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Platinum-resistant ovarian cancer: from drug resistance mechanisms to liquid biopsy-based biomarkers for disease management

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Abstract

Resistance to platinum-based chemotherapy is a major clinical challenge in ovarian cancer, contributing to the high mortality-to-incidence ratio. Management of the platinum-resistant disease has been difficult due to diverse underlying molecular mechanisms. Over the past several years, research has revealed several novel molecular targets that are being explored as biomarkers for treatment planning and monitoring of response. The therapeutic landscape of ovarian cancer is also rapidly evolving, and alternative therapies are becoming available for the recurrent platinum-resistant disease. This review provides a snapshot of platinum resistance mechanisms and discusses liquid-based biomarkers and their potential utility in effective management of platinum-resistant ovarian cancer.

Keywords

Platinum resistance; Ovarian cancer; Biomarkers; Paclitaxel; DNA repair; Cisplatin; Epigenetic

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Conflict of Interest

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1. Introduction

Ovarian cancer (OC) is the seventh most common cancer worldwide and ranks eighth in women's cancer-related mortalities. Moreover, its incidence is much higher in developed countries than in developing countries [1]. In the United States, OC is the second most common gynecological malignancy, causing more deaths than any other cancer of the female reproductive system [2]. Most OCs are of epithelial origin (epithelial ovarian cancer, EOC) and classified into five major histological subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), and mucinous carcinoma (MC). These distinct EOC histological subtypes differ in their prevalence, clinicopathological characteristics, and molecular features [3–5].

Clinical management of EOC has been difficult due to the lack of effective screening and prognostic biomarkers and lack of effective treatment strategies for the advanced disease. In the prostate, lung, colorectal, and ovarian cancer screening (PLCO) trial, CA-125 and transvaginal ultrasound failed to provide the mortality benefit of screening to the EOC patients [6]. Similarly, platinum-based drugs used in combination with taxanes as a primary line of therapy are not very effective against the advanced EOC [7]. The response to chemotherapy varies among different EOC subtypes due to inherent or acquired chemoresistance. Non-serous subtypes such as CCC and MC generally exhibit a more insufficient response to platinum therapy due to their genetic landscape. HGSC, on the other hand, initially respond well to platinum-based treatments, but the disease eventually relapses in a significant majority of patients due to therapy failure.

Developing a precise understanding of inherent or acquired chemoresistance mechanisms is highly critical to achieving optimal clinical management of OC. Over the years, we have uncovered several pathways involved in the platinum resistance of OC. This information can be useful in developing alternative therapies or enhancing existing platinum-based treatments by targeting resistance pathways. Further, advances in molecular biology techniques, such as next-generation sequencing (NGS), are revolutionizing the therapeutic management of cancer by providing information on the genetic contexture of the disease. NGS can provide information on multiple genomic and transcriptomic alterations at once with high precision and therefore being increasingly used in oncology for improved therapeutic planning [8].

The use of liquid biopsies to determine the molecular features of cancer is gaining momentum due to its several advantages. In contrast to tissue biopsy, liquid biopsy is minimally invasive and can be performed repeatedly without complications as required for disease monitoring. It is also less cumbersome and less expensive and has a shorter turnaround time if we consider the longer scheduling time needed for the tissue biopsy [9]. More importantly, liquid biopsy can theoretically capture tumor heterogeneity and the overall tumor burden more efficiently than the tumor biopsy [10, 11]. In the following sections, we provide a background of platinum-based therapy and underlying drug resistance mechanisms and focus on potential clinical applications of liquid biopsies and treatment paradigms of platinum-resistant ovarian cancer.

2. Platinum-based therapy and associated chemoresistance mechanisms

Platinum drugs function by forming DNA adducts that halt DNA replication and induce cell death in rapidly dividing tumor cells [12]. They are the mainstay of treatment for patients with advanced EOC in combination with other drugs; however, despite an early response, tumor recurrence is fairly common due to inherent or acquired resistance mechanisms (Figure 1). Below we discuss the existing knowledge on these resistance mechanisms.

2.1. Drug influx and efflux pathways

Platinum-based drugs enter the cancer cells either by passive diffusion or through facilitated transport [13]. Cancer cells can effectively expel out these drugs to protect themselves. Varieties of transporter proteins regulate the influx and efflux of platinum compounds, and thus their altered expression may induce chemoresistance. Transporters associated with the influx of platinum drugs are members of the solute carrier superfamily, such as organic cation transporter (OCT) 1, 2, and 6 and copper transporter 1/2 (CTR1/2) [14, 15]. Since both OCT and CTR proteins facilitate the entry of cisplatin inside the cells, their downregulation reduces the treatment efficacy of platinum-based drugs. Although there has been no significant study reporting the downregulation of OCT1/2 in platinum resistance, OCT6 downregulation directly correlates with cisplatin resistance in lung cancer [16]. Similarly, decreased expression of CTR1 is associated with poor disease-free survival after platinum-based therapy [17, 18].

Copper exporters (ATP7A and ATP7B) also play a critical role in the induction of cisplatin resistance as they facilitate the expulsion of cisplatin from OC cells, thus reducing the effective cisplatin concentration [19]. Overexpression of ATP7A and ATP7B is also linked to the resistance to the cytotoxicity caused by cisplatin and its analogs [20, 21]. Platinum resistance can also be manifested due to the altered expression and action of the multi-drug resistance proteins (MRP). These proteins belong to the ATP binding cassette superfamily and are significant in non-specific drug resistance [22]. High expression of MRP2 and MRP4 in OC has been associated with cisplatin resistance and poor clinical outcome [23]. A distinct mechanism involving an overexpression of cell trafficking protein, annexin A4, has been reported in CCC in another study, which enhances platinum efflux causing its insufficient accumulation [24].

2.2. Intracellular redox balance and drug modification

Reactive oxygen species (ROS) are byproducts of aerobic metabolism and can also be generated under stress conditions [25]. The physiological balance of ROS is maintained by ROS-induced adaptive upregulation of antioxidant systems [26]. Compared to normal cells, cancer cells have higher intracellular ROS levels, which play a significant role in pathogenesis [27, 28]. However, excess generation of ROS caused by ionizing radiation and chemotherapeutic agents is associated with tumor cell death [29]. To counter the detrimental effect of ROS, cancer cells overexpress antioxidant enzymes that provide them a survival benefit. Elevated glutathione (GSH) levels are reported in several cancers including OC and linked with chemoresistance [30–32]. A high level of GSH in tumor cells is associated with increased expression and activity of GSH-related enzymes and exporter proteins, such as

γ-glutamyl-cysteine ligase (GCL), γ-glutamyl-transpeptidase (GGT), and GSH-transporting export pumps [33, 34]. GSH also has a high affinity toward platinum and forms cisplatin-thiol conjugates reducing cisplatin cytotoxicity [35]. It was recently shown that a plant-derived agent, sanguinarine, reduced the GSH levels in PROC cells and sensitized them to cisplatin toxicity [36]. Also, cellular chelating agents such as metallothioneins caused sequestration of platinum compounds, reducing their availability and contributing towards platinum resistance [37].

2.3. Tumor microenvironment, cell adhesion molecules, and stem cell-associated mechanism

The tumor microenvironment (TME) consists of various host cells, including fibroblasts, adipocytes, mesothelial cells, and immune cells (neutrophils, natural killer cells, macrophages, polymorphonuclear neutrophils, myeloid-derived suppressor cells, etc). It also has biomolecules secreted by tumor and TME-associated host cells referred to as the extracellular matrix (ECM) [38]. Clinical studies have reported a correlation between platinum resistance and interaction between ECM and cell adhesion molecules like CD44, CD117, CD133, and β-integrin with poor prognosis in OC patients [39]. Binding with ECM components like the integrin family of proteins seems to provide a survival advantage for tumor cells when exposed to cytostatic drugs. Activation of integrin-linked kinase (ILK) is significantly higher in PROC as compared to platinum-sensitive OC [40]. Enhanced activity of focal adhesion kinase (FAK), a downstream effector of integrin signaling, is reported in OC exhibiting resistance to carboplatin and paclitaxel [41]. Phosphorylation of FAK increases after the cisplatin treatment and activates β-catenin signaling to support pluripotency and DNA repair [41]. Tumor-infiltrating lymphocytes and the presence of high Treg (regulatory T cells) count are associated with platinum resistance and disease recurrence [42]. Cytokines secreted by tumor-associated macrophages (TAMs) also promote platinum resistance by inducing epithelial to mesenchymal transition (EMT) and ECM remodeling [43, 44]. An increased presence of cancer stem cells (CSCs) has also been implicated in therapy resistance and cancer relapse [45]. Overexpression of CSC markers is associated with enhanced EMT features and multi-drug resistance in OC [46]. Cisplatin induces the expression of EMT and CSC markers and promotes aggressiveness and chemoresistance of OC cells [39]. Several stem cell markers, including aldehyde dehydrogenase (ALDH), CD44, CD24, CD133, CD117, and CXCR4, are overexpressed in PROC as compared to the platinum-sensitive ones [46–48]. ALDH1A1 expression is further correlated with lower progression-free survival of OC patients [49, 50]. An enhanced expression of stemness-maintaining proteins such as Nanog, Oct4, and CD73 is also linked to aggressive and chemoresistant OC [51–53]. Thus, inherent or TME-induced stemness potential is also an effective mechanism of platinum resistance in OC.

2.4. DNA damage repair machinery

As previously described, platinum-based drugs confer cytotoxicity by forming DNA adducts [12]. Thus, resistance to platinum therapy could be induced by the upregulation of DNA repair proteins that catalyze the removal of platinum adducts and repair the damage [7]. Indeed, most platinum-resistant cancers show an upregulation of DNA damage repair proteins, including but are not limited to BRCA1/2, mismatch repair proteins (MSH1,

MSH2), excision repair cross-complementing (ERCC) member proteins, RAD51 and Fanconi Anemia Complementation Group D2 [7, 54]. Even the presence of mutant BRCA1 is sufficient to initiate DNA damage repair by loading of RAD51 protein on the DNA [55]. Loss of proteins essential for replication fork stabilization, such as pax transactivation-domain interacting protein (PTIP), also renders the cells resistant to platinum-based drugs. OC patients diagnosed with the *BRCA1* mutation, but having high PTIP expression, show a more prolonged progression-free survival than those with low PTIP [56]. Replication protein A (RPA) is crucial for stabilizing DNA during replication and cells deficient in RPA show impaired nucleotide excision repair (NER), and thus less protection of replication fork making OC cells sensitive to platinum therapy [57]. Ataxia-telangiectasia and Rad3-related protein (ATR) is an important DNA damage sensor, which activates the homologous recombination (HR) pathway in response to DNA damaging agents [58]. ATR thus initiates the repair of cisplatin treatment-induced stalled replication forks, thereby rendering the cells therapy-resistant [59]. Translesion DNA synthesis (TLS) is a process by which cells allow themselves to replicate despite harboring errors in the underlying DNA sequence. Thus, the upregulation of proteins involved in TLS confers platinum resistance by sustaining the replication of damaged DNA [60]. DNA polymerase eta (Pol η) is crucial for the TLS after the formation of 8-Oxo-Guanine, making it a potential therapeutic target [61].

2.5. Epigenetic mechanisms

Epigenetic silencing of *BRCA1* is suggested to be an additional mechanism for its loss of function in cancer. However, the data associating *BRCA1* methylation in OC with clinical hallmarks and outcomes after platinum chemotherapy is inconsistent. While some studies suggest statistically significant association of BRACA1 promoter methylation with patient survival following platinum therapy [62, 63], others report an inverse trend or no significant association [64–66]. OC cells show a high expression profile of enhancer of zeste homolog 2 (EZH2), associated with methylation of H3K27 and gene silencing [67]. EZH2 is also predicted to be responsible for *BRCA1* downregulation and shift towards an advanced OC stage, platinum resistance, and poor patient survival [68, 69]. ARID1A, a subunit of SWI/SNF chromatin remodeling complex, is frequently mutated or repressed in CCC and associated with platinum resistance [70, 71]. Cisplatin treatment also induces epidermal growth factor receptor (EGFR)-mediated upregulation in DNA methyltransferase (DNMT) [72]. Enhanced DNMT1 activity affects the expression of genes associated with the critical cellular processes, such as proliferation, migration and invasion, and chemoresistance [73]. Abrogation of EGFR expression augmented cisplatin sensitivity of the OC cells accompanied by halted DNMT activity and DNA methylation. The methylation status of p27, a CDK inhibitor, is also linked to cisplatin sensitivity. PROC cells show significant downregulation of p27 due to promoter hypermethylation, overcoming cell cycle arrest induced by cisplatin treatment [74]. Administration of demethylating agents, 5-aza-2’-deoxycytidine, restores p27 expression and increases cisplatin sensitivity [74]. Promoter hypermethylation of ubiquitin carboxyl-terminal hydrolase 1 (UCHL1) has been linked to the upregulation of anti-apoptotic proteins BCl-2 and XIAP and thereby promotes cisplatin resistance in OC cells [75]. In another report, ten eleven translocation (TET) proteins belonging to the family of cytosine demethylases were also associated with

platinum-resistance, as evident from their ability to regulate the expression of vimentin, one of the critical players in EMT [76].

Promoter hypomethylation of TMEM88 is associated with platinum resistance in all OC histological subtypes [77]. TMEM88 causes downregulation of canonical Wnt signaling by interacting with its effector protein, Dishevelled, to induce dormancy and resist the cytotoxic effects of platinum therapy [78]. Cisplatin-resistant OC cells show a higher expression of HDAC1, and its knockdown leads to growth arrest and apoptosis in cisplatin-resistant OC cells [79]. HDAC1 inhibition decreases c-MYC expression and upregulates tumor suppressor miR-34a linking the HDAC1/c-MYC/miR34a axis to cisplatin sensitivity [79]. Another histone deacetylase, HDAC10, also supports platinum resistance by facilitating DNA damage repair even in BRCA1 negative background [80]. SIRT5, a member of the sirtuin class of histone deacetylases, is upregulated in various cancers, and its overexpression is reported in cisplatin-resistant OC cells where it abrogates cisplatin-induced ROS to sustain cell survival [81].

MicroRNAs (miRNAs) represent another important class of epigenetic regulators that has been associated with platinum resistance. miR-214 promotes platinum resistance in OC by downregulating PTEN expression [82]. PTEN is targeted by other deregulated miRNAs in OC, such as miR-130a and miR-186 and thus appears to be a significant determinant of sensitivity to platinum drugs [83, 84]. Decreased expression of miR-137 is also associated with platinum resistance that causes upregulation of MYC and EZH2 [85]. miR-21–3p promotes platinum resistance via downregulation of neuron navigator 3 [86]. In other reports, PROC cells are shown to have a downregulated expression of miR-1294 and miR-139–5p, whose restoration increased platinum sensitivity by inhibiting insulin-like growth factor 1 and c-jun expression, respectively [87, 88]. miR-199a, which targets mTOR and hypoxia-inducible factor-alpha, is also associated with cisplatin resistance [89, 90]. Thus, miRNAs could serve as clinically useful therapeutic targets to overcome platinum resistance in OC.

3. Molecular biomarkers of platinum resistance in ovarian cancer

Identification of molecular biomarkers associated with platinum resistance could significantly improve the clinical management of PROC by aiding in the early prediction of inherent resistance to guide therapeutic selection. These markers can also be very useful in monitoring the response of OC to platinum therapy and signal acquisition of chemoresistance. Below we discuss several potential biomarkers that have shown a strong association with platinum resistance in mechanistic and clinical studies. These candidate biomarkers can be explored further for PROC diagnosis, monitoring, and treatment guidance (Figure 2).

3.1. BRCA1/2, CCNE1, and ERCC1

BRCA1/2 mutations are frequently reported in HSGC and associated with sensitivity to platinum therapy [91, 92]. In several cases, reversion mutations in *BRCA1/2* that restore the gene functionality have been reported and associated with acquired resistance to platinum-based drugs and PARP inhibitors [92, 93]. In another study, amplification of *CCNE1*, a

gene encoding for cyclin E1, was reported in OC independent of *BRCA1/2* mutations and associated with resistance to platinum-based drugs [94]. Increased expression of excision repair cross complementation group-1 (ERCC1) along with BRCA1 is also suggested to serve as a biomarker to identify patients at high risk for developing platinum resistance. Increased expression of a larger novel transcript of ERCC1, initiated upstream of the normal transcription initiation site, was observed in cisplatin-treated OC cells [95]. Higher expression of this novel transcript was also found in the PROC patients compared to the platinum-sensitive ones, suggesting that it could be used to predict the outcome of platinum therapy in OC patients [95]. In a comparative analysis, CCC, which are more likely to exhibit de novo resistance to platinum-based drugs, were found to express higher levels of ERCC compared to other subtypes supporting its utility as a potentially useful biomarker [96].

3.2. ARID1A, TERT and HNF-1β

Loss of expression or inactivating mutation in tumor suppressor gene, AT-rich interaction domain 1A (ARID1A), are reported in CCC and correlated with poor overall survival of the patients treated with platinum therapy [71]. Mutations in telomerase reverse transcriptase (TERT) promoter leading to increased TERT mRNA levels are also reported in non-serous subtypes of OC [97]. These mutations correlate with the loss of ARID1A expression in CCC, promote cancer stem cell-like properties and induce platinum resistance [98, 99]. Hepatocyte nuclear factor-1 beta (HNF-1β) appears to be more frequently expressed in CCC tissue than other OC histological subtypes [100]. Functional studies have shown that HNF1β confers platinum resistance by upregulating glutathione synthesis and supporting cell survival [101]. Thus, HNF-1β could potentially be exploited as a biomarker of platinum resistance in OC.

3.3. TP53

TP53 is more frequently mutated in HGSC than other OC subtypes, and its loss of function due to inactivating mutations is shown to confer platinum resistance in ovarian tumor cells [102, 103]. However, there appears to be ambiguity about the role of p53 since another study reports greater efficacy of cisplatin in OC cells having no or mutant *TP53* compared to those with wild-type *TP53* [104]. In another study, it was found that platinum treatment led to an additional mutation, S185G, in the mutant *TP53* (R273H) and was associated with acquired chemoresistance in OC cells [105]. Therefore, the *TP53* mutational frequency could serve as a biomarker of inherent or acquired platinum resistance and assist in therapeutic planning. *TP53* clonal somatic variants have also been identified in patients with HGSOC. Notably, these variants were the same identified six years prior to OC diagnosis in the Papanicolaou tests of the afflicted individuals [106]. Thus, these clonal variants should be explored as the risk predictor for HGSOC development. In a more recent study, *TP53* mutations were identified in a significant majority of OC with a greater frequency in HGSOC. Moreover, they often co-occurred with *BRCA1* or *BRCA2* mutations and associated with platinum sensitivity, but not the overall survival [107]. Thus, it appears that *BRCA* mutations may serve as major confounding factors in determining the clinicopathologic association of *TP53* mutations with disease status and outcomes. All of these observations indicate that *TP53*

could be a useful biomarker of platinum resistance, but a more precise understanding of its function in different molecular contexts is required before clinical exploitation.

3.4. DNA methylation

Aberrant DNA methylation can control both ovarian tumorigenesis and platinum resistance [108]. Thus, measuring the nature and extent of methylation could serve as plausible means for biomarker development for early OC diagnosis and prediction of platinum resistance. A comparative genome-wide study of CCC and non-CCC subtypes suggested that the CCC had a distinct methylation profile. It showed hypomethylation of the stress-associated genes while the genes involved in tumor development, such as estrogen receptor alpha, were hypermethylated [109]. Hypomethylation of human endogenous retrovirus K is also observed in CCC and correlated with platinum resistance [110]. In other reports, hypermethylation in the promoter region of a mismatch repair gene hMSH2 (muts homolog 2) or hypomethylation of CpG sites within the Msh homeobox 1 gene (MSX1) have been associated with platinum resistance in OC [111, 112]. A recent CpG methylome and transcriptome study also identified a panel of differentially expressed genes (*IL6, IL6ST, SMAD3, KLF4, TGFBR1, EGF, JUN, PPARG, PPARGC1A,* and *AR)* in cisplatin-resistant OC cells. Among these genes, *KLF4* and *IL6* were the strongest candidates for predicting platinum resistance [113]. Another study suggested a role of hypermethylation of *MLH1* and *ZIC1* gene promoters in cisplatin resistance of OC cells [114]. A phase II clinical trial conducted to test the therapeutic efficacy of low-dose decitabine (demethylation agent) before carboplatin-treatment revealed that the number of demethylated genes in ovarian tumor samples was directly proportional to progression-free survival [115]. Furthermore, the study suggested that the demethylation in a set of genes (*RASSF1A, AKT1S1, MLH1*, *HOXA10,* and *HOXA11*) [115] could be used as a biomarker to stratify PROC patients as candidates for the treatment with demethylation agents. Hypermethylation is also reported in *BRCA1* promoter in OC patients and associated with sensitivity to platinum drugs [116].

3.5. MicroRNAs and long noncoding RNAs

A substantial number of studies have demonstrated the functional roles of microRNAs and other noncoding RNAs in OC cancer pathogenesis and platinum resistance [117, 118]. Marked loss of let-7g in OC tissues and sera is associated with platinum resistance, suggesting its utility as a biomarker for treatment guidance and therapeutic failure [119]. Another member of the let-7 family, miR-98–5p, is highly expressed in cisplatin-resistant ovarian tumor cells and associated with inadequate therapy response [117]. miR-622 is shown to induce resistance to platinum drugs and PARP inhibitors in *BRCA1/2* mutant OC by activating homologous recombination dependent DNA double-strand breaks repair in the treated cells [120]. miR-622 is highly expressed in HGSC and is associated with worse outcomes after platinum drug treatment [120] and thus could be used as a predictive biomarker for treatment planning and monitoring the therapy-response. In other studies, overexpression of miR-454–3p, miR-98–5p, miR-183–5p, and miR-22–3p and downregulation of miR-484, miR-642, and miR-217 has also been associated with platinum resistance [121, 122]. Mining of the cancer genome atlas (TCGA) identified 32 dysregulated long noncoding RNAs (lncRNAs) in PROC, suggesting their clinical utility as biomarkers [123]. Another study found an eight lncRNAs signature as a predictor of treatment response

in OC patients [124]. The expression of noncoding RNA, HOTAIR, was also associated with poor survival in carboplatin-treated OC patients [125].

3.6. CA-125 and glycan biomarkers

CA-125, a serum-based biomarker, is used to monitor therapy response and disease relapse in OC patients [126]. CA-125 is also known as mucin 16 (MUC16), a member of the mucin glycoprotein family. Differential expression of CA-125/MUC16 and MUC1 is reported in PROC cases [127]. An increase in CA-125 level following oral glucose intake is also suggested as a multi-drug resistance predictive biomarker [128]. To predict a decline in CA-125 level with the duration of treatments in OC patients, a unique model referred to as CA-125 elimination rate constant K (KELIM) was developed, and a high KELIM value was suggested to be an indicator of better therapeutic response [129]. CA-125, IL6, and leptin or serum CA-125 and ascites leptin can also be used as potential novel biomarkers to predict baseline clinical resistance to first-line treatment and poor outcome in HGSC patients [130, 131]. A recent study conducted to determine the predictive and prognostic potential of CA-125 in PROC patients, who received second-line therapy (platinum-based drug combined with bevacizumab), suggested its utility as an independent predictor of therapeutic response and OC recurrence [132].

Aberrant glycosylation of proteins, including mucins, is reported in several malignancies and used as a biomarker [133, 134]. Increased levels of poly-LacNAc and low levels of α2–6-linked sialic structures are reported in cisplatin-resistance OC cells, potentially suggesting their utility as PROC biomarker [135]. An altered expression in five glyco-subclasses and five single glycans is reported in recurrent and PROC patients. Further, a panel of three glycans, Lewis type N-glycans, α2,3 sialic acid, and multi-branch glycans (tri- and tetra-antennary glycans), was significantly altered in OC patients with the response of platinum-based drug [136]. Recently, N-glycomic profiling was carried out in tissue and serum samples obtained from advanced-stage high-grade OC patients. Data suggested a differential expression of N-glycans in OC samples and further found a positive association between tissue N-glycans and platinum resistance compared to serum N-glycans [137]. Thus, these glycans could be used as a predictor of chemotherapeutic response in PROC patients.

3.7. Metabolomic biomarkers

Metabolomics is the large-scale study of small metabolites in biological samples that can provide comprehensive information on cellular metabolism and be exploited for biomarker development [138]. Human Metabolome Database (https://hmdb.ca/) contains information on >25,000 small molecule metabolites present in the human body and serves as a valuable resource for biochemical studies and biomarker discovery. A clinical trial is ongoing to generate multi-omics (exome sequencing, transcriptomics, and metabolomics) findings on EOC patients of different clinical stages and pathological subtypes (NCT03742856). Another trial is aimed at determining the presence of prostaglandin metabolite in urine samples of OC patients (NCT00900523). Several urine metabolites have been identified to exhibit differential levels in OC patients and healthy subjects suggesting their potential utility as disease biomarkers [139]. Studies also suggest that metabolic alterations are

associated with cancer progression and chemotherapy resistance [140, 141]. Metabolic profiling of platinum-sensitive and -resistant OC cells revealed an association of altered cysteine and methionine metabolism with platinum resistance [142]. In another study, metabolic comparison between serous (OVCAR3) and non-serous (ES2) cancer cells suggested the presence of a distinct amino acid pool such as L-threonine, L-tyrosine and L-phenylalanine, and L-asparagine and ornithine (non-proteinogenic amino acid). Furthermore, carboplatin treatment facilitated increased GSH accumulation in non-serous OC compared to serous and imparted platinum resistance by forming platinum-thiol conjugates [101]. A study uncovered differences in lipid composition between platinum-resistant and -sensitive OC cells. PROC cells had lower lipids, for example, PC38:4, PC38:6, dehydrosphinganine, and lactosyl-ceramide, compared to the platinum-sensitive OC cells, suggesting an increased lipid utilization or decreased biosynthesis [143]. Levels of amino acid and associated metabolites such as histidine, tryptophan, phenylalanine, and kynurenine, among others, are reported to be significantly high in the plasma of relapsed OC patients [144]. Serum metabolome profiling also identified differential levels of six metabolites, calycanthidine, 1-monopalmitin, ricinoleic, methlester, polyoxyethylene-(600) mono-ricinoleate/glycidyl stearate and dodemorph, in PROC patients, which could be further examined for their potential use as biomarkers [145]. Thus, metabolites have good potential to be developed as biomarkers of disease progression and therapeutic response.

4. Liquid biopsy for ovarian cancer management

“Liquid biopsy” is a new concept that has gained substantial attention due to its several potential benefits over classical “tumor biopsy.” A liquid biopsy collects a sample of body fluid that is later analyzed to gather molecular information on the tumor type, its severity, and its response to therapeutic interventions [11, 146]. It overcomes several challenges associated with solid biopsy procedures, such as the tumor’s location and size, risk of potential spread, etc. Further, a liquid biopsy can be cost-effective, performed with ease, and potentially capture tumor heterogeneity more effectively than a solid biopsy [146, 147]. Liquid biopsy contains circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), extracellular microRNA (ex-miRNA), proteins, and metabolites that can be used for biomarker development and applications, as discussed below.

4.1. Circulating tumor cells (CTCs)

Disseminated tumor cells or CTCs can be originated from the primary or metastatic tumor sites and travel to other parts of the body through the bloodstream or lymphatic system [148]. Various methods have been studied to detect CTCs in liquid biopsy, but the CELLSEARCH® CTC Test is the only test that has received FDA clearance for detecting CTCs in the patients’ blood samples. Another method, CellCollector, has also been developed, which showed improved efficacy over CellSearch® in a comparative analysis in patients with neuroendocrine tumors [149]. However, both of these methods solely depend on the presence of EpCAM and certain cytokeratins on CTCs. A recent study tested an electrically conducive chip, incorporating a nano-roughened microfluidic platform to capture CTCs expressing different antigens (EpCAM, TROP-2, EGFR, vimentin, and N-cadherin) in OC patients. The CTC-cluster with a cutpoint of ≥3 CTCs showed a reduction in

progression-free survival and positivity correlated with platinum resistance [150]. In another study, Wimberger and colleagues reported the prevalence of EpCAM-positive disseminated cancer cells in the bone marrow of OC patients treated with platinum-based drugs, which suggested a high chance of disease relapse [151]. Molecular characterization of circulating OC tumor cells has indicated that patients treated with platinum-based therapy show a more predominant expression of peptidylprolyl isomerase C (PPIC) than the EpCAM expression. Furthermore, OC patients with PPIC-positive CTCs were shown to have a poorer overall- and disease-free survival compared to PPIC negative patients [152]. Another study reported that platinum-sensitive OC patients with $PPIC^{+}$ CTCs had high levels of neopterin and Kyn/Trp, associated with advanced disease, peritoneal carcinomatosis, ascites, sub-optimal debulking, inadequate response to therapy, and worse outcome. Moreover, neopterin and Kyn/Trp levels were heightened in CTC-positive patients, both at diagnosis and at follow-up in platinum-sensitive disease [153]. Interestingly, while ERCC1 expression in tumor tissue did not show any clinical significance [154], the presence of ERCC1- positive CTCs at the time of primary diagnosis served as an independent predictor of patients' survival and platinum resistance [155]. Therefore, characterization of CTCs for different antigens or a combination of antigens can be an effective tool for OC diagnosis and predicting the chances of therapeutic success or failure and disease recurrence.

4.2. Cell-free circulating tumor DNA (ctDNA)

Cell-free circulating tumor DNA (ctDNA) has also been studied for monitoring drug response and disease recurrence in OC patients. In a recent study, genome-wide copy number alterations in ctDNA were examined as novel biomarkers in high-grade serous OC patients [156]. Shallow whole-genome sequencing of liquid biopsy demonstrated a gain in clonal regions, *3q26.2* and *8q24.3*, in a significant majority of plasma samples, mirroring solid biopsies from the same cases. A heterogeneous pattern of genomic amplification was also observed in OC patients before and after platinum-based therapy in the *19p31.11* and *19q13.42* regions. Further, ctDNA analysis outperformed CA-125 in anticipating clinical and radiological progression, suggesting its utility to monitor disease evolution following treatment and disease relapse prediction [156]. *BRCA1/2* reversion mutations have also been detected in the ctDNA in the plasma of PROC patients [157, 158]. In a cohort of gynecologic cancer patients, ctDNA analysis of PROC cases (78%) showed mutations in many genes, including *EGFR, KRAS, TP53, PIK3CA, MYC, BRAF, MET, CCNE1, and CDK6*. Moreover, a higher ctDNA mutation frequency was associated with worse overall survival [159]. Similarly, *TP53* mutations have been detected in circulating tumor DNA (ctDNA) samples of OC patients, and a marked reduction in mutant *TP53* in ctDNA is reported following treatment with platinum and non-platinum drugs in HGSC patients [160, 161]. CpG methylation has also been reported in the peripheral blood DNA of OC patients treated with platinum-based drugs by performing bisulfite sequencing during the first relapse. Therefore, blood-based DNA methylation can be used as a novel biomarker to predict the overall survival of PROC patients [162]. A clinical trial is currently ongoing to evaluate ctDNA as an early biomarker of disease recurrence and platinum-based treatment efficacy in OC patients (NCT03302884).

4.3. Extracellular Vesicles (EVs) and microRNAs (ex-miRNA)

Tumor cells release tiny membrane vesicles in the extracellular spaces to exert biological functions locally and at distant sites [28, 163]. These extracellular vesicles (EVs) harbor tumor-specific biomolecules (DNA, RNA, protein, and metabolites) and can be easily isolated from body fluids such as blood, urine, etc. In recent years, several novel methods have been developed for the characterization of EVs for clinical application. A label-free, high-throughput approach for quantitative analysis of exosomes or smaller-sized EVs was developed and used to analyze ascites samples from OC patients. This nano-plasmonic exosome (nPLEX) assay was based on transmission surface plasmon resonance through periodic nanohole arrays functionalized with antibodies to enable profiling of exosome surface proteins. CD24- and EpCAM- positive exosomes were identified using this method, suggesting its utility for biomarker development and future clinical applications [164]. Another technique, ExoCounter, has also been used to quantify the number of exosomes in the serum of OC patients using CD9, CD63, CD147, and HER2 as surface markers [165]. Since EVs derived from PROC cells have been shown to impart chemoresistance in platinum-sensitive cells [166], they could potentially be exploited to predict chemoresistance and monitor therapeutic responses. Characterization of embedded biomaterial in EVs can also be a valuable source for developing precise tumor-specific biomarkers.

Circulating extracellular miRNAs (ex-miRNAs) have been examined as biomarkers for platinum resistance in OC patients. Cf-miRNAs are quite stable as they remain protected from nuclease activity by high-density lipoprotein, miRNA-binding proteins, argonaute2, or EV encapsulation [167–169]. cf-miRNAs can be isolated from various body fluids and profiled using high-throughput approaches, such as miRNA microarrays or next-generation sequencing (NGS). Previous studies, including ours, have shown altered release of EVs and encapsulated miRNAs in response to tumor hypoxia and exposure to chemotherapeutic drug supporting their clinical utility as liquid biopsy-based biomarkers [28, 170]. A major limitation; however, is the lack of defined endogenous controls for serum miRNAs. Nonetheless, miR-16, RNU-6B, and RNU-48 or let-7d, let-7 g, and let-7i have often been used as referenced genes and yielded reliable normalization [169]. NGS-based detection of EV-derived miRNAs in plasma samples revealed that miR-1908, miR-181a, miR-486, miR223, and miR-21 were overexpressed in PROC patients [171]. In another study, PROC patients showed higher serum miR-130a, which correlated with tumor progression and lymph node metastasis [83]. Increased serum level of U2–1 snRNA fragment (RNU2–1f) was also reported in OC patients but did not show any association with histological subtype or platinum resistance [172]. The enhanced level of serum miR-622 associated significantly with lower progression-free and overall survival of OC patients and was an independent predictive biomarker of response to platinum-based drugs both in newly diagnosed and relapsed OC cases [173]. Another study showed a lower level of serum miR-125b in patients exhibiting chemoresistance than those who responded favorably to chemotherapy. Moreover, serum miR-125b combined with serum CA125 improved sensitivity and specificity of EOC diagnosis [174]. A reduction in the level of circulating miR-148–5p has been reported in OC patients treated with chemotherapeutic drugs, carboplatin and decitabine, and associated with poor progression-free survival [175]. Clearly, cf-miRNAs hold immense potential to

be exploited as biomarkers for inherent and acquired chemoresistance as well as disease diagnosis.

4.4. Serum proteins

Teng and et al. identified 16 differentially expressed proteins in the secretome of the platinum-sensitive and -resistant OC cells. Among these proteins, COL11A1 was highly expressed in PROC cells [176]. Similarly, another study demonstrated increased levels of soluble PD-L1 (sPD-L1) and decreased levels of sPD-L2 in serum samples of OC patients. Enhanced sPD-L1 was associated significantly with residual tumor burden, while reduced sPD-L2 levels predicted platinum resistance. Furthermore, sPD-L1 levels were negatively associated with overall and progression-free survival, although only in platinum-sensitive patients [177]. Therefore, both sPD-L1 and sPD-L2 should be investigated further in larger cohorts to explore their utility as serum biomarkers of unfavorable disease outcomes despite drug sensitivity. Serum lactate dehydrogenase (LDH) has been used to monitor radiotherapy and chemotherapy responses in many cancer types. Recently, Ikeda et al. reported high serum LDH in PROC patients and suggested its use as a marker for platinum-resistant disease [178]. Robust reduction in serum VEGF-A is also associated with inadequate therapeutic response and worse prognosis in PROC patients treated with gemcitabine combined with anti-angiogenic drug, bevacizumab [179]. Thus, serum VEGF-A could be exploited as a liquid biopsy biomarker for therapeutic response prediction in PROC patients. Calcium-binding protein calretinin was present in the serum of OC patients at significantly higher levels than the healthy subjects and was an independent biomarker of platinum resistance [180]. Annexin A3, a member of the calcium and phospholipid-binding protein family, is highly overexpressed in PROC cell lines and tissues but does not show any significant clinical association in PROC patients [181]. It could be due to tumor heterogeneity or interaction of Annexin A3 with other serum factors interfering with its capture and measurement. Therefore, not all secreted proteins, overexpressed in tumor tissues and exhibiting clinicopathological association, could be used as liquid biopsy biomarkers. Moreover, the detection procedure may also need to be optimized for each protein biomarker.

5. Conclusion and future perspective

Platinum-based therapy remains the first line of treatment for OC patients, but disease relapse is inevitable in most cases due to inherent or acquired chemoresistance [7, 182]. Years of research have identified several molecular mechanisms underlying platinum resistance, as discussed earlier, and this information has helped develop alternative therapeutic strategies. While most genes implicated in platinum resistance belong to DNA damage repair machinery, some other proteins also make a substantial contribution. In many instances, the development of platinum resistance could be multifactorial due to disease heterogeneity. Thus, understanding the molecular nature and then formulating the best combination therapy regimen would be crucial in achieving the best possible clinical outcome.

Molecular markers suggestive of different underlying platinum-resistance mechanism(s) could be of immense help in the treatment planning. Since platinum resistance could also be dynamic or some mechanisms could dominate over others at initial presentation, constant monitoring of therapeutic responses using biomarker sets will be required throughout the treatment and afterward. This greatly emphasizes the need for reliable, mechanism-specific biomarkers and approaches to assist in repeated monitoring of the disease. Although we have several good leads for biomarker development, we do not yet have the bonafide ones for accurate tracking, surveillance, or treatment guidance of PROC. The use of approaches that can capture the tumor heterogeneity is also crucial to better plan the therapeutic course of action. In that regard, liquid biopsy-based biomarkers could be ideal, requiring less invasive procedures and theoretically providing comprehensive information on the molecular landscape of the disease. However, discrepancies across studies could arise due to the use of different sampling and analytical methods. Lack of established endogenous controls is also a significant bottleneck in cases where quantification of the biomarker is required to diagnose or base the therapeutic decision. We have also had limited success in having a superior treatment choice to improve patients' survival. Treatment response varies considerably among different subtypes of OC or even within a subtype due to inherent genetic, epigenetic, and microenvironmental differences supporting distinct chemoresistance pathways. Multifocal and integrative genomic/epigenomic profiling in a subtype-specific manner could help identify the compendium of altered genetic and epigenetic landscape therein. This, in turn, will provide a rationale to move forward with functional validation to ultimately define the target(s) for therapeutics.

It is high time that more efforts are directed towards biomarker testing in larger cohorts in randomized trials. A multicenter comprehensive analysis of carefully chosen sample cohorts will be required to achieve this goal. The approaches described above for genome and epigenome profiling could serve as a unique platform for biomarker discovery followed by stringent validation. However, it could be a difficult task to achieve since platinum drugs are delivered in combination with other agents, and their joint action could complicate mechanistic interpretations. Therefore, molecular and/or immune profiling before and after such treatments may aid in refining biomarkers and developing alternate treatment strategies. Immunotherapy is currently under the reincarnation phase to successfully treat human malignancies, and its thoughtful use could help overcome platinum resistance. To achieve an optimal outcome, it would be necessary to first stratify the patients that would benefit from specific immunotherapeutic modalities based on existing and novel biomarkers under development. At this time, clinical and basic research endeavors ought to be combined while wisely utilizing the technological advancements to achieve paradigm-shifting progress in the management of platinum-resistant ovarian cancer.

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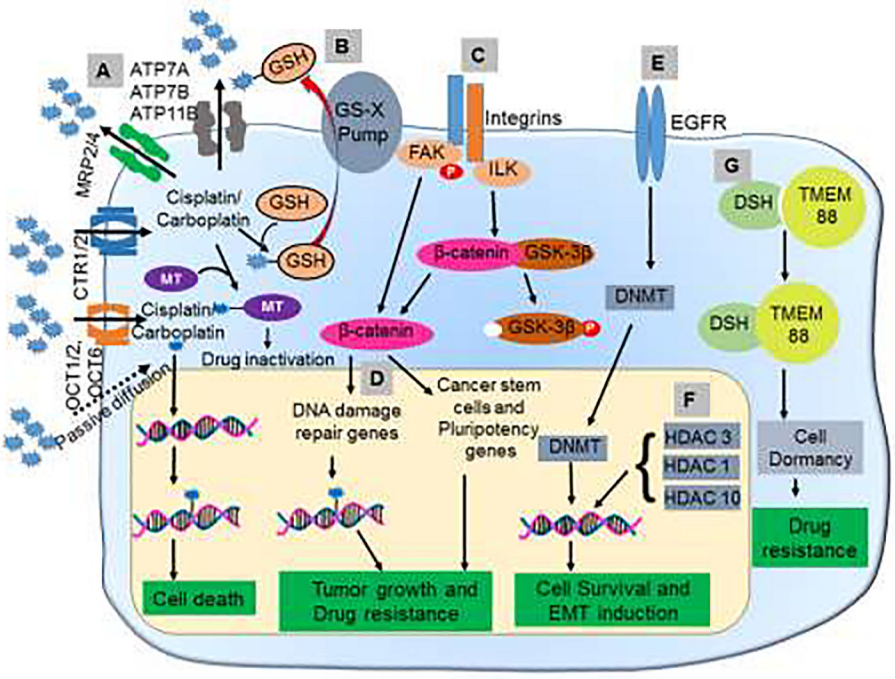

Figure 1. Mechanisms underlying platinum resistance in ovarian cancer.

(A) Dysregulation of transporters associated with cisplatin/carboplatin leads to the reduced influx and increased efflux. **(B)** GSH and metallothionein mediate the inactivation of platinum compounds via the formation of drug conjugates. **(C)** Interaction between integrin and ECM promotes platinum resistance by inducing DNA damage repair proteins and CSC genes. **(D)** Upregulation of DNA damage repair proteins such as BRCA1 enables cancer cells to repair the DNA damage induced by platinum-based drugs and become resistant. **(E)** The upregulation of EGFR enhances the activity of DNMTs and leads to global methylation and downregulation of proteins regulating proliferation, migration, and invasion. **(F)** HDACs downregulate genes responsible for apoptosis and proliferation. **(G)** Inhibition of Wnt signaling mediated through the binding of Dishevelled to TMEM88 leads to cell dormancy and thus resists the action of the cytotoxic drugs. **MT**=Metallothionein; **DSH**=Dishevelled; **FAK**=focal adhesion kinase; **ILK**=Integrin-linked kinase; **OCT**=organic cation transporter; **GSH**=Glutathione; **GS-X**=Glutathione conjugate export pump; **GSK**= Glycogen synthase kinase 3; **DNMT**= DNA Methyltransferase; **HDAC**=Histone deacetylases; **TMEM**=Transmembrane Protein 88; **EGFR**=Epidermal Growth Factor Receptor

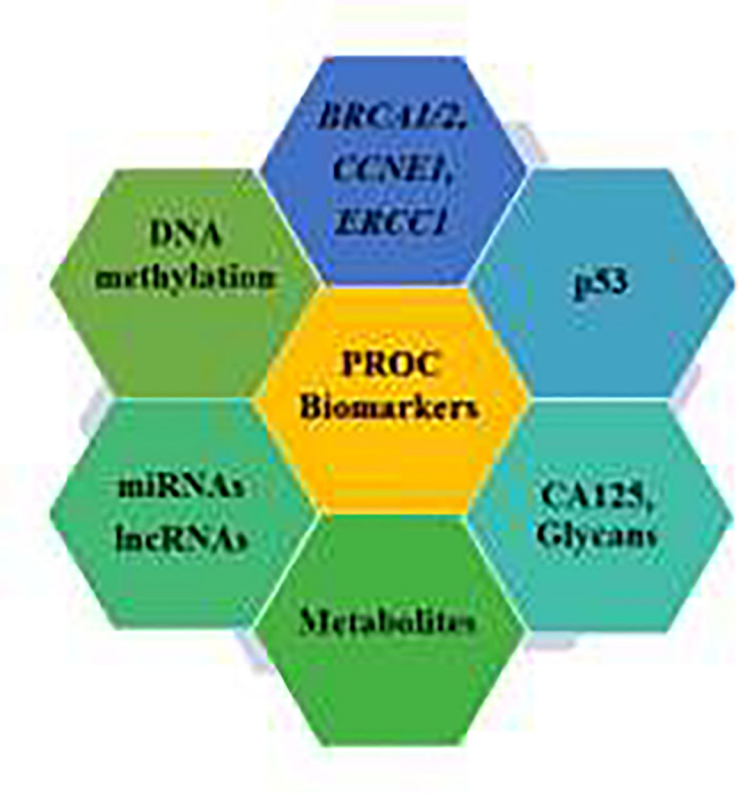

Figure 2. Biomarkers of platinum-resistant ovarian cancer.

Molecular analysis of clinical specimens and laboratory studies have identified several molecular alterations associated with platinum-resistant ovarian cancer. These signature alterations can be exploited as molecular biomarkers to predict the nature of platinum resistance and monitor the response of ovarian cancer to therapy.