



Integrative omics of ovarian cancer

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ABSTRACT. Omics such as genomics, transcriptomics, proteomics, and metabolomics are gathering the study of entire characterization and molecular biology processes of organisms. The advancement in studying omics has become useful and widely applied to many human diseases. For ovarian cancer, pathogenic mechanisms at molecular levels resulting in the development of cancer are the continual debate. Due to the exact cancer causing is still unclear, no matter genetics (endogenous) or environmental pollutant (exogenous) factors. Integrative omics of ovarian cancer in this review has been provided the potential molecular mechanisms, which has better improvement and effectiveness of the diagnosis, prognosis, and treatment for personalized ovarian cancer in clinical practice.

Keywords: Ovarian cancer; Genomics; Transcriptomics; Proteomics; Metabolomics

INTRODUCTION

Ovarian cancer (OC) is the deadliest of all gynecological cancers in the Western world. This is due to the vagueness of symptoms and lack of reliable screening test. Patients are often diagnosed when they got with advanced or late-stage diseases (stage III or IV), that means 5-year survival rate is less than 20%. While 5-year survival rate for people diagnosed with early-stage (Stage I or II) is up to 90%. Approximately 80% of ovarian cancer arises from the epithelium (surface cells), 10-15% of germ cells, and 5-10% of stromal cells.

In epithelial ovarian cancer (EOC) is divided into 4 subtypes, serous, endometrioid, clear cell, and mucinous. Recently, EOC has been broadly classified into 2 distinct types. Type I includes low-grade serous carcinoma (LGSC), endometrioid, clear cell, mucinous, transitional cell carcinomas (TCC), and less responsiveness to chemotherapy. Type II includes high-grade serous carcinoma (HGSC), undifferentiated carcinomas, and carcinosarcomas responsiveness to chemotherapy. Even current early diagnostic tests are available including the CA125 blood test and transvaginal ultrasound but there is limitation in terms of accuracy. Debulking surgery followed by platinum-based chemotherapy schemes is considered as standard treatment for patients diagnosed with ovarian cancer. However, about 80% of patients relapsed, and became resistant to chemotherapy remain a major challenge of this cancer. Improving reliable screening test and surveillance of chemotherapy-resistant have been required.

Advances in omics studies such as genomics, transcriptomics, proteomics, and metabolomics based on the high-throughput identification and quantification technologies of molecules revealed complex biological networks of most human diseases. In this review, aims to discuss the potential molecular mechanisms of oncogenesis of ovarian cancer. Integrative omics of ovarian cancer have also revealed significant new opportunities which might be used as biomarkers, which is better improvement and effectiveness of diagnosis, prognosis, and treatment for personalized ovarian cancer (Karczewski et al., 2018).

Genomics-based of ovarian cancer

Genomics is the study of the full genetic complement of an organism (genome). It employs recombinant DNA, DNA sequencing methods, and bioinformatics to sequence, assemble, and analyze the structure and function of genomes.

Most common genomic alterations in patients with recurrent ovarian cancer were TP53, MYC, BRCA1/2, KRAS, NF1, ERBB2 point mutation, and cMET amplification. BRCA1/2 somatic mutations as a significant feature of HGSC, such serous, and also known to confer some sensitivity to DNA damaging agents, such platinum, or possibly agents that inhibit DNA repair pathways such as PARP inhibitors. Germline BRCA1 or BRCA2 mutations in individual patients, loss of BRCA1 promoter methylation, and recurrent SLC25A40-ABCB1 promoter fusion associated with overexpression of drug efflux pump multidrug-resistant protein 1 (MDR1).

MDR1, encoded by ABCB1, is an efflux pump for various chemotherapeutic agents used in the treatment of ovarian cancer including paclitaxel, etoposide, and doxorubicin. Identification of patients with SLC25A40-ABCB1 promoter fusion may allow clinicians to prioritize treatment with chemotherapy that is not a substrate of MDR1, more targeted use of MDR1 inhibitors, and use of new PARP inhibitors that are poor MDR1 substrates (Jaspers et al., 2013; Patch et al., 2015).

ERBB2 (HER2) alterations, the V842I ERBB2 mutation were identified in a patient with an advanced CCC in the kinase domain of HER2 receptor (amino acids 720–987). HER2 overexpression in ovarian cancer is potentially associated with poor prognosis (Ross et al., 2013). Furthermore, APOBEC-mediated deamination was identified in CCC and implicated as a clonal diversity-generating mechanism. As such, APOBEC mutational has been proposed as a therapeutic target to prevent ongoing clonal evolution in disease progression as shown in Table 1 (Wang et al., 2017). Thus, OC identifies the high frequency of genomic alterations could influence on the prognostic features, such as tumor histology, response to chemotherapy, and patient survival for selecting the most appropriate treatment for individual patients.

Table 1. Genomic analysis of ovarian cancer

Omics Studies	References	Objectives	Study Groups	Analytical Methods	Highlight Results
Genomics-Based	Patch et al. (2015)	To identify extensive structural genomic variation and clinical outcome by initial chemo-sensitivity, followed by the frequent emergence of chemotherapy resistance	Ovarian cancer patients with sensitive, resistant, and refractory treatment response ($n=92$) vs fallopian tube specimens ($n=7$)	Whole genome sequencing	<ol style="list-style-type: none"> 1. <i>RBI</i>, <i>NF1</i>, <i>RAD51B</i>, <i>PTEN</i>, <i>CCNE1</i>, and <i>BRCA1</i> or <i>BRCA2</i> commonly characterized in HGSC and contributes to chemotherapy resistance. 2. These novel fusion event may allow clinicians to prioritize treatment with chemotherapy that is not a substrate of MDR1.
	Ross et al. (2013)	To identify targetable genomic alterations (GA) for patients with recurrent ovarian cancer	Relapsed OC specimens ($n=48$)	Targeted NGS	<ol style="list-style-type: none"> 1. <i>TP53</i>, <i>MYC</i>, <i>BRCA1/2</i>, <i>KRAS</i>, and <i>NF1</i> were most common genomic alterations (GA) in patients with recurrent ovarian cancer. 2. NGS assessment of therapy resistant OC identifies high frequency of GA that could influence targeted therapy for the disease.
	Wang et al. (2017)	To identify the whole genome point mutation and structural variation patterns in ovarian cancer	Ovarian cancer tumors ($n=133$) [HGSC ($n=59$), CCC ($n=35$), ENOC ($n=29$), and GCT ($n=10$)]	Whole genome sequencing	<ol style="list-style-type: none"> 1. Transcending <i>BRCA1</i> and <i>BRCA2</i> mutation were identified in HGSC. APOBEC deamination was identified in CCOC. Microsatellite instability with a distinct mismatch-repair mutation signature was identified in ENOCs. 2. These establish reflect diverse DNA repair deficiencies, to stratify ovarian cancers into distinct biological strata within the major histotypes.

Transcriptomics-based of ovarian cancer

Transcriptomics is the study of the transcriptome, which is the complete set of RNA transcripts that are produced by the genome, under specific circumstances or in a specific cell by using high-throughput methods such as microarray analysis. Comparison of transcriptomes allows the identification of genes that are differentially expressed in distinct cell populations, or in response to different treatments.

Transcriptomics has been widely used for identifying tumor-specific molecules. Of the 6 topmost ovarian tumor-specific mRNA isoforms, *ETV4*, *FOXM1*, *LSR*, *CD9*, *RAB11FIP4*, and *FGFRL1* were expressed in most of the HGSC but not in normal tissues (ovary, fallopian, heart, kidney, liver, brain, colon, lung, pancreas, muscle, skin, and spleen). These 6 isoforms have shown oncogenic properties, which induce abnormal cell proliferation and therefore tumor development. To follow this finding would allow these isoforms to be potential in early detection, diagnosis, prognosis, and therapeutic targets including monoclonal antibodies and T-cell-based vaccines (Barrett et al., 2015).

Better understanding in the DNA methylation at specific loci is specified in developing tissues, and tumor evolution. However, epigenetic status is very important in transcriptional gene regulation and is potentially heterogeneous even within a relatively homogeneous cell type, due to different cell subpopulations present as shown in Table 2. DNA methylation and transcriptional changes associated with drug resistance have been detected in several genomic sites in both cell lines and patient specimens. For example, the reduction of CpG methylation levels and transcriptional silencing of *KLF4*, and *IL6* have been associated with cisplatin resistance. *KLF4* is a transcription factor, which involved in regulation of proliferation, differentiation, apoptosis, somatic cell reprogramming of differentiated cells back to pluripotent stem cell stage, modulation of cancer properties, and stimulate epithelial to mesenchymal transition (EMT) by promoting or maintaining stemness of cancer cells.

KLF4 together with a panel of genes (*ST3GAL5*, *SYNE1*, *CXCL8/IL8*, *HERC5*, *FOSL1*, *ARRDC4*) were also detected differential expression between cisplatin sensitive and resistant cells. While, increased expression of *IL6* has been linked to ovarian cancer with poor clinical outcome (Lund et al., 2017). In addition, *IL6* can also interact with tumor cells with tumor microenvironment (TME), including surrounding blood

vessels, immune cells, fibroblast, bone marrow-derived inflammatory cells, signaling molecules, and extracellular matrix (ECM) plays a crucial role in tumorigenesis, angiogenesis, progression, immune tolerance, and chemotherapy resistance, and also linked to ovarian cancer with poor clinical outcome. Interaction of tumor cells with their TME such as tumor-driven macrophages are involved multiple proteins that function in many pathways and networks operating of ovarian cancer-associated carcinogenesis.

Table 2. Transcriptomic analysis of ovarian cancer

Omics Studies	References	Objectives	Study Groups	Analytical Methods	Highlight Results
Transcriptomics-Based	Barrett et al. (2015)	To identify mRNA isoforms with ovarian tumor-specific expression	HGSC ($n=296$) vs normal ovary and fallopian tissues ($n=1,839$)	1. RNA-seq 2. RT-qPCR	<i>ETV4</i> , <i>FOXM1</i> , <i>LSR</i> , <i>CD9</i> , <i>RAB11FIP4</i> , and <i>FGFRL1</i> were identified for HGSC which would allow them to be potential therapeutic targets.
	Lund et al. (2017)	To identify DNA methylome and transcriptomic changes associated with cisplatin resistant in HGSC	Ovarian cancer cell lines M019i (after platinum-taxane chemotherapy) and OC002 (before platinum-taxane chemotherapy)	1. NGS 2. RNA-seq 3. RRBS 4. RT-qPCR	1. Decreased CpG methylation levels were observed in the cisplatin resistant compared with sensitive cell lines. 2. <i>KLF4</i> , and <i>IL6</i> were associated with cisplatin resistance.
	Reinartz et al. (2016)	To construct a signaling network operating in OC microenvironment	HGSC ($n=1,018$)	1. RNA-seq 2. RT-qPCR	STAT3-inducing cytokines, WNT, semaphorins and ephrins, TGF β , and AA metabolites were defined the tumor cells and macrophage-driven pathways in OC microenvironment
	Meng et al. (2015)	To quantify the deregulated levels of microRNAs could to facilitate earlier diagnosis and improve prognosis of EOC	Serum EOC patients ($n=180$) vs healthy women ($n=66$)	TagMan PCR microRNA assays	1. Diagnostic potential of miR-7, miR-25, miR-93 and the prognostic potential of miR-429 in EOC. 2. This microRNA panel may be promising molecules to be targeted in the treatment of EOC.
	Vafee et al. (2017)	To identify lncRNAs that contribute to the tumor-promoting phenotype of CAFs	HGSC ($n=67$) vs NOF ($n=10$)	Gene expression array	1. <i>NEAT1</i> , <i>TUG1</i> , <i>MALAT1</i> , <i>H19</i> , <i>XIST</i> , <i>GAS5</i> , and <i>MEG3</i> lncRNAs were identified as having differential expression of CAFs vs NOFs. 2. CAFs are well known to play important roles in cancer and metastasis, represent an attractive target for novel therapies.
	Li et al. (2017)	To analyze genome-wide DNA methylation in single ovarian cancer cells	Serous FPPE specimens	Sequencing PCR	1. Human chromosome 19 at locus 2, 6, and chromosome 1 at locus 7 of different single human ovarian cancer cells were shown to have heterogeneous DNA methylation statuses in the same cell populations. 2. Better understanding the DNA methylation at specific loci is specified in developing tissues, and tumor evolution.

For STAT3-inducing cytokines such as interleukin (IL)-6, IL-10, tumor-associated macrophages (TAM), and leukemia inhibitory factor (LIF) were deregulated in ovarian cancer. LIF is a member of the interleukin 6 family cytokine. The protein encoded by LIF is producing or having multiple cytokine effects, which is involved in hematopoietic differentiation in normal and myeloid leukemia cells, neuronal cell differentiation, the regulator of mesenchymal to epithelial conversion, and may also offer function in TAM polarization. TAMs produce immunosuppressive cytokines like IL-10, TGF β and PGE2, and low levels of inflammatory cytokines (IL-12, IL-1 β , TNF α , IL-6), which played an important role in their protumorigenic properties of ovarian cancer. Polarized macrophages are a process by which macrophages infiltrated in tumor cells are driven by tumor-derived and T cell-derived cytokines to acquire specific polarized M2 phenotype (Mantovani et al., 2002). These functionally polarized cells are causing the subversion of adaptive immunity and inflammatory circuits that promote tumor growth and progression, thus pointing to the targeting of TAM may be a novel therapeutic strategy against cancer. These findings support a tumor-promoting role of axon guidance molecules in ovarian cancer such as angiogenesis, invasion, migration, and metastasis (Reinartz et al., 2016).

Additionally, transcriptional noise such non-coding RNAs are increasingly being recognized as epigenetic regulators of gene transcription. Serum levels of circulating miR-7, miR-25, miR-93, and miR-429

were significantly deregulated in the serum of EOC patients. The upregulated expression of miR-7 was associated with EOC progression, potentially owing to cell migration and invasion. miR-429 either as tumour suppressor or oncogene, in this study found that this miRNA can act as an oncogene (in vivo) and a tumour-suppressor gene (in vitro), presumably owing to its wavelike features during primary disease, migration/invasion and metastasis (Meng et al., 2015).

Long non-coding RNAs (lncRNAs) represent another potential candidate for regulating gene expression and function in cancer-associated fibroblasts (CAFs). NEAT1, TUG1, MALAT1, H19, XIST, GAS5, and MEG3 lncRNAs were identified as differentially expressed in CAFs vs normal ovarian fibroblast (NOFs). CAFs are well known to play significant roles in cancer and metastasis and as such, represent an attractive target for novel therapies in multiple cancer types. Better understanding of the molecular factors that differentiate CAFs from normal fibroblasts is essential for the development of therapies that specifically target CAFs (Vafae et al., 2017). Recently, single-cell analyses have emerged as an important to improve in sensitivity and throughput sufficiently to begin to measure and understand the heterogeneity in complex biological systems and correlating it with changes in biological functions and disease processes.

Proteomics-based of ovarian cancer

Proteomics refers to the study of proteomes, to understand protein content and function at a global level of biological effect. Due to most biological functions are made by proteins encoded in the genome. The techniques used to determine the entire set of proteins of an organism or system such as protein purification and mass spectrometry.

Identified proteins, Enolase 1 (ENO1), known as the 2-phosphate-D-glycerate hydrolase, catalyzes the formation of phosphoenolpyruvate from 2-phosphoglycerate in the process of glycolysis resulting in promote chemoresistance in cancers (Chen et al., 2014). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) overexpression may stimulate glycolysis, increase cellular ATP levels, and promote autophagy, thereby preventing caspase-independent cell death, which stimulates glycolysis resulting in promote chemoresistance in cancers. Proteomics combined with pathway analysis provided information for an effective combined treatment approach overcoming drug resistance, and potential prognostic biomarkers for ovarian cancer (Cruz et al., 2017).

Integration of genomic, proteomic, and phosphoproteomic measurements identified differentially regulated pathways and functional that have significant associations with patient outcomes, including homologous recombination deficiency (HRD) and survival. Specific protein acetylations associated with HRD such as simultaneous acetylation of K12 and K16 on histone H4 may provide an alternative biomarker of HRD for stratifying patients for therapy in future clinical trials of HDAC inhibitors, alone or combination with PARP inhibition.

Proteins associated with copy-number alterations (CNAs) pathways on the basis of survival, including the PDGFR-beta signaling pathway associated with angiogenesis, the RhoA regulatory and integrin-linked kinase pathways associated with cell motility, invasion, chemokine signaling, and adaptive immunity. Increasing invasiveness and motility associated with short overall survival (OS) may help to explain more aggressive mechanisms of dissemination in ovarian cancer, and could potentially for selective enrollment in trials of anti-angiogenic therapy such as bevacizumab as a first-line therapy in ovarian cancer patients (Zhang et al., 2016). Interestingly, application of protein cell line signature has been divided into 2 core clusters, predominantly epithelial and mesenchymal HGSC.

Fallopian tube epithelial cell (FTEC) was isolated in the epithelial cluster, while immortalized ovarian surface epithelial cells (IOSEs) in the mesenchymal cluster. FTEC cluster increased levels of known HGSC proteins such as MUC16 (CA-125), PAX8, and MSLN. Moreover, also revealed novel markers for FTEC-derived HGSC cell lines such as CRABP2 and ASS1, which are increased in serous compared with clear cell, endometrioid, and mucinous subtypes; CRYAB, a p53 target gene, which is associated with serous, but not non-

serous. As regard IOSE cluster were increased levels of a small set of mesenchymal proteins including GJA1, $\alpha 5$ -integrin (ITGA5), HMOX1, SMTN, and SACS. GJA1 associated with cell adhesion, invasion, and metastasis. $\alpha 5$ -integrin (ITGA5) is regulated by epithelial differentiation marker E-cadherin (CDH1) and the absence of CDH1 is a predictor of poor survival in ovarian cancer patients. These proteomics-based epithelial and mesenchymal of cell lines and human tumors indicate a possible origin of HGSC from either the fallopian tube or ovarian surface epithelium as shown in Table 3 (Coscia et al., 2016).

Table 3. Proteomic analysis of ovarian cancer

Omics Studies	References	Objectives	Study Groups	Analytical Methods	Highlight Results
Proteomics-Based	Cruz et al. (2017)	To identify protein markers of drug resistant ovarian cancer	Human ovarian cancer cell lines, PEO1; PEO1CarbR; and PEO1TaxR vs biopsy specimen, ovarian cancer ($n=4$), and endometriosis ($n=1$)	1. 2D-GE 2. LC-MS/MS	1. ENOA, EFTU, GAPDH, stress-70 protein, GRP75, APOA1, PRDX2, and ANXA as candidate biomarkers of drug-resistant disease. 2. Proteomics combined with pathway analysis provided information for an effective combined treatment approach overcoming drug resistance, and potential prognostic biomarkers for ovarian cancer.
	Zhang et al. (2016)	To identify the molecular components and underlying mechanisms associated with OC	HGSC ($n=169$)	MS-based proteomics	1. Identify pathways and functional associations with patient outcomes, including survival and HRD. 2. PDGFR-beta signaling pathway, RhoA regulatory and integrin-linked kinase pathways associated with CNAs of survival pathways. 3. Simultaneous acetylation of K12 and K16 on histone H4 associated with HRD. 4. These identified pathways could potentially for therapy in OC patients.
	Coscia et al. (2016)	To integrate proteomic analysis in OC cell lines, HGSC, and normal (OSE and FTEC)	OC cell lines ($n=30$); HGSC, CCC, and IOSE), HGSC patients ($n=5$) vs normal (OSE and FTEC)	MS	1. Protein cell line signature divided into epithelial and mesenchymal HGSC. 2. FTEC was isolated in epithelial cluster, which increased levels of MUC16 (CA-125), PAX8, and MSLN, CRABP2, ASS1, and CRYAB. 3. IOSEs in mesenchymal cluster, which increased levels of GJA1, and $\alpha 5$ -integrin (ITGA5) 4. These proteomics-based epithelial and mesenchymal of cell lines and human tumors indicates a possible origin of HGSOC either from fallopian tube or ovarian surface epithelium.

Metabolomics-based of ovarian cancer

Metabolomics refers to the systematic identification and quantification of the small molecule metabolic products or metabolome of a biological system such as a cell, tissue, organ, biological fluid, or organism at a specific point in time. The techniques most often used for metabolome profiling are mass spectrometry (MS) and nuclear magnetic resonance spectroscopy (NMR) spectroscopy.

Significant metabolic changes were detected in primary epithelial ovarian cancer (EOC) and metastatic tumors resulting from primary ovarian cancer (MOC) compared with normal ovarian specimens. The increasing in carnitine, acetylcarnitine, and butyrylcarnitine were associated with glycolysis and β -oxidation of fatty acid (FAs) in EOC and MOC. Because of a shift of glycolysis or glucose metabolism to less efficient glycolytic pathways in response to regional hypoxia and evolution of aerobic glycolysis in many cancer phenotypes (Gatenby et al., 2007). While β -oxidation of FAs or FAs oxidation promote tumorigenesis and tumor progression (Röhrig et al., 2016). Increases in phenylpyruvate and phenylactate were associated with phenylalanine catabolism in EOC. These phenylalanine catabolism alterations could be altered due to reduced activity of enzymes, which are converted phenylalanine to tyrosine (Wiggins et al., 2015). Increases in 2-aminobutyrate and tocopherols were enhanced oxidative stress in EOC, and MOC, respectively.

Oxidative stress interacts with at least 3 stages of cancers, initiation, promotion, and progression. During the initiation stage, reactive oxygen species (ROS) cause DNA damage by introducing gene mutations, DNA breaks, and chromosome breakage. In the promotion stage, ROS can contribute to abnormal gene expression, blockage of cell communication, and modification of second messenger systems, thus resulting in an increased cell proliferation or decrease in apoptosis of the initiated cells. Finally, in the progression stage, by adding further DNA alterations to the initiated cells (Reuter et al., 2010; Fong et al., 2011).

In addition, eleven diagnostic metabolites as reported in the database that are able to distinguish early-stage OC with 100% accuracy including cortisone, lysophatidylinositol (18:1), aspartyl-glutamic acid, 16-(6-butoxy-3-hydroxy-4,5-dimethylcyclohex-1-en-1-yl)-6,10-dihydroxy-2,6,10,14-tetramethyl hexadecanoic acid, ceramide, lysophosphatidylethanolamine (22:6), 2-hydroxyl nonanoic acid, iso-1,2-octadecanediol, 3-hydroxyl dodecanedioic acid, phosphatidylinositol (20:4/18:1), and 7,9,13-trihydroxyoctacos-16,22-dienoic acid. Most of the identified aberrant metabolites were lipids or fatty acids. These alterations have been linked to the aberrant expression of genes involved in lipid or fatty acid synthesis.

For example, tumor suppressor gene p53 (TP53) is mutated in >95% of HGSC (Havrilesky et al., 2003). Thus, p53 interacts with sterol regulatory element-binding proteins (SREBPs) and guanidinoacetate N-methyltransferase (GAMT) resulting in elevated enzymes involved in fatty acid and cholesterol biosynthesis and the inhibition of fatty acid oxidation leading to lipid anabolism and accelerated tumor growth and progression (Gaul et al., 2015). Some novel metabolite markers in primary EOC patients decreased levels of tetracosahexaenoic acid, 2-octenoic acid, 12,13-DiHODE and 19,20-DiHDPAs were observed. Changes in these lipid-related metabolites can affect numerous cellular processes, including cell growth, proliferation, differentiation, and motility, which contribute to tumorigenesis and malignancy.

Decreased p-Salicylic acid indicated energy disorders commonly seen in EOC. Because of p-Salicylic acid metabolite involved in ubiquinone biosynthesis, which plays an important role in mitochondrial respiratory and energy production (Lenaz et al., 2009). Curative surgery between pre- and post-operative EOC patients can affect metabolic changes such as attributed to oxidative stress, and nutritional supplementation, or surgical curative effect. Decreased levels of 3-indolepropionic acid and indoxylsulfuric acid might be altered oxidative stress in post-operative EOC patients. Increased levels of capric acid, caprylic acid, and α -linolenic acid) might be attributable to nutritional supplementation such as fat emulsion for intravenous injection during surgery, which is routinely performed to improve clinical outcome in major abdominal surgery (Cerantola et al., 2011).

Recurrent EOC patients, amino acid-related metabolites such as l-histidine, l-tryptophan, l-phenylalanine, kynurenine, 2,3-dihydroxyvaleric acid, glyceric acid, and α -ketoisovaleric acid were remarkably increased in relapsed EOC patients compared with the primary EOC patients. Moreover, significant alterations in lipids-related metabolites such as increased levels of LPCs, LPEs, and fatty acids were indicated. Therefore, altered pathways of amino acids- and lipids-related metabolites have been suggested to contribute to platinum resistance in ovarian cancer cells as shown in Table 4 (Poisson et al., 2015; Ke et al., 2016). Thus, based on these metabolites are provided information of lipid metabolism aberration in ovarian cancer progression, such disease stage, and serve as a foundation of the diagnostic test.

Table 4. Metabolomic analysis of ovarian cancer.

Omics Studies	References	Objectives	Study Groups	Analytical Methods	Highlight Results
Metabolomics-Based	Fong et al. (2011)	To identify metabolic profile of normal ovaries, EOC, and MOC	Normal ovarian specimen (n=12) vs EOC (n=11), and MOC (n=7)	1. GC/MS 2. LC/MS/MS	1. Altering metabolites associated with glycolysis and β -oxidation of FAs in EOC and MOC by increases in carnitine, acetylcarnitine, and butyrylcarnitine. 2. Changes in phenylalanine catabolism by increases in phenylpyruvate, and phenyllactate in EOC. 3. Enhanced oxidative stress by increases in 2-aminobutyrate in EOC, and tocopherols in MOC.

Gaul et al. (2015)	To interrogate the serum metabolome of OC patients	Early stage (I/II) serous EOC (<i>n</i> =46) vs normal healthy controls (<i>n</i> =49)	1. UPLC-MS 2. MS/MS 3. SVM-based	4. These compounds have clinical utility in the diagnosis or management of OC patients. Eleven diagnostic metabolites are able to distinguish early-stage OC with 100% accuracy.
Ke et al. (2016)	1. To investigate metabolic alterations for advanced EOC, surgical intervention, and disease relapse 2. To discover potential biomarkers for monitor EOC surgical efficacy, and disease relapse	Primary EOC patients vs benign ovarian tumor or uterine fibroid patients	MS	1. Decreased tetracosahexanoic acid, 2-octenoic acid, 12,13-DiHODE and 19,20-DiHDEA related lipid metabolites, and <i>p</i> -Salicylic acid indicated energy disorders were indicated in primary EOC. 2. Decreased levels of 3-indolepropionic acid and indoxylsulfuric acid might be altered oxidative stress in post-operative EOC patients. 3. Increased amino acid-related metabolites such as l-histidine, l-tryptophan, l-phenylalanine, kynurenine, 2,3-dihydroxyvaleric acid, glyceric acid, and α -ketoisovaleric acid, and lipids-related metabolites such as LPCs, LPEs, and fatty acids were indicated in recurrent EOC.

DISCUSSION

The goals of cancer research are also advanced by high-throughput profiling efforts of non-disease cells and tissues. The knowledge and special tools have great potential to provide similar insight into the causes of cancer or responses to targeted chemotherapy, such as, when applied to the precision medicine. Integrating omics data with epidemiological data from well-defined cohorts improves our ability to associate genetic alterations with environmental exposures and specific clinical phenotypes, which has the potential to improve our current understanding of cancer biology and ultimately patient management. Future design of technological developments have enabled much of the focus will shift to study design, interpretation, and clinical applicability.

CONCLUSION

In conclusion, integrative omics, including genomics, transcriptomics, proteomics, and metabolomics enable a clearer picture of molecular mechanisms of oncogenesis of ovarian cancer. Overall presented that the initial screening to specific therapies, molecular omics play an important role in ovarian cancer carcinogenesis, and may potentially result in clinically useful biomarkers, such as disease stage, tumor histology, response to chemotherapy, and patient survival for extremely specific diagnostics and therapeutics. In the future, as large-scale omics data showing a strong and consistent target for disease risk assessment, it is likely useful for medical research and facilitates clinical diagnosis and specific therapies.

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