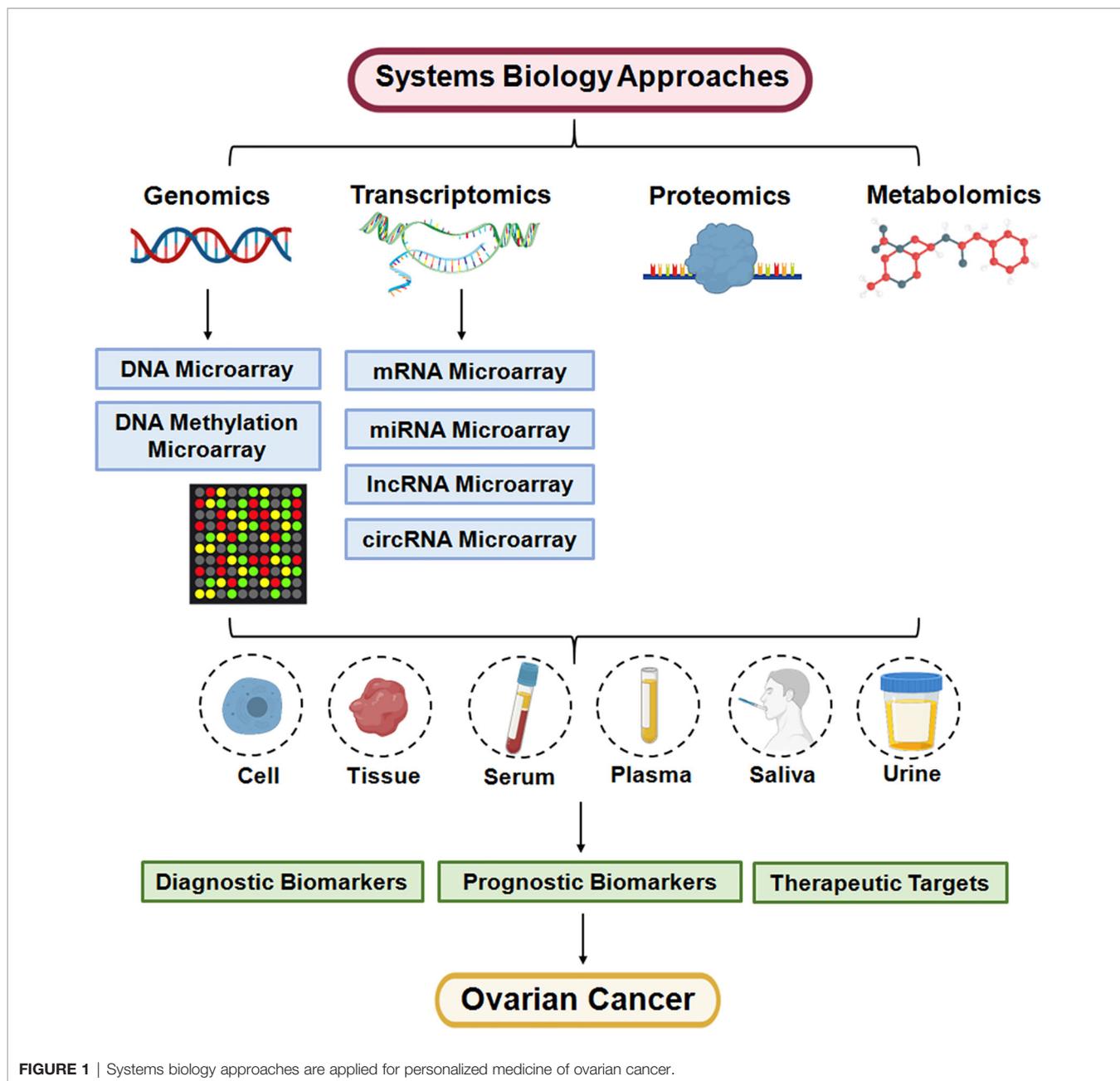
Metabolomics is considered a high-throughput technology to complement the genotype-phenotype landscape, and can be applied to explore hundreds to thousands of metabolites in biofluids, cells, and tissues (33). Metabolomics is a promising tool for cancer research, and mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy are commonly used techniques (34). Moreover, multi-omics approaches have been applied in OC and are helpful for improving the diagnosis and prognosis evaluation of OC (**Figure 1**).

### Genomics

Genomics is a technique giving us the ability to investigate the genome-wide structure, function and regulation (35). The application of genomics in OC generally illustrates the regulation of oncogene and antioncogene profiles at the DNA level (**Table 1**). DNA microarrays are used for exploring the genomic profiles *via* a collection of microscopic spots with thousands of probes attached to a solid surface (23). The probes of DNA microarrays are either complementary DNA (cDNA) or shorter oligodeoxynucleotide sequences (74). Moreover, DNA methylation microarrays are employed to assess the epigenetic modifications, which could regulate gene expression with no changes in the nucleotide sequence (75).

### DNA Microarrays

Gene microarray analysis showed that higher expression of karyopherin 2 (KPNA2) was detected in EOC tissues than in human ovarian surface epithelial tissues (36). Moreover, the overexpression of KPNA2 was correlated with an advanced stage, a high histologic grade, and tumor recurrence and predicted a poor prognosis in EOC patients (36). Another study established oligonucleotide microarray analysis in different histological OCs, and showed that galectin 4 (LGALS4) was highly and specifically expressed in mucinous EOC but exhibited lower expression in benign mucinous cysts and borderline (atypical proliferative) tumor (37). One study performed gene expression profiling to point out that mammaglobin b (SCGB2A1) was the most prominent differentially expressed gene in OC of all major histological types (38). Upregulation of 468 genes and downregulation of 994 genes were detected in EOC tissues *versus* normal endometrial (NE) tissues, while 596 upregulated genes and 883 downregulated genes were identified in clear-cell EOC tissues *versus* NE tissues by oligonucleotide microarray analysis (39). Notably, forkhead box M1 (FOXM1) was overexpressed in both epithelial and clear-cell EOC tissues, potentially serving as a negative indicator of non-serous EOC patient outcomes, and



promoted cancer progression in all platinum-resistant EOC patients (39). Based on microarray analysis, 10 genes, including integrin beta 1 binding protein 3 (ITGB1BP3), collagen type III alpha 1 (COL3A1), collagen type V alpha 2 (COL5A2), collagen type XV alpha 1 (COL15A1), transforming growth factor beta induced (TGFBI), decorin (DCN), lumican (LUM), matrilin 2 (MATN2), periostin (POSTN) and EGF-like domain multiple 6 (EGFL6), were upregulated, and 7 genes such as integrin subunit alpha 1 (ITGA1), collagen type 1 alpha 2 (COL1A2), laminin subunit alpha 1 (LAMA2), glypican 3 (GPC3), keratin 23 (KRT23), vitrin (VIT) and hemicentin 1 (HMCN1) were downregulated in chemo-resistant sublines compared to chemosensitive OC cells (40). The expression of insulin-like growth factor 1 receptor (IGF-

1R) and Erb-B2 receptor tyrosine kinase 3 (ERBB3, also known as HER3) genes was increased in the trastuzumab-resistant OC cell line (SKOV3/T) compared to the parent SKOV3 OC cell lines by microarray analysis (41). In addition, 204 genes were identified as differentially expressed between platinum-resistant and platinum-sensitive OC by microarray analysis; IGF1 was mostly upregulated in platinum-resistant OC (42). Notably, the IGF1, phosphatidylinositol 3-kinase (PI3K), nuclear factor kappa B (NFκB), extracellular signal-regulated kinase (ERK) signalling pathways were associated with chemoresistance in high-grade serous ovarian cancer (HGSO) (42).

The expression of catechol-O-methyltransferase (COMT), neuroleukin (NLK), high mobility group I proteins (HMGI), ERBB3, S100- $\alpha$  protein and acyl-CoA-binding protein (ACBP)

**TABLE 1 |** The application of genomics for exploring the candidate biomarkers for ovarian cancer.

Applied Methods	Subjects	Gene Symbol(s)	Ref.
DNA microarray	Tissues	KPNA2	(36)
DNA microarray	Tissues	LGALS4	(37)
DNA microarray	Tissues	SCGB2A1	(38)
DNA microarray	Tissues	FOXM1	(39)
DNA microarray	Cells	ITGB1BP3, COL3A1, COL5A2, COL15A1, TGFB1, DCN, LUM, MATN2, POSTN, EGFL6, ITGA1, COL1A2, LAMA2, GPC3, KRT23, VIT, HMCN1	(40)
DNA microarray	Cells	IGF-1R, HER3	(41)
DNA microarray	Tissues	IGF1/P13K/NFκB/ERK signaling pathway	(42)
DNA microarray	Tissues	COMT, NLK, HMGI, ErbB-3, S100-α protein, ACBP, COUP-TFII	(43)
DNA microarray	Cells	ARL4C	(44)
DNA microarray	Cells	p53	(45)
DNA microarray	Tissues	COL11A1	(46)
DNA microarray	Tissues	TMPRSS4, MASP1/3, SPC18, PSMB1, IGFBP2, CFI - encoding Complement Factor I, MMP9, ADAM-10	(47)
DNA microarray	Cells	LMX1B	(48)
DNA microarray	Cells	AIFM2, AKTIP, AXIN2, CASP5, FILIP1L, RBBP8, RGC32, RUVBL1, STAG3	(49)
DNA microarray	Cells	ASXL1, H3F3B, CDC73, TGF-beta receptor pathway members, YAP1-MAML2, IKZF2/ERBB4	(50)
DNA microarray	Tissues	PIK3R3	(51)
DNA microarray	Tissues	PKCι, PKCβ1, PKCγ, PKCξ, PKCθ	(52)
DNA microarray	Tissues	RNU6-135P, RNU61262P, VTRNA1-1, MCAM, genes belonging to SNAR gene family	(53)
DNA microarray	Tissues	CREB/ATF, NF-κB/Rel, STAT, Ets family transcription factors	(54)
DNA microarray	Tissues	EGR1, FOSB	(55)
DNA microarray	Cells	EFEMP1	(56)
DNA microarray	Cells	SPARC	(57)
DNA microarray	Tissues	CD9	(58)
DNA microarray	Cells	GLUT-1	(59)
DNA microarray	Tissues	AGR2	(60)
DNA microarray	Cells	CKB	(61)
DNA microarray	Cells	ALDH1A2	(62)
DNA microarray	Cells	ALDH1A1	(63)
DNA microarray	Cells	CCNA1	(64)
DNA microarray	Cells	CDK1	(65)
DNA microarray	Cells	GSK-3α	(66)
DNA microarray	Cells	STAT1	(67)
DNA microarray	Tissues	STAT1, CXCL10, CREB1, MKNK1, MAP3K7, CFL1, PTK2, RIPK1, MYD88, CCL8, CCL7	(68)
DNA Methylation Microarray	Cells	ARNTL	(69)
DNA Methylation Microarray	Tissues	CT45	(70)
DNA Methylation Microarray	Tissues	EGFL7, RASSF1	(71)
DNA Methylation Microarray	Tissues	RUNX3, CAMK2N1	(72)
DNA Methylation Microarray	Cells	ARHGDB1, ARMCX2, COL1A, FLNA, FLNC, MEST, MLH1, NTS, PSMB9	(73)

was upregulated, and the expression of chicken ovalbumin upstream promoter transcription factor II (COUP-TFII) was downregulated in OC tissues *versus* normal tissues, as indicated by DNA microarray analysis (43). This study showed that most dysregulated genes in OC were involved in the process of glucose/insulin metabolism (43). Comparative genomic hybridization (CGH) analysis identified 6 genes situated at 2q36.1-37.3 that were downregulated in an OC cell line with high metastatic potential (HO-8910PM), and the downregulation of ADP-ribosylation factor-like 4C (ARL4C) facilitated the migration but had no effect on the proliferation of HO-8910PM cells (44). The whole human genome microarray indicated that mutant p53 positively regulated the integrin β4 and Akt signalling pathways, which facilitated the adhesion of OC cells to mesothelial cells (45). Collagen type XI alpha 1 (COL11A1) was identified as a disease progression-related gene by DNA microarray, and

COL11A1 facilitated the progression of OC and indicated a poor prognosis in OC patients (46). CLIP-CHIP microarray analysis revealed that 7 genes, including transmembrane serine protease 4 (TMPRSS4), mannan-binding lectin-associated serine protease 1/3 (MASP1/3), signal peptidase complex 18 (SPC18), proteasome 20S subunit beta 1 (PSMB1), IGF binding protein 2 (IGFBP2), CFI-encoding complement factor I, and matrix metalloproteinase 9 (MMP9), were upregulated, while one gene (ADAM-10) was downregulated in patients with early OC recurrence *versus* those with late or no OC recurrence (47). Moreover, higher expression of ADAM-10 was related to a lower risk of progression, while higher expression of CFI was associated with a higher risk of progression of OC (47). Genome-wide copy number analysis identified a recurrent amplification domain on mouse chromosome 2qB, and the LIM homeobox transcription factor 1 beta (LMX1B) gene was located at

this site (48). Notably, LMX1B facilitated the migration of human OC cells and enhanced xenograft growth in nude mice (48). Moreover, global gene expression analysis identified that the NF $\kappa$ B pathway may serve as a mediator of LMX1B-overexpressing OC progression (48). Microcell-mediated chromosome transfer and expression microarray analysis demonstrated that nine genes, including apoptosis inducing factor mitochondria associated 2 (AIFM2), Akt interacting protein (AKTIP), Axin 2 (AXIN2), caspase 5 (CASP5), filamin A interacting protein 1 like (FILIP1L), RB binding protein 8 (RBBP8), response gene to complement 32 (RGC32), RuvB like AAA ATPase 1 (RUVBL1), and stromal antigen 3 (STAG3), were correlated with functional inhibition of OC cell oncogenicity (49). Notably, this study confirmed that a common allele of STAG3 was involved in the development of EOC (49). Genome-wide analyses showed that the amplification or upregulation of additional sex combs like 1 (ASXL1) and histone 3 family 3B (H3F3B), deletion or downregulation of CDC73 and transforming growth factor beta (TGF- $\beta$ ) receptor pathway members, and rearrangements of Yes 1 associated transcriptional regulator (YAP1)/mastermind like transcriptional coactivator 2 (MAML2) and IKAROS family zinc finger 2 (IKZF2)/ERBB4 may play a role in the development of ovarian cancer (50). Based on high resolution array comparative genomic hybridization and microarray retrieval approaches, this study indicated that PI3K regulatory subunit 3 (PIK3R3), a member of the PI3K family, had significant DNA copy number gains and that the expression of PIK3R3 mRNA was upregulated in OC compared with normal ovaries (51). Furthermore, the siRNA-induced knockdown of PIK3R3 promoted the apoptosis of OC cells (51). Another study indicated that protein kinase C (PKC) family members (PKC $\alpha$ , PKC $\beta$ 1, PKC $\gamma$ , PKC $\xi$ , PKC $\theta$ ) showed significant DNA copy number gains in OC tissues and indicated that the expression of PKC $\alpha$  may play an oncogenic role in human OC (52).

Based on genome-wide transcriptome analysis, in the comparison of primary OC and the peritoneal tumoral implant, the RNU6-135P (RNA, U6 small nuclear 135, pseudogene), RNU61262P, and VTRNA1-1 (Vault RNA) genes were overexpressed in primary OC, while melanoma cell adhesion molecule (MCAM) and genes belonging to the small NF90-associated RNAs (SNAR) gene family were overexpressed in peritoneal tumoral implants (53). When compared primary OC with malignant cells in the ascites, 762 genes were overexpressed in primary OC and 216 genes were overexpressed in malignant cells in ascites (53). Between malignant cells in the ascites and the peritoneal tumoral implant, 515 genes were overexpressed in the peritoneal tumoral implant, and 133 genes were overexpressed in the malignant cells in ascites (53). Notably, this study demonstrated that the ubiquitin-specific protease-17 (USP17) gene family was potentially a target for epithelial-mesenchymal transition (EMT) in HGSOc (53). DNA microarray analyses revealed that 266 human transcripts were aberrantly expressed in OC *versus* normal tissues from patients with elevated biobehavioral risk factors (high depressive symptoms and low social support) with respect to grade- and stage-matched OC from low-risk patients (54). Notably,  $\beta$ -adrenergically-linked transcription control pathways,

including cyclic AMP response element binding protein (CREB)/activating transcription factor (ATF), NF- $\kappa$ B/Rel, signal transducer and activator of transcription (STAT), and Ets family transcription factors, were activated in high biobehavioral risk patients (54). Oligonucleotide microarray analysis revealed that 52 candidate genes in the stroma were related to the progression-free survival (PFS) of EOC patients (55). Moreover, the overexpression of the early growth response 1 (EGR1) and FBJ murine osteosarcoma viral oncogene homologue B (FOSB) genes in stromal cells indicated a poor prognosis in EOC patients (55). One study performed whole-genome analysis and found that loss of heterozygosity (LOH) of the 13q domain potentially predicted prolonged PFS in OC patients (76).

The complementary DNA (cDNA) microarray showed that 1596 genes were differentially expressed between OC subclones with low invasive potential and those with high invasive potential (56). Moreover, epidermal growth factor-containing fibulin-like extracellular matrix protein 1, fibulin-3 (EFEMP1) was significantly upregulated in a highly invasive subclone and promoted the invasion and metastasis of OC cells by activating the PI3K/AKT pathway (56). Another study revealed that the expression level of secreted protein acidic and rich in cysteine (SPARC) was higher in highly invasive subclone than in less invasive subclone of OC cells by cDNA microarray analysis; high SPARC expression was correlated with lymph node metastasis, low differentiation, high stage and a poor outcome in OC patients (57). Furthermore, silencing SPARC attenuated the proliferation, invasion and metastasis and promoted the apoptosis of OC cells (57). In addition, overexpression of CD9 was found in borderline and serous-type OC by cDNA microarray profile, and the increased expression of CD9 promoted cell growth by activating the NF- $\kappa$ B pathway (58). A cDNA microarray was performed to display that the expression of glucose transporter-1 (GLUT-1) was elevated in EOC cells compared to normal ovarian cells, and the overexpression of GLUT-1 was associated with a poor outcome in EOC patients (59). Moreover, cDNA microarray analysis indicated that the expression of human anterior gradient 2 (AGR2) was upregulated in OC tissues compared to paired normal ovarian tissues (60). Further study demonstrated that AGR2 potentially served as a biomarker for diagnosing mucinous OC and facilitated the proliferative and migratory ability of OC cells (60). One study demonstrated that creatine kinase B (CKB) was upregulated in OC cells compared with normal ovary surface epithelial cells by cDNA microarray analysis (61). Moreover, 24957 genes were dysregulated between OC cells and normal ovarian cells by cDNA microarray analysis (62). Fifteen ALDH (aldehyde dehydrogenase) isoforms exhibited differential expression patterns; for example, the downregulation of ALDH1A2 (aldehyde dehydrogenase 1 family member A2), ALDH1B1 and ALDH9A1 and the upregulation of ALDH3A1 were observed in OC cells (62). ALDH1A2 was the most significantly downregulated gene, and lower expression of ALDH1A2 was associated with a worse prognosis of OC patients (62). Another study performed oligonucleotide microarray analysis to illustrate that ALDH1A1 was significantly upregulated in paclitaxel- and topotecan-resistant OC cells and potentially contributed to the development of drug resistance in OC (63).

cDNA microarray analysis showed that cyclin A1 (CCNA1) was the most highly overexpressed gene in OC cells *versus* normal cells, and was prominently correlated with the paclitaxel-, doxorubicin and 5-fluorouracil -resistance of OC cells (64). Moreover, cyclin-dependent kinase 1 (CDK1) was upregulated in paclitaxel-resistant EOC cells compared to normal EOC cells according to cDNA microarray analysis, and CDK1 served as a target of paclitaxel resistance-related transcription factors (65). Furthermore, elevated expression of glycogen synthase kinase-3 $\alpha$  (GSK-3 $\alpha$ ) was found in paclitaxel-resistant OC cells by cDNA microarray analysis (66). One study conducted cDNA microarray analysis to reveal that the expression of STAT1 was correlated with decreased sensitivity to cisplatin and cis-diamminedichloro (2-methylpyridine) platinum (II) (AMD473) in OC cells (67). Similarly, one group applied a NanoString nCounter platform with a panel of 184 human inflammation genes in 15 chemoresistant and 19 chemosensitive HGSOC (68). This study illustrated that 11 genes, including STAT1, C-X-C motif chemokine ligand 1 (CXCL10), CAMP responsive element binding protein 1 (CREB1), MAPK interacting serine/threonine kinase 1 (MKNK1), mitogen-activated protein kinase kinase 7 (MAP3K7), cofilin 1 (CFL1), protein tyrosine kinase 2 (PTK2), receptor interacting serine/threonine kinase 1 (RIPK1), myeloid differentiation primary response 88 (MYD88), C-C motif chemokine ligand 8 (CCL8) and CCL7, were upregulated in chemosensitive HGSOC *versus* chemoresistant HGSOC, and STAT1 was the most significantly upregulated gene (68). Taken together, DNA microarray technology provides the chance to obtain a genome-wide scale for rapid analysis of mechanism involved in OC initiation and progression.

### DNA Methylation Microarrays

DNA methylation microarrays can obtain the methylation profile of DNA promoter regions and CpG islands using affinity-based isolation methods, such as methylated DNA immunoprecipitation (MDIP) assay, which will help us understand the molecular mechanism of epigenetic events. One study carried out MDIP-chip analysis in various OC cell lines and clarified that aryl hydrocarbon receptor nuclear translocator-like (ARNTL), which is an HLH-containing transcription factor, was methylated in a subset of OC cell lines (69). The upregulation of ARNTL attenuated the growth and improved the cisplatin-sensitivity of OC cells; however, ARNTL was epigenetically silenced in OC cells (69). One group conducted a DNA methylation microarray in normal ovarian tissues and EOC tissues (70). This report indicated that cancer testis antigen 45 (CT45) was downregulated and hypermethylated in normal ovarian tissues, and was upregulated in EOC tissues concomitant with DNA promoter hypomethylation (70). Another study detected that epidermal growth factor-like 7 (EGFL7) and ras association domain-containing protein 1 (RASSF1) exhibited prominently higher promoter methylation in EOC tissues than in benign ovarian tissues according to DNA methylation array (71). Genome-wide methylation analysis revealed 106 hypo- and 114 hypermethylated regions in ovarian cancer tissues from patients with a poor prognosis compared to those from patients with a good prognosis (72). Notably, the hypermethylation of RUNX family transcription factor 3 (RUNX3) and calcium/calmodulin-dependent

protein kinase II inhibitor 1 (CAMK2N1) was correlated with a detrimental prognosis in EOC patients (72). Moreover, genome-wide DNA methylation analysis showed that 9 genes, including Rho GDP dissociation inhibitor beta (ARHGDI2), armadillo repeat containing X-linked 2 (ARMCX2), COL1A1, filamin A (FLNA), filamin C (FLNC), mesoderm specific transcript (MEST), mutL homolog 1 (MLH1), neurotensin (NTS) and proteasome 20S subunit beta 9 (PSMB9), were hypermethylated in OC at relapse following chemotherapy or in chemo-resistant cell lines obtained at the time of patient relapse (73). In addition, 5 genes such as ARMCX2, COL1A1, midkine (MDK), MEST and MLH1) were methylated in drug-resistant ovarian cancer cells (73). In summary, DNA methylation microarrays provide the global alterations of DNA methylation in ovarian oncogenesis and progression, which could help us understand the epigenetic regulation of genes in ovarian tumorigenesis.

### Transcriptomics

Transcriptomics is often used to obtain profiles of the RNA transcripts (transcriptomes) in a specific cell or organism with a specific condition or a specific time, which provides a connection between the genome and proteome. The transcriptome comprises coding mRNAs and ncRNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), ribosomal RNAs (rRNAs), and transfer RNAs (tRNAs) (77). Specifically, mRNA arrays, miRNA arrays, lncRNA arrays, and circRNA arrays have been performed to explore the molecular mechanisms of OC (Table 2).

### mRNA Microarrays

It is known that mRNA microarrays are used to obtain a comprehensive view of changes in mRNA expression patterns *via* a molecular hybridization between oligonucleotide probes and fragments of complementary mRNA from the interested samples. Analysis of one mRNA microarray indicated that 444 genes were upregulated and 529 genes were downregulated; the expression of mucin 13 (MUC13) mRNA was significantly elevated in metastatic implants from ovarian cancer xenografts *versus* ovarian cancer cells (78). Moreover, MUC13 promoter regions were hypomethylated in OC xenografts, and the overexpression of MUC13 enhanced the migratory and invasive abilities of OC cells (78). One study conducted salivary mRNA microarray analysis of samples from OC patients and healthy controls, and the expression of the 1-acylglycerol-3-phosphate O-acyltransferase 1 (AGPAT1), beta-2-microglobulin (B2M), brain acid soluble protein 2 (BASP2), immediate early response 3 (IER3), and interleukin 1 beta (IL1B) mRNA biomarkers was downregulated in the saliva of OC patients (79). Moreover, the combination of these five mRNA biomarkers in saliva could be used to distinguish OC patients from healthy controls (79). When the lncRNA antisense noncoding RNA in the INK4 locus (ANRIL) was silenced by siRNA in a highly metastatic SOC cell line (SK-OV-3.ip1), four downregulated genes (MMP3, metastasis associated 1 (MTA1), fibronectin 1 (FN1) and MET) and two upregulated genes, including CDH1 and TIMP metalloproteinase inhibitor 2 (TIMP2) genes were detected through tumor metastasis-related mRNA microarray analysis (80). Moreover, the mRNA expression

**TABLE 2** | The application of transcriptomics for exploring the candidate biomarkers for ovarian cancer .

Applied Methods	Subjects	RNA Symbol(s)	Ref.
MRNA microarray	Tissues	MUC13	(78)
MRNA microarray	Saliva	AGPAT1, B2M, BASP2, IER3, IL1B	(79)
MRNA microarray	Cells	MMP3, MTA1, FN1, MET, CDH1, TIMP2	(80)
MRNA microarray	Cells	CAMK2D, SMARCA2	(81)
MiRNA microarray	Serum	Has-let-7d-3p	(82)
MiRNA microarray	Serum	miRNAs-21, 92, 93, 126, 29a, 155, 127, 99b	(83)
MiRNA microarray	Serum	miR-486-5p	(84)
MiRNA microarray	Serum	hsa-miR-1273g-3p	(85)
MiRNA microarray	Tissues	miR-196b	(86)
MiRNA microarray	Tissues	miR-551b, miR-19b, miR-196b, miR-3198, miR-8084, miR-3201, miR-3613, miR-7515	(87)
MiRNA microarray	Tissues	miR-199a-3p, miR-199a-5p, miR-181a-5p, let-7g-5p	(88)
MiRNA microarray	Tissues	miR-182	(89)
MiRNA microarray	Serum	miR-132, miR-26a, let-7b, miR-145	(90)
MiRNA microarray	Tissues	miR-129-1-3p, miR-542-5p, miR-450a-5p, miR-129-2-3p, miR-424-5p	(91)
MiRNA microarray	Cells	miR-22	(92)
MiRNA microarray	Tissues	miR-21, miR-125a, miR-125b, miR-100, miR-145, miR-16, miR-99a, miR-200, miR-141, miR-18a, miR-93, and miR-429, let-7b, miR-199a	(93)
MiRNA microarray	Tissues	miR-410, miR-645	(94)
MiRNA microarray	Tissues	miR-337, miR-376b, miR-432, miR-376a, miR-368, miR-495, miR-377, miR-419	(95)
MiRNA microarray	Tissues	miR-1183, miR-126-3p, miR-139-3p, miR-802, miR-23a-5p, miR-23a-3p, miR-802, miR-1234	(96)
MiRNA microarray	Cells	miR-141-3p	(97)
MiRNA microarray	Cells	miR-363, miR-29a,	(98)
MiRNA microarray	Cells	miR-335-5p	(99)
MiRNA microarray	Cells	miR-130a	(100)
MiRNA microarray	Cells	miR-30c, miR-130a, miR-335	(101)
MiRNA microarray	Tissues	miR-9, miR-640	(102)
MiRNA microarray	Cells	miR-17-92	(103)
MiRNA microarray	Cells	miR-106a, miR-591	(104)
MiRNA microarray	Tissues	miRNA-1307	(105)
MiRNA microarray	Tissues	miRNA let-7i	(106)
MiRNA microarray	Cells	miR-21	(107)
MiRNA microarray	Cells	miR-129b-1-3p, miR-139-5p, miR-1290, miR-3131	(108)

(Continued)

TABLE 2 | Continued

Applied Methods	Subjects	RNA Symbol(s)	Ref.
MiRNA microarray	Cells	miR-99a-5p	(109)
LncRNA microarray	Cells	lncRNA NPBWR1-2	(110)
LncRNA microarray	Tissues	lncRNA HCP5	(111)
LncRNA microarray	Tissues	Linc00152	(112)
LncRNA microarray	Tissues	BC041954, ENST00000423200, uc.428+, BC028018, ENST00000433201, ENST00000458624, ENST00000453838, CR601061, ENST00000505048, ENST00000502715, AK123324, AF087976, NR_001284, ENST00000474313, AL832916, AF086261, BC070168, uc001zfv.1, NR_023313, uc002btm.2	(113)
LncRNA microarray	Tissues	lncRNA RHPN1-AS1	(114)
LncRNA microarray	Tissues	HMGA1P6	(115)
LncRNA microarray	Tissues	lncRNA SOCAR	(116)
LncRNA microarray	Tissues	lncRNA MIAT	(117)
LncRNA microarray	Tissues	lncRNA CTD-2020K17.1	(118)
LncRNA microarray	Cells	lncRNA MALAT1, H19, UCA1, CCAT1, LOC645249, LOC100128881, LOC100292680	(119)
LncRNA microarray	Cells	lncRNA TC0101441	(120)
LncRNA microarray	Cells	LINC01118	(121)
LncRNA microarray	Cells	lncRNA UCA1	(122)
LncRNA microarray	Tissues	lncRNA UCA1	(123)
LncRNA microarray	Tissues	lncRNA linc00161	(124)
LncRNA microarray	Cells	lncRNA ENST00000457645	(125)
LncRNA microarray	Tissues	lncRNA GAS5	(126)
CircRNA microarray	Tissues	circRNA1656	(127)
CircRNA microarray	Tissues	circEXOC6B, circ-N4BP2L2	(128)
CircRNA microarray	Tissues	hsa_circ_0063809	(129)
CircRNA microarray	Tissues	circRNA Cdr1as	(130)

levels of CAMK II $\delta$  (CAMK2D) and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 2 (SMARCA2) were elevated in cisplatin-resistant OC cells, as detected by next-generation sequencing, and this change was confirmed to enhance the cisplatin resistance of OC cells (81). Clearly, mRNA expression patterns from mRNA microarray in ovarian tumor tissues are pivotal in exploring the underlying mechanisms of ovarian oncogenesis. However, the alteration of mRNAs need to be validated by other methods, such as RT-PCR.

### MiRNA Microarrays

MiRNAs are a type of small, single-stranded noncoding RNAs and miRNA microarrays are utilized to obtain the changes in the miRNA expression profile on a global scale, which can analyze

the differential miRNA expression between tumors and normal tissues. The aberrant expression of distinct miRNAs is associated with several malignancies, including OC (131). Based on the profiling of circulating miRNA/small nuclear RNA (snRNA), higher expression of 6 miRNAs and U2-1 snRNA fragment (RNU2-1f), and lower expression of 16 miRNAs were found in the serum of OC patients than in the serum of healthy controls (132). Moreover, snRNA RNU2-1f abundance dynamics were beneficial for predicting the high risk of recurrence and a detrimental outcome in OC patients following adjuvant chemotherapy (132). In addition, 31 miRNAs were differentially expressed between the serum of EOC patients and that of healthy patients, which was confirmed by miRNA microarray analysis (82). Moreover, the miRNA hsa-let-7d-3p

was downregulated in EOC patients, and ROC curve analysis suggested that hsa-let-7d-3p could discriminate EOC patients from healthy patients (82). The combination of miRNA microarray with real-time PCR revealed that miRNA-21, 92, 93, 126 and 29a were significantly upregulated and that miRNA-155, 127 and 99b were downregulated in the serum from OC patients *versus* that of healthy controls (83). MiRNA microarray analysis was performed to assess the serum of patients with ovarian endometrioma and endometriosis-associated OC, and showed that 51 miRNAs were dysregulated (84). MiR-486-5p was upregulated and promoted the proliferation and migration of endometriosis-associated OC cells (84). Moreover, miRNA microarray analysis indicated that hsa-miR-1273g-3p was downregulated in recurrent EOC serum samples *versus* healthy control serum samples (85). The circulating hsa-miR-1273g-3p level could potentially distinguish recurrent EOC patients from healthy controls (85). Another study demonstrated that higher expression of 33 miRNAs and lower expression of 18 miRNAs were found in recurrent EOC than in primary EOC by miRNA microarray (86). Furthermore, the upregulation of miR-196b facilitated the invasion of recurrent EOC by targeting homeobox A9 (HOXA9) (86). The miRNA microarray analysis showed that miR-551b, miR-19b, miR-196b and miR-3198 were significantly upregulated and that miR-8084, miR-3201, miR-3613 and miR-7515 were significantly downregulated in recurrent EOC tissues *versus* primary EOC tissues (87). One study showed that 369 miRNAs were dysregulated between matched OC tissues obtained at an initial laparoscopic evaluation and interval-debulking surgery (IDS) after four cycles of platinum-based chemotherapy by miRNA microarray, which can be classified into five families: miR-199, let-7, miR-30, miR-181 and miR-29 (88). Moreover, the expression levels of miR-199a-3p, miR-199a-5p, miR-181a-5p and let-7g-5p were related to overall survival (OS) and PFS, while those of miR-199a-3p, miR-199a-5p and miR-181a-5p were correlated with residual tumor volume and platinum-free interval of OC patients (88). Moreover, 164 miRNAs were upregulated and 194 miRNAs were downregulated in EOC tissues compared with normal ovarian tissues by miRNA microarray (89). This report also indicated that higher expression of miR-182 was associated with a shorter OS of EOC patients (89). Frequent copy number gains in the sequences mapping for miR-182 within 7q32.2 were related to the overexpression of miR-182 in EOC tissues, which was demonstrated by array-based comparative genomic hybridization (aCGH) analysis (89). Microarray methylation analysis showed that methylation of the miR-182 promoter was correlated with the downregulation of miR-182 in EOC tissues (89).

Lower expression of 95 miRNAs and higher expression of 88 miRNAs were detected in the serum, tissue, and ascites of OC patients than in those of healthy patients by miRNA microarray analysis (90). Moreover, the downregulation of serum miR-132, miR-26a, let-7b and miR-145 could act as biomarkers for SOC (90). Downregulation of 63 miRNAs and upregulation of 43 miRNAs were detected in SOC tissues *versus* normal oviduct tissues by miRNA microarray (91). Among these dysregulated miRNAs, miR-129-1-3p, miR-542-5p, miR-450a-5p, miR-129-2-

3p and miR-424-5p were significantly downregulated in SOC tissues (91). The miRNA microarray profile illustrated that lower expression of miR-22 was found in highly metastatic human SOC SKOV-3ip cells than in less metastatic human SOC SKOV-3 cells and demonstrated that miR-22 suppressed the migratory and invasive abilities of OC cells (92). Based on a miRNA microarray, the expression of miR-21, miR-125a, miR-125b, miR-100, miR-145, miR-16, and miR-99a was aberrantly expressed in SOC compared to normal ovarian tissues (93). Moreover, the upregulation of miR-200, miR-141, miR-18a, miR-93, and miR-429 and the downregulation of let-7b and miR-199a were associated with a poor clinical outcome of SOC patients (93). In addition, microRNA microarray hybridization indicated that the miRNA survival signature (MiSS) comprising miR-410 and miR-645 predicted poor OS in advanced SOC patients (94). Eight miRNAs situated on the chromosome 14 miRNA cluster (Dlk1-Gtl2 region) could act as tumor suppressor genes in EOC, which was confirmed by miRNA microarray, aCGH, cDNA microarray and tissue array analyses (95).

By applying miRNA microarray and multivariate analysis approaches, Ahmad et al. found that miR-1183 and miR-126-3p were correlated with OS; miR-139-3p and miR-802 were associated with the time to progression; and miR-23a-5p, miR-23a-3p and miR-802 were related to the PFS; and miR-1234 was associated with the chemotherapy resistance of EOC (96). Four miRNAs were downregulated and 13 miRNAs were upregulated in COC1/DDP (platinum-resistant) OC cells *versus* COC1 (platinum-sensitive) cells; miR-141-3p was the most upregulated miRNA (97). In addition, miRNA microarray analysis was performed to explore the miRNA expression changes in cisplatin (CIS)-, topotecan (TOP)-, doxorubicin (DOX)- and paclitaxel (PAC)-resistant OC cell lines and demonstrated that 21 miRNAs were upregulated and 19 miRNAs were downregulated in at least one drug-resistant cell line (98). Moreover, this study suggested that these miRNAs targeted key drug resistance genes to exert drug resistance properties in OC (98). For PAC-resistant cell lines, miR-363 inversely regulated the expression of ATP binding cassette subfamily B member 1 (ABCB1) (98). In TOP-resistant cell lines, the downregulation of miR-29a upregulated the expression of collagen type III alpha 1 chain gene (COL3A1) (98). Additionally, 9 aberrantly expressed miRNAs were found between cisplatin-resistant (A2780/DDP) and cisplatin-sensitive (A2780) OC cells by miRNA microarray analysis (99). MiR-335-5p was downregulated in A2780/DDP cells compared with A2780 cells, and the overexpression of miR-335-5p sensitized OC cells to cisplatin by inhibiting the expression of BCL2 like 2 (BCL2L2) (99). Another study reported that higher expression of 24 miRNAs and lower expression of 8 miRNAs were found in A2780/DDP cells than in A2780 cells by miRNA microarray; miR-130a was upregulated in A2780/DDP cells (100). Moreover, miR-130a attenuated the cisplatin sensitivity of A2780 cells by upregulating the expression of MDR1 and phosphatase and tensin homologue located on chromosome 10 (PTEN) (100). Furthermore, the downregulation of miR-30c, miR-130a and miR-335 was found in PAC- and cisplatin-resistant OC cells based on a miRNA microarray, and the activation of the M-CSF gene may contribute to the decrease in

miR-130a (101). Increased expression of 16 miRNAs and decreased expression of 23 miRNAs were found in PAC-resistant ST30 OC cells by miRNA microarray (102). Overexpression of miR-9 and miR-640 predicted a favorable prognosis for OC patients, and the mRNA RAB34 was a target of miR-9 (102). Another study indicated that 69 miRNAs were overexpressed and 102 miRNAs were downregulated in PAC-resistant SKOV3-TR30 OC cells by miRNA microarray analysis; the expression of miR-17~92 was upregulated in SKOV3-TR30 cells (103). Moreover, downregulated expression of miR-17~92 contributed to cell cycle arrest in the G2/M phase, suppressed cell growth, and improved the response to PAC by upregulating BCL1-like 11 (BCL2L11, BIM) in ovarian cancer cells (103). Notably, miR-106a was upregulated and miR-591 was downregulated in PAC-resistant SKpac OC cells compared to PAC-sensitive SKOV3 OC cells based on a miRNA microarray (104). Furthermore, the regulation of miR-106a and miR-591 could re-sensitize PAC-resistant cancer cells by promoting apoptosis and suppressing cell migration and proliferation by targeting BCL10, caspase-7, and zinc finger E-box binding homeobox 1 (ZEB1) (104). Using miRNA microarray and gene ontology analysis approaches, this study showed that miRNA-1307 was overexpressed in chemoresistant EOC tissues *versus* chemosensitive counterparts, and the candidate target genes of miR-1307 were involved in nucleotide synthesis and metabolism, cell proliferation and differentiation, and lymphocyte activation (105). The miRNA microarray showed that the expression of miRNA let-7i was downregulated in chemoresistant patients and potentially acted as an indicator of poor PFS in late-stage OC patients (106). Additionally, the expression of miR-21 was elevated in chemoresistant OC cells based on a miRNA microarray, and suppression of miR-21 facilitated apoptosis and ameliorated the chemosensitivity of OC cells (107).

The miRNA microarray analysis exhibited that the 4 miRNAs (miR-129b-1-3p, miR-139-5p, miR-1290, and miR-3131) were more highly expressed in exosomes originating from HGSOc cells (HeyA8 and TYK-nu cell lines) than exosomes originating from normal ovarian epithelial cells (the IOSE cell line) (108). Among these four miRNAs, miR-1290 was the most upregulated and acted as a potential biomarker to discriminate HGSOc patients from OC patients with other histological types (108). Another study reported higher expression of 9 miRNAs (miR-99a-5p, miR-100-5p, miR-125b-1-3p, miR-139-5p, miR-451a, miR-500a-3p, miR-1290, miR-3131, miR-3153) in exosomes derived from HeyA8 and TYK-nu cells than those derived from IOSE cells by exosomal miRNA microarray analysis (109). Moreover, exosomal miR-99a-5p increased the invasive capacity of HGSOc cells by upregulating the expression of fibronectin and vitronectin in neighboring human peritoneal mesothelial cells (109). It is necessary to note that miRNA expression profile on a global scale from the miRNA microarray needs to be further validated due to that it is unclear how each miRNA exerts its function in ovarian cancer development and progression.

### LncRNA Microarray

Long noncoding RNAs (lncRNAs) are a class of noncoding, endogenous, single-stranded RNAs with a length of more than

22 nucleotides (133). Moreover, lncRNAs can regulate gene expression at different levels *via* mechanisms, including chromatin modification, transcription and post-transcriptional processing and can take part in the modulation of the biological behavior of human cancers (134). lncRNA microarrays are utilized to efficiently screen differential lncRNAs in cancers, which can provide theoretical basis for exploring the molecular mechanisms of tumorigenesis. One group used a lncRNA microarray approach and showed the downregulation of 699 lncRNAs and upregulation of 110 lncRNAs in OC cells compared with ovarian epithelial cells (110). lncRNA neuropeptides B and W receptor 1-2 (NPBWR1-2) was downregulated more than two-fold in OC cells, and vector-mediated NPBWR1-2 overexpression decreased cell viability, inhibited the proliferative, migratory and invasive ability, and facilitated the apoptosis of OC cells by targeting multiple miRNAs (110). Furthermore, overexpression of lncRNA HCP5 was detected in OC by lncRNA microarray (111). Downregulation of lncRNA HCP5 attenuated the proliferative, invasive, migratory abilities of OC and inhibited the EMT process, which might occur through miR-525-5p/PRC1 (polycomb repressive complex 1) crosstalk and the Wnt/ $\beta$ -catenin signalling pathway (111). Additionally, higher expression levels of 9 lncRNAs and lower expression levels of 5 lncRNAs were found in OC tissues than in their normal counterparts, which was confirmed by lncRNA microarray analysis (112). Among these dysregulated lncRNAs, Linc00152 was upregulated in OC and silencing Linc00152 attenuated OC cell proliferation and promoted cell cycle arrest (112). Another study demonstrated that 795 lncRNAs were upregulated and 2075 lncRNAs were downregulated in OC tissues compared with normal ovarian tissues (113). The top 10 most overexpressed lncRNAs in OC were BC041954, ENST00000423200, uc.428+, BC028018, ENST00000433201, ENST00000458624, ENST00000453838, CR601061, ENST00000505048 and ENST00000502715, while the top 10 most decreased lncRNAs in OC were AK123324, AF087976, NR\_001284, ENST00000474313, AL832916, AF086261, BC070168, uc001zfv.1, NR\_023313 and uc002btm.2 (113). These dysregulated lncRNAs can be categorized into four types: lincRNAs, HOX clusters, long-intergenic non-coding RNAs (lincRNAs) near coding genes and enhancer lncRNAs near coding genes (113). A total of 326 dysregulated lncRNAs were detected in EOC *versus* para-cancerous control tissues by lncRNA microarray analysis (114). Among these lncRNAs, the lncRNA RHPN1-AS1 was overexpressed and facilitated the carcinogenesis and metastasis of EOC by serving as a ceRNA to sponge miR-596 and activating leucine zipper/EF hand-containing transmembrane-1 (LETM1) expression and the FAK/PI3K/Akt pathway (114). One report demonstrated that 577 pseudogenes were dysregulated in HGSOc *versus* normal fallopian tubes by lncRNA microarray analysis, among which 538 pseudogenes were upregulated (115). High mobility group AT-hook 1 pseudogene 6 (HMGA1P6) was one of the upregulated pseudogenes and exerted an oncogenic role in OC by serving as a competitive endogenous RNA, contributing to a shorter overall survival in OC patients (115).

A lncRNA microarray was applied and illustrated that 37 lncRNAs were upregulated and 22 lncRNAs were downregulated

in omental metastasis tissues (OMTs) *versus* paired primary OC tissues (POCTs) (116). This study also indicated that the upregulation of SOCAR, which is a novel OC metastasis-related lncRNA that facilitates the proliferative, migratory and invasive abilities of OC cells by elevating the expression of matrix metalloproteinase 9 (MMP9) through activation of the Wnt/ $\beta$ -catenin signalling pathway (116). Moreover, the expression of myocardial infarction-associated transcript (MIAT) was increased, and the expression of small nucleolar RNA, C/D Box 114 cluster (SNORD114) family members SNORD114-10, SNORD114-2 and SNORD114-11 was decreased in OMTs compared to matched POCTs by lncRNA microarray analysis (117). The lncRNA microarray showed that higher expression of 37 lncRNAs and lower expression of 22 lncRNAs were found in OMTs than in paired POCTs (118). Among these aberrantly expressed lncRNAs, the lncRNA CTD-2020K17.1 was overexpressed in OMTs and facilitated the migratory, invasive, and proliferative abilities of serous OC cells (118). The lncRNA microarray demonstrated that 583 lncRNAs were upregulated and 578 lncRNAs were downregulated in SKOV-3ip cells compared to parental SKOV3 cells; lncRNAs metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), H19, urothelial cancer associated 1 (UCA1), colon cancer-associated transcript 1 (CCAT1), LOC645249, LOC100128881, and LOC100292680 were downregulated in SKOV-3ip cells (119). Estrogen (E2) aberrantly regulated the expression of 115 lncRNAs in E2 receptor (ER)  $\alpha$  (ER $\alpha$ )-positive EOC cells compared to E2-untreated controls according to lncRNA microarray analysis (120). Furthermore, E2-mediated upregulation of lncRNA TC0101441 promoted the migration and invasion of ER $\alpha$ -positive EOC cells by regulating the expression of MMP2 and MMP3 (120).

Similarly, 40830 dysregulated lncRNAs were found between PAC-resistant OC cells and PAC-sensitive OC cells by lncRNA microarray analysis (121). Furthermore, LINC01118 was upregulated in PAC-resistant OC cells, and promoted PAC resistance, invasion and migration while attenuating apoptosis in EOC cells through modulating the miR-134/ATP binding cassette C1 (ABCC1) axis (121). Based on lncRNA microarray analysis, one study revealed that lncRNA UCA1 was upregulated in PAC-resistant OC cells *versus* PAC-sensitive OC cells and enhanced the resistance of OC to PAC (122). In addition, upregulation of lncRNA UCA1 was observed in cisplatin-resistant OC samples compared to cisplatin-sensitive OC samples by lncRNA microarray analysis (123). Moreover, the lncRNA UCA1 negatively regulated miR-143 and subsequently modulated the expression of FOSL2, which enhanced the cisplatin resistance of OC (123). Another group indicated that lncRNA linc00161 exhibited higher expression in cisplatin-resistant OC than in cisplatin-sensitive OC by lncRNA microarray analysis (124). Notably, linc00161 downregulated the expression of microRNA-128 and subsequently upregulated the expression of mitogen-activated protein kinase 1 (MAPK1), which promoted cisplatin resistance in OC cells (124). One lncRNA microarray demonstrated that 1033 lncRNAs were upregulated and 869 lncRNAs, including lncRNA ENST00000457645, were downregulated in A2780 cells *versus* cisplatin-resistant CP70

OC cells (125). This study also indicated that lncRNA ENST00000457645 decreased the viability and migratory ability of cisplatin-resistant OC cells, suggesting that lncRNA ENST00000457645 could reserve cisplatin resistance in CP70 cells (125). In addition, lower expression of lncRNA growth arrest-specific transcript 5 (GAS5) was found in EOC tissues than in normal ovarian tissues by lncRNA microarray analysis (126). Moreover, upregulated expression of lncRNA GAS5 could improve the sensitivity of OC to cisplatin by reducing the expression of poly (ADP-ribose) polymerase1 (PARP1) by recruiting transcription factor E2F4 to its promoter and subsequently modulating the MAPK signalling pathway (126). It is required to further investigate which lncRNAs obtained from lncRNA microarray analysis are more important in ovarian tumorigenesis.

### CircRNA Microarrays

Circular RNAs (circRNAs) are a new subtype of regulatory noncoding RNA (ncRNA) molecules that are characterized by covalently closed-loop structures without 5' caps or 3' polyadenylated tails (135). Moreover, the stable structure, tissue- and/or development-specific expression patterns, and good conservation are the major properties of circRNAs (136). CircRNA microarrays can provide genome-wide circRNA expression profiles between tumor specimens and normal tissues. High-throughput sequencing of circRNAs indicated increased expression of 354 circRNAs and decreased expression of 356 circRNAs in HGSOV tissues compared to normal ovarian tissues (127). Among these dysregulated circRNAs, circRNA1656 was downregulated and the expression of circRNA1656 was associated with the FIGO stages of OC patients (127). In addition, circRNA sequencing-based circRNA expression profiles showed that 2556 circRNAs were upregulated and 1832 circRNAs were downregulated in EOC tissues compared with normal ovarian tissues (128). Higher expression of circEXOC6B and circ-N4BP2L2 indicated a better prognosis in EOC patients (128). CircRNA microarray analysis was also performed in PAC-sensitive and PAC-resistant OC tissues (129). This study showed that 341 circRNAs were upregulated and 492 circRNAs were downregulated with fold change  $\geq 2.0$ , and the length of most circRNAs was less than 1500 bp (129). Among these dysregulated circRNAs, hsa\_circ\_0063809, hsa\_circ\_0001946, hsa\_circ\_0026134, hsa\_circ\_0025033, and hsa\_circ\_0014130 were the five most upregulated circRNAs (129). In particular, the suppression of hsa\_circ\_0063809 can reverse PAC resistance in OC cells (129). Upregulation of 148 circRNAs and downregulation of 191 circRNAs between cisplatin-sensitive and cisplatin-resistant OC tissues were observed by circRNA microarray analysis (130). Among these circRNAs, Cdr1as was downregulated in cisplatin-resistant OC, and Cdr1as sensitized OC to cisplatin by suppressing miR-1270 expression and subsequently upregulating suppressor of cancer cell invasion (SCAI) expression (130). In conclusion, a genome-wide circRNA expression profile is *via* lncRNA microarray could facilitate the understanding of ovarian oncogenesis and drug resistance.

## Proteomics

Proteomics techniques can provide the whole proteome or all proteins from a particular cell, tissue, biofluid or organism. Protein expression profiling by proteomics facilitates the identification of potential biomarkers for disease diagnosis and prognosis prediction. Moreover, proteomics techniques are widely applied to assess OC carcinogenesis, and a panel of proteins that are considered helpful biomarkers for OC patients has been identified (**Table 3**).

By employing peptide ligand library beads (PLLB) and 1D gel liquid chromatography tandem mass spectrometry (LC-MS/MS) approaches, one report found that retinol binding protein 4 (RBP4) was highly expressed in the serum of OC patients (137). Lectin-directed tandem labelling (LTL) and isobaric tags for relative and absolute quantitation (iTRAQ) proteomics approaches identified 45 N-linked sialylated glycopeptides comprising 46 glycosylation sites, among which 10 sialylated glycopeptides were overexpressed in the serum of OC patients (138). Moreover, glycoproteomic analysis was performed in endometrioid OC tissues and normal ovarian tissues, and periostin and thrombospondin were confirmed as candidate biomarkers with tumor-specific glycosylation in endometrioid OC patients (139). In addition, iTRAQ-tagging and mass spectrometry analysis showed that the serum proteins serotransferrin, albumin, hemopexin, C-reactive protein and amyloid A1 were dysregulated in OC samples compared with benign ovarian tumor samples and healthy control samples (140). Notably, the combination of serum amyloid A1, albumin, serotransferrin, human epididymis protein 4 (HE4) and CA125 elevated the diagnostic capacity for differentiating

benign and malignant OC (140). Increased expression of 52 peptides and decreased expression of 52 peptides were detected in the ascites fluid of OC patients compared to that of those with benign gynecological conditions (150). Label-free liquid chromatography-mass spectrometry was performed between favorable prognosis and poor prognosis primary HGSOc specimen and revealed that higher expression of 288 proteins was found in the favorable prognosis cluster, while higher expression of 370 proteins was found in the poor prognosis cluster (141). Additionally, the overexpression of  $\alpha$ 1-antitrypsin (AAT), NF $\kappa$ B, and phosphomevalonate kinase (PMVK) predicted a favorable PFS, and the overexpression of vascular adhesion protein 1 (VAP1), fatty acid-binding protein 4 (FABP4), and platelet factor 4 (PF4) indicated a poor PFS of HGSOc patients (141). Upregulation of 8 proteins, including actin beta (ACTB), T-cell immunoglobulin mucin (TIM), protein disulfide isomerase A3 (PDIA3), PDIA1, dynactin subunit 2 (DCTN2), KIC17, SIAS, and KIC10) and downregulation of 9 proteins, such as KIC18, G protein-coupled receptor 78 (GRP78), capping actin protein, gelsolin like (CAPG), peptidylprolyl isomerase A (PPIA), replication origin activator 2 (ROA2), lamin A/C (LMNA), EZRI, ADRM1, and ENOA) were detected in vascular endothelial growth factor (VEGF)-treated OC cells compared with normal OC cells through proteomic analysis by two-dimensional electrophoresis (2-DE) (142). These 17 proteins are frequently involved in cell growth and metabolism processes (142).

DIGE quantitative proteomics analysis revealed the downregulation of UBC13 (UBE2N, ubiquitin conjugating enzyme E2 N) in PAC-resistant OC cells, and UBC13

**TABLE 3 |** The application of proteomics for exploring the candidate biomarkers for ovarian cancer.

Applied Methods	Subjects	Protein Symbol(s)	Ref.
LC-MS/MS	Serum	RBP4	(137)
LTL, iTRAQ	Serum	N-linked sialylated glycopeptides	(138)
MS	Tissues	periostin, thrombospondin	(139)
iTRAQ, MS	Serum	Serotransferrin, Albumin, Hemopexin, C-reactive protein, Amyloid A1	(140)
LC-MS	Tissues	AAT, NF $\kappa$ B, PMVK, VAP1, FABP4, PF4	(141)
2-DE, MALDI-TOF MS	Cells	ACTB, TIM, PDIA3, PDIA1, DCTN2, KIC17, SIAS, KIC10, KIC18, GRP78, CAPG, PPIA, ROA2, LMNA, EZRI, ADRM1, ENOA	(142)
MALDI-TOF/TOF, MS/MS	Cells	UBC13	(143)
iTRAQ, LC-MS/MS	Tissues	Ptxdc2, CK7	(144)
MP, MAC	Cells	palmitoylprotein thioesterase 1 precursor, triose phosphate isomerase, ER-associated DNAJ, tumor rejection antigen (gp96) 1	(145)
LC-MS/MS	Cells	AKAP12	(146)
RPPA	Tissues	PDGFR $\beta$ , VEGFR2	(147)
2-DE, MALDI-TOF-MS	Serum	haptoglobin proteins, transthyretin, apolipoprotein E, alpha-1-antitrypsin, clusterin, carbonic anhydrase 1	(148)
2-DE	Tissues	stress-70 protein, elongation factor Tu, PRDX2, G3P, GRP75, ENOA, APOA1, EFTU, ANXA	(149)

modulated PAC sensitivity through the DNA methyltransferase 1 (DNMT1) checkpoint with forkhead and ring finger domain (CHFR)-aurora kinase A (Aurora A) signalling pathway in OC cells (143). iTRAQ-based proteomic analysis in combination with LC-MS/MS revealed that the expression of plexin domain containing 2 (Plxdc2) and cytokeratin 7 (CK7) proteins was elevated in PAC-resistant OC tissues (144). One study indicated that 47 proteins were upregulated and 309 proteins were downregulated both at more than 1.5-fold quantitative alterations in PAC-resistant OC cells *versus* PAC-sensitive OC cells, through LC-MS/MS label-free quantitative proteomics (151). Most of the 356 identified differential proteins were related to pyruvate metabolism, metabolic pathways, glycolysis/gluconeogenesis, protein processing in the endoplasmic reticulum, regulation of actin cytoskeleton, systemic lupus erythematosus, tight junctions and ribosomes (151). Multiplexed proteomics (MP) technology and multilectin affinity chromatography (MAC) indicated that four glycoproteins (palmitoyl protein thioesterase 1 precursor, triose phosphate isomerase, ER-associated DNAJ and tumor rejection antigen (gp96) 1) were upregulated in PAC-resistant A2780TC1 OC cells compared with A2780 OC cells (145). A kinase (PRKA) anchor protein 12 (AKAP12) was overexpressed in the PAC-resistant HGSOC cell secretome according to proteomic analysis, and the upregulation of AKAP12 indicated a poor prognosis in HGSOC patients (146). Strikingly, 11 signalling pathway proteins were upregulated in platinum-resistant OC compared with platinum-sensitive OC according to reversed-phase protein array (RPPA) analysis; the platelet-derived growth factor receptor beta (PDGFR $\beta$ ) and VEGF receptor 2 (VEGFR2) proteins were most prominently overexpressed (147). Moreover, higher expression of PDGFR $\beta$  was associated with worse progression-free and overall survival, while VEGFR2 expression had no considerable relationship with the OS of OC patients (147). Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) indicated that serum haptoglobin proteins, transthyretin and apolipoprotein E were upregulated, while serum alpha-1-antitrypsin, clusterin, and carbonic anhydrase 1 were downregulated in chemo-sensitive EOC patients compared with chemo-resistant EOC patients (148). Proteomics analysis of OC tissues illustrated that stress-70 protein, elongation factor Tu, peroxiredoxin (PRDX2), glyceraldehyde 3-phosphate dehydrogenase (G3P), mitochondrial GRP75,  $\alpha$ -enolase (ENOA), apolipoprotein A-1 (APOA1), mitochondrial EFTU and annexin A (ANXA) were considered predictive indicators of drug-resistant OC (149). Taken together, whole proteome profiles in ovarian cancer give us a chance to determine the mechanism of ovarian tumorigenesis. However, the changes of all proteins in ovarian cancer should be validated by other approaches such as western blotting analysis.

## Metabolomics

Metabolomics are utilized to obtain metabolites expression profiles in a specific cell, tissue or biofluid *via* a high-throughput technology, which can help us understand the cellular metabolism. Metabolomics function in identifying and quantifying the alteration of diverse metabolite levels of samples in response to

disease status, dietary patterns and pharmaceutical interventions (152). Metabolomics is a promising tool for cancer research, and mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy are commonly used techniques (34). Metabolite profiling by metabolomics helps researchers to gain deeper insight into the changes and interactions of metabolites related to ovarian cancer biology and could improve the personalized clinical treatment of ovarian cancer patients (**Table 4**).

According to ultra-performance liquid chromatography and quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF MS), metabolites, including 2-piperidinone and 1-heptadecanoylglycerophosphoethanolamine, in the serum were closely associated with OC and could potentially serve as biomarkers of OC (153). Wide spectrum targeted metabolomics showed that lipid compounds (lysoPC a C16:1, PC aa C32:2, PC aa C34:4 and PC aa C 36:6) in serum were correlated with OC metabolism and potentially related to the growth and progression of OC (154). Moreover, increased expression of saturated fatty acids and decreased expression of unsaturated fatty acids were detected in the serum of EOC patients compared to that of healthy controls, which was confirmed by the gas chromatography-mass spectrometry (GC-MS) metabolomics approach (155). Moreover, serum esterified fatty acids (EFAs) (C16:0), EFAs (C18:0) and free fatty acids (FFAs) (C16:0) were considered biomarkers for discriminating EOC patients from healthy controls (155). Using hydrophilic interaction liquid chromatography (HILIC) and tandem mass spectrometry, this report integrated serum maltose, maltotriose, raffinose, and mannitol into the panel for differentiating OC patients from benign ovarian tumor patients and healthy patients (156). Ultra performance liquid chromatographic-mass spectrometry (UPLC-MS) showed that the upregulation of serum 27-nor-5 $\beta$ -cholestane-3,7,12,24,25 pentol glucuronide (CPG) could be a predictive indicator for EOC in the early stage (157). Metabolic profiling based on UPLC-MS revealed that plasma piperine, 3-indolepropionic acid, 5-hydroxyindoleacetaldehyde and hydroxyphenyllactate could be used for differentiating EOCs from benign ovarian tumors (BOTs)/uterine fibroids (UFs), and for differentiating early-stage EOCs from late-stage EOCs (158). Additionally, one study explored the metabolomics profiles of plasma samples from early-stage EOC patients and healthy controls by UPLC/Q-TOF MS, and 18 metabolites were dysregulated in early stage EOC (159). Among these metabolites, adrenoyl ethanolamide, lysophospholipids (LysoPCs), LysoPE and one unknown compound were identified as potentially useful for discriminating early-stage EOC patients from healthy controls (159). Global metabolomic profiles in the pre- and post-operative plasma of EOC patients were assessed, and the results identified hydroxyphenyllactic acid, coproporphyrinogen, uric acid, lysine, 3-(3,5-diiodo-4-hydroxyphenyl) lactate, 24,25-hydroxyvitamin D3, carnitine, creatinine, l-beta-aspartyl-l-glutamic acid and phosphohydroxypyruvic acid as predictive biomarkers for the recurrence of EOC, and indicated that the combination of pre- and post-operative serum biomarkers showed the best predictive capacity for the recurrence of EOC (160).

The concentrations of four dysregulated urinary metabolomics markers, including N4-acetylcytidine, succinic acid, urate-3-ribonucleoside, and pseudouridine, showed a trend towards the

**TABLE 4 |** The application of metabolomics for exploring the candidate biomarkers for ovarian cancer.

Applied Methods	Subjects	Metabolite Symbol(s)	Ref.
UPLC/Q-TOF MS	Serum	2-piperidinone, 1-heptadecanoylglycerophosphoethanolamine	(153)
Wide spectrum targeted metabolomics	Serum	lysoPC a C16:1, PC aa C32:2, PC aa C34:4, PC aa C 36:6	(154)
GC-MS	Serum	EFA (C16:0), EFA (C18:0), FFA(C16:0)	(155)
HILIC, MS/MS	Serum	combination of serum maltose, maltotriose, raffinose, and mannitol	(156)
UPLC-MS	Serum	CPG	(157)
UPLC-MS	Plasm	piperine, 3-indolepropionic acid, 5-hydroxyindoleacetaldehyde hydroxyphenyllactate	(158)
UPLC/Q-TOF/MS	Plasm	adrenoyl ethanolamide, LysoPCs, LysoPE	(159)
RRLC-MS	Plasm	hydroxyphenyllactic acid, coproporphyrinogen, uric acid, lysine, 3-(3,5-diiodo-4-hydroxyphenyl) lactate, 24,25-hydroxyvitamin D3, carnitine, creatinine, l-beta-aspartyl-l-glutamic acid phosphohydroxypyruvic acid	(160)
UPLC-QTOF/MS	Urine	N4-acetylcytidine, succinic acid, urate-3-ribonucleoside, pseudouridine	(161)
HILIC, RPLC, MS	Urine	homovanillic acid sulfate, phytosphingosine, hippuric acid, pseudouridine	(162)
GC/TOF-MS	Tissues	glucose	(163)

normal level in the post-operative condition compared with the preoperative condition of EOC patients according to UPLC/Q-TOF MS (161). Based on HILIC and reversed-phase liquid chromatography (RPLC) coupled to mass spectrometry, this study identified five urinary metabolites specific to OC, including homovanillic acid sulfate, phytosphingosine, hippuric acid and pseudouridine, and one unknown component (162). Gas chromatography/time of flight mass spectrometry (GC/TOF-MS)-based metabolomics analysis revealed that a higher concentration of glucose and other metabolites from carbohydrate metabolism were found in AMP-activated protein kinase (AMPK)-negative OC than those in the AMPK-positive OC (163). Based on a genome-scale metabolic model and microarray data, one study demonstrated that cisplatin could not kill resistant OC cells, but it could confer a more vulnerable metabolic condition in the cancer cells (164). Metabolites expression profiles in ovarian cancer could enhance the understanding of cellular metabolism, leading to contribution to combating ovarian cancer *via* targeting tumor cell metabolism.

## CONCLUSION AND PERSPECTIVE

Multi-omics has been used to discover the biomarkers for ovarian cancer prognosis and therapeutic efficacy. However, several disadvantages of multi-omics must be discussed. For example, several factors of technical, instrumental and computational nature will affect the precision of microarray data. The poor storage of clinical sample in hospitals causes the poor quality of RNA samples, leading to inaccurate data by transcriptomics. Moreover, no standard methodology is available for microarrays so far. It is also difficult to develop standard methods to integrate data obtained from various types of microarrays. Appropriate statistical analyses are necessary to analyze multi-omics approaches.

Through different microarrays, thousands of genes and proteins are changed in ovarian carcinogenesis and promotion. How can we judge which genes and proteins are key drivers to induce ovarian tumorigenesis? Different microarray approaches often obtain inconsistent results, which could be due to biological heterogeneity, different statistical and computational analyses, and target selection criterion, indicating that identified genes and proteins by each microarray method should be validated by other several approaches. Transcriptome profiles need to be validated by other methods, such as RT-PCR assay.

In summary, multi-omics approaches are applied to study the molecular mechanism of the development and progression of OC (Figure 1). The combination of genomics, transcriptomics, proteomics and metabolomics is helpful for exploring diagnostic and prognostic biomarkers of OC and for gaining deeper insight into the mechanism of OC chemoresistance. Without a doubt, there is a long way to use multi-omics approaches for personalized therapy in ovarian cancer patients.

## AUTHOR CONTRIBUTIONS

MY and XZ wrote this manuscript. YL and SP prepared the figures and tables. Z-wW performed data accusation and discussion. All authors contributed to the article and approved the submitted version.

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