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REVIEW ARTICLE

# Revisiting chemoresistance in ovarian cancer: Mechanism, biomarkers, and precision medicine

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**Abstract** Among the gynecological cancers, ovarian cancer is the most lethal. Its therapeutic options include a combination of chemotherapy with platinum-based compounds and cytoreductive surgery. Most ovarian cancer patients exhibit an initial response to platinum-based therapy, however, platinum resistance has led to up to 80% of this responsive cohort becoming refractory. Ovarian cancer recurrence and drug resistance to current chemotherapeutic options is a global challenge. Chemo-resistance is a complex phenomenon that involves multiple genes and signal transduction pathways. Therefore, it is important to elucidate on the underlying molecular mechanisms involved in chemo-resistance. This inform decisions regarding therapeutic management and help in the identification of novel and effective drug targets. Studies have documented the individual biomarkers of platinum-resistance in ovarian cancer that are potential therapeutic targets. This review summarizes the molecular mechanisms of platinum resistance in ovarian cancer, novel drug targets, and clinical outcomes.


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## Introduction

Globally, ovarian cancer (OC) is the eighth most common malignant tumor among women. In the female reproductive system, cervical and endometrial cancers are the only ones with a higher occurrence rates than ovarian cancer.[1] There are four types of recurrent ovarian cancers (ROC), that is; platinum-sensitive cancer (patients with platinum-sensitive OC attain clinical remission after initial platinum-based combination chemotherapy, and have a recurrence 6 months after discontinuing chemotherapy), platinum-resistant cancer (patients with platinum-sensitive OC attain clinical remission after initial platinum-based combination chemotherapy, but have relapse within 6 months after discontinuing chemotherapy), persistent OC (patients exhibit a clinical response or obvious reaction to the initial platinum-based chemotherapy, but show residual lesions upon further examination) and refractory OC (patients do not respond to platinum-based chemotherapy, including stabilization or progression during treatment).[2]

The therapeutic options for ROC include secondary surgery, chemotherapy, hormonal therapy, targeted therapy, and immunotherapy, among others. Patients with isolated and resectable lesions, or lesions that can be removed by surgical procedures at multiple levels, and without the risks associated with a decline in life quality can be treated with secondary surgery and effective chemotherapies.[3] Chemotherapy is an effective ROC treatment technique and should be comprehensively considered depending on the patients' response to first line chemotherapy, platinum-free interval, side effects, etc.[4] Hormone therapy for ROC antagonizes the tumor cells based on the differential expression of hormone receptors.[5] Approved and effective targeted drugs for ROC include PARP (poly-ADP-ribose polymerase) inhibitors. Several studies are aimed at developing new treatment options for ROC.[6] Immunotherapy effectively controls and eliminates tumors by restarting and maintaining tumor immune cycles and restoring normal anti-tumor immune responses.[7]

Cytoreductive surgery and platinum-based chemotherapy are basic OC treatment options. Combination chemotherapies have been shown to exhibit enhanced clinical effects, however, primary and secondary platinum-resistance of OC exerts therapeutic challenges. The mechanisms of platinum-resistance are multi-faceted and include metabolism, apoptosis, and DNA damage repair, among others. Therefore, elucidating the mechanisms of platinum-resistance in OC will provide potential therapeutic targets. There are several kinds of ovarian cancers with complex structures. According to their tissue structures, there are three main types of ovarian cancers: epithelial cancers; germ cell cancers; and sexual cord stromal tumors. Epithelial cancer is the most common. It accounts for 90% of all ovarian cancers and can be classified as benign, malignant and borderline. Most epithelial ovarian cancers originate from epithelial cysts in the oviduct or ovarian cortex. Cancers that were associated with the ovarian epithelium have now been shown to originate at the end of the fallopian tube. Epithelialized cortical inclusion cysts are derived from the constantly renewing surface epithelium of the ovary or oviduct. Cysts may metaplasia or transform into different epithelial cancers. Depending on to the epithelial type, the cancers are grouped into serous, mucous and endometrioid, etc. Ovarian cord stromal tumor originates from indifferent gonad and stromal tissues evolves into different cell types in males and females to form certain tissue structures. The female sex cord stromal cells are referred to as granulosa and follicular membrane cells while the male sex cord stromal cells are referred to as support cells and stromal cells. In women, these cells form granulosa cancer and follicular mesenchymoma, respectively while in men, they form support cell cancers and stromal cell cancers. In combination, they can also form granulocyte - follicular mesenchymoma or supportal-stromal cell cancers. The germ cell origin accounts for about a quarter of all ovarian tumors. Sixty percent of ovarian tumors in children and adolescents are germ cell tumors.

Primitive germ cells exhibit the potential to differentiate in different directions. A tumor that is derived from a primitive germ cell is referred to as an asexual cell tumor. The differentiation of primitive germ cells into embryonic body wall cells is called teratoma. Primitive germ cells differentiate into the extracellular tissues, and the cancer cells resemble the mesenchymal cells of the placenta or their precursors, which are called yolk sac tumors. The differentiation of primitive germ cells into embryonic chorionic cells is known as choriocarcinoma.

## Mechanisms of platinum resistance in ovarian cancer

### miRNA induced OC resistance mechanisms

microRNAs are a group of non-coding RNAs with a length of 18—25 nucleotides. They bind the 3′untranslated region (3′UTR) of target mRNAs and mediate its functions. miRNA dysregulation has been shown to be a platinum-resistance mechanism in numerous cancers, particularly OC.[8,9]

Studies have documented that the miRNAs implicated in OC platinum-resistance are potential therapeutic targets for OC (Table 1). miR-139-5p levels were found to be suppressed in OC cells. It was also shown to inhibit cancer cell apoptosis while inducing cisplatin resistance through the c-Jun/Bcl-xl pathway.[10] Moreover, miR-1294 regulates OC cisplatin resistance by up-regulating IGF1R. IGF1R knockdown enhances proliferation, migration, invasion and EMT, and therefore, promotes cisplatin resistance. However, the overexpression of miR-1294 was shown to exhibit the opposite effects.[11] miR-7 DNA methylation enhances poor OC platinum-response through MAFG.[12] In addition, miR-622 regulates responsiveness to platinum through the HR and NHEJ pathways[13]; miR-493-5p enhances chemo-resistance and poor OC prognosis through RNASEH2A, FEN1, and the SSRP1 genes[14]; miR-551b promotes cancer cell proliferation, invasion, colony formation and chemo-resistance through Foxo3 and TRIM31[15]; miR-21 promotes OC cell tumorigenesis and chemo-resistance through the JNK-1/c-Jun pathway[16]; miR-142-5p targets anti-apoptotic genes (XIAP, BIRC3, BCL2L2 and MCL1) to promote chemo-resistance[17]; miR-483-3p enhances cell proliferation and inhibits apoptosis through PRKCA[18]; miR-182 has been

**Table 1** miRNAs associated with mechanism of platinum-based chemo-resistance in ovarian cancer.

| miRNA | Cell lines/tissues | Expression/Action | Effect on platinum resistance | Resistance against | Reference |
|---|---|---|---|---|---|
| miR-139-5p | SKOV3 and A2780 | Down-regulation | Inhibited apoptosis | Cisplatin | [10] |
| miR-411 | SKOV3 and OVCAR3 | Down-regulation | Tumor growth and poor patient survival | Cisplatin | [150] |
| miR-1294 | SKOV3 | Down-regulation | Induce the cisplatin-resistance | Cisplatin | [11] |
| miR-7 | H23R, IMIM-PC2, LoVo, A2780R, A2780S and HEK-293T | DNA methylation and epigenetic regulation | Induce the cisplatin-resistance | Cisplatin | [12] |
| miR-622 | UWB1.289 | Up-regulation | Poor OS and DFS | Cisplatin | [13] |
| miR-493-5p | OVSAHO, Kuramochi, and VU423 | Up-regulation | Induce the cisplatin-resistance and poor prognosis | Cisplatin | [14] |
| miR-31 | A2780, MCP1 and CP70 | Up-regulation | Increased resistance | Cisplatin | [151] |
| miR-211 | | Up-regulation | Enhanced platinum-sensitivity | Platinum drugs | [21] |
| miR-551b | HEK293T, SK-OV-3 and 8910 | Up-regulation | Proliferation, invasion, colony formation and cisplatin-resistance | Cisplatin | [15] |
| miR-21 | A2780 and A2780CIS | Up-regulation | Proliferation, invasion, colony formation and cisplatin-resistance | Cisplatin | [16] |
| miR-142-5p | OVCAR3 and SKOV3 | Down-regulation | Inhibited apoptosis | Cisplatin | [17] |
| miR-483-3p | IGROV-1, A2780 and OVCAR-5 | Up-regulation | Inhibited apoptosis, promote proliferation and induce resistance | Platinum drugs | [18] |
| miR-182 | | Down-regulation | Poor PFS and OS | Platinum drugs | [19] |
| miR-30 | | Up-regulation | Increased resistance | cisplatin | [20] |
| miR-30a | | Up-regulation | Reversed cisplatin-resistance | cisplatin | [22] |
| miR-9 | OV2008, C13, SKOV3, A2780 and CaOV3 | Up-regulation | Improved therapeutic efficacy | cisplatin | [23] |
| miR-515-3p | RMUG-L-ip1 and RMUG-S-ip1 | Up-regulation | Increased sensitivity | Oxaliplatin | [24] |

associated with poor PFS and OS of OC patients through DDR2[19] while miR-30 promotes platinum resistance through the MYPT1 gene and hippo pathway.[20]

Certain miRNAs have also been shown to enhance OC cell chemo-sensitivity. They include: miR-211 that enhances OC cell platinum sensitivity by inhibiting DDR[21]; miR-30a inhibits the ET-1/ETAR axis to reverse chemo-resistance in chemo-resistant OC cells[22]; miR-9 improves chemotherapeutic efficacy by down-regulating BRCA1 and mediating the HR pathway[23]; miR-515-3p enhances OC cell sensitivity to oxaliplatin by regulating AGO2, AXL genes and the PRKRA/PACT axis.[24]

## Long non-coding RNA induced OC resistance mechanisms

lncRNAs are a type of non-protein coding transcripts. They are RNAs with a length of over 200 nucleotides. lncRNAs have been documented to play key roles in OC platinum-resistance.[25] The effects of lncRNAs on chemo-resistance are manifested in altered drug efflux systems,[26] altered cell cycles,[27] abnormal apoptosis,[28] autophagy,[29] epigenetic changes, exosome and oxidative stress (Table 2).

Cancer-associated fibroblasts promote the over-expression of midkine that elevates ANRIL expression leading to the induction of tumor cell cisplatin-resistance. ANRIL knockdown suppresses the expression of drug transporters (ABCC2 and MRP1) that inhibit proliferation induces apoptosis. These transporters also enhance the efficacy of cisplatin in OC. This implies that ANRIL induces cisplatin-resistance in OC by acting on drug transporters to promote drug efflux.[30] HOTAIR is an lncRNA that is strongly associated with tumor progression and poor OC prognosis. A high expression of HOTAIR promotes the expression of cyclin D1 and CDK4. In addition, it upregulates the expression of β-catenin. β-catenin is a key regulator of the Wnt/β-catenin pathway that activates cyclin D1 and its ligands to accelerate cell cycle progression while inhibiting cell cycle arrest at the G0/G1 phase. These effects lead to reduced chemotherapeutic sensitivity. HOTAIR contributes to platinum resistance by manipulating the cell cycle (fast cell proliferation) through the Wnt/β-catenin pathway.[31]

PVT1 is a candidate oncogene that is adjacently located to the MYC locus on chromosomal region 8q24. It has been shown to be over-expressed in tumor tissues of cisplatin-resistant patients.[32] TGF-β1, p-Smad4 and Caspase-3 were found to be significantly overexpressed in tumor cells after PVT1 knock down. When transfected with LV-PVT1-GFP, PVT1 expression and cell viabilities of cisplatin-sensitive cells were markedly enhanced while the apoptosis index decreased. These effects reversed cisplatin-resistance in cancer cell lines. This implies that PVT1 over-expression promotes OC cisplatin-resistance by inhibiting apoptosis.

MALAT1 has been reported to be upregulated during OC tumorigenesis. MALAT1 knockdown has also been shown to suppress the Notch pathway. A previous study documented that TGF-β induced the up-regulation of MALAT1 while MALAT1 knockdown inhibited TGF-β-induced autophagy. In addition, miR-200a inhibits MALATI expression and autophagy.[33] OC cell sensitivity to cisplatin can be enhanced by over-expressing miR-200c.[34] In summary, the over-expression of MALAT1 enhances TGF-β-induced autophagy and Notch pathway, thereby, suppressing cisplatin-sensitivity in OC cells.

H19 has been shown to be up-regulated in cisplatin-resistant OC cells,[35] and manifest its effects through GSH metabolism. Nrf2 is an important regulator of antioxidant molecule expressions. Nrf2 is degraded by Keap1 in cisplatin-sensitive cells and is stabilized by H19 in cisplatin-resistant OC cells.[36] Valproic acid is a therapeutic option for epilepsy that epigenetically down-regulates H19 and enhances cisplatin-sensitivity in OC cells by down-regulating EZH2 and its target genes (p21 and PTEN).[37] In conclusion, H19 regulates cisplatin-resistance in OC cells through epigenetic modification and the cisplatin-associated oxidative-stress pathway. The role of H19 in the oxide-reduction pathway and its specific mechanisms in epigenetic modification have not been established.

MEG3 is a tumor suppressive lncRNA in multiple cancers. It was up-regulated in curcumin-treated and untreated anti-cisplatin OC cells. Therefore, the ability of extracellular vesicles from curcumin treated OC cells to induce cisplatin-resistance was compromised. Curcumin increases lncRNA MEG3 by MEG3 demethylation, whose restoration attenuates the extracellular vesicles' ability to promote cisplatin-resistance by suppressing miR-214[38]. In conclusion, curcumin inhibits miR-214 metastasis by up-regulating MEG3 to inhibit cisplatin-resistance in OC cells.

## CircRNA induced OC resistance mechanisms

CircRNAs are a type of non-coding RNAs that were initially regarded as functionless products of pre-mRNA splicing errors.[39] They are pervasive regulatory molecules that are comparable to their canonical linear counterparts.[40,41] Studies on differentially expressed circRNAs and their functions in OC have shown that they are potential novel biomarkers or therapeutic agents in OC. Cdr1as is located at chrX:139865339−139866824. Its genomic length and spliced mature sequence length are both 1485 bp.[42] Zhao et al[43] documented that the cisplatin-sensitivity of OC cells is enhanced by Cdr1as which functions as a molecular sponge of miR-1270. This outcome decreases the inhibitory effect of miRNA on its downstream target SCAI. Cdr1as has

**Table 2** LncRNAs associated with mechanism of platinum-based chemo-resistance in ovarian cancer.

| LncRNAs | Cell lines/tissues | Expression/Action | Effect on platinum resistance | Resistance against | Reference |
|---|---|---|---|---|---|
| DNM3OS | ovarian cancer tissues | Up-regulation | inhibited apoptosis | Cisplatin | 152,153 |
| H19 | A2780-DR | Up-regulation | Oxidative stress Nrf2; Epigenomics EZH2 | Cisplatin | 36,37 |
| PVT1 | SKOV-3, SKOV-3/DDP, 2780, A2780/DDP | Up-regulation | apoptosis | Cisplatin | 32 |
| MALAT1 | A2780, OVCAR3, COC1, A2780/CDDP, COC1/CDDP, OVCAR3/DDP | Up-regulation | EMT; apoptosis, autophagy | Cisplatin | 33,154,155 |
| ANRIL | A2780 | Up-regulation | Changes in drug effluent system | Cisplatin | 30 |
| UCA1 | SKOV3 | Up-regulation | apoptosis | Cisplatin | 156 |
| MEG3 | A2780cp, A2780, SKOV3 and OVCAR-3 | Down-regulation | Exosomes | Cisplatin | 38 |
| ENST00000457645 | A2780, CP70, SKOV3, and SKOV3/DDP | Down-regulation | Cell cycle changes | Cisplatin | 157 |
| HOTAIR | IGROV, OVSAHO, OVMUNA, SKOV3, A2780, HEYC2, A2780-CR5, OV90, HO-8910 | Up-regulation | cell cycle changes; EMT; drug effluent system | Carboplatin | 31,158,159 |
| GAS5 | A2780, SKOV-3, A2780/DDP, SKOV-3/DDP | Down-regulation | apoptosis | Platinum drugs | 160 |

also been shown to be down-regulated in OC tissues of cisplatin-resistant or cisplatin-sensitive patients. The ectopic expression of Cdr1as promotes the apoptosis of cisplatin-resistant cells and inhibits proliferation. Cdr1as and the SCAI 3′ UTR share identical miR-1270 response elements, therefore, Cdr1as can act as miRNA-1270 sponges to negatively control targeted miRNA-1270. This leads to the partial abolition of the translational repression of its target gene SCAI that sensitizes OC cells to cisplatin.

### Ovarian cancer stem cell induced OC resistance mechanisms

As the process of the ovarian cancer stem cells (OCSCs) has not been elucidated, OCSCs model of disease progression has also not been established. Due to their capacity for self-renewal, OCSCs initiate and maintain tumorigenesis, thereby, enhancing tumorigenicity and chemo-resistance.[44,45] Biomarkers of OCSCs such as aldehyde dehydrogenase1 (ALDH1) and cluster of differentiation 133 (CD133) have been extensively studied in OC. These markers are the most consistently replicated markers in model systems and OC.[46] CD133 and ALDH1 influence HGSOC patients' survival and are attributed to the phenotypical changes during the progression of OC.[46] Recurrent tumors are densely composed of putative OCSCs as characterized by ALDH1 and CD133 than their matched primary OC specimens. This implies that OCSCs are responsible for the clinic-meaningful OC initiation or recurrence.[46,47] However, the fact that these biomarkers, particularly ALDH1, were found to be highly expressed not only in OCSCs is the main limitation. BMP2 is the most promising OCSCs marker for the development of new therapeutic options for OC.[48,49] A hierarchical differentiation pattern reported that BMP2 acts as a feedback mechanism with important roles in promoting OCSC expansion while suppressing progenitor proliferation.[50] In addition, over-expression of OCSCs markers are correlated with residual chemo-resistant patients at the end of primary therapy and resistant OC enriched with genes involved in stem cell pathways.[47] Patients usually exhibit excellent initial responses to chemotherapy, which suggests that a majority of primary cancers are actually sensitive to chemotherapy. Although the populations exhibiting chemo-resistance are increasing, recurrent cancers are not completely composed of OCSCs. This shows that OCSCs exhibit a differentiation capacity that rapidly produces marker-negative cells, or both, even in chemoresistant populations. The limitation of the above study was the specific examination of stem cell pathways. OCSCs have enhanced DNA repair mechanisms that allow its survival when its exposure to DNA-damaging insults is prolonged.[51,52] Stem cell reprogramming factor PBX1 is also involved in chemotherapeutic resistance while its elevated expression levels have been correlated with shorter survival outcomes in post-chemotherapeutic OC patients. Hyaluronan is the major glycosaminoglycan in the extracellular matrix. It activates Nanog through CD44. Activated Nanog stimulates STAT3 to activate EMT and MDR1 that enhance chemotherapeutic resistance.[53] The mechanism of OCSCs associated platinum-resistance has not been characterized. However, OCSC quiescence during chemotherapy has been hypothesized to be the most likely mechanism as it relies on cell division to damage DNA.[54] Although OCSCs as targetable biomarkers for platinum-resistance is compelling, OCSCs-related prognostic testing or development of targeted treatments has not been achieved.

### Epithelial—mesenchymal transition induced OC resistance mechanisms

During the epithelial to mesenchymal transition (EMT) process, cells undergo a series of changes that involve acquired resistance to several chemotherapeutic agents.[45] The evolutionarily conserved EMT developmental process is regulated by a diverse array of cytokines and growth factors such as transforming growth factor beta (TGF-β) or receptor tyrosine kinase (RTK). This process is intricately linked to the presence of OCSCs. TGF-β is secreted by macrophages and other white blood cells in the tumor microenvironment. It activates tissue transglutaminase that induces the potency to form spheroids and develop EMT. TGF-β secreted in the OC microenvironment regulates TG2 expression and functions. TG2 is an enzyme that is associated with chemo-resistance during metastasis. It primarily activates the canonical SMAD pathway. TGF-β1 induced TG2 contributes to EMT and OC aggregation as spheroids.[55,56] Cisplatin-induced activation of pro-Caspases-9 and -3 in cells engineered to express reduced TG2 amounts is enhanced and this activation can be prevented by reconstituting the activated p65 subunit of NF-κB.[55] Davidson validated the role of 10 EMT-related proteins and OCSCs phenotype in subclassifying OC with respect to chemo-response. It was found that EMT is a vital component of cancer progression and is associated with chemo-resistance.[57] In 70% of cases, resistant-relapsing tumors in the same patient are associated with the differential expression of genes (such as TLR4). ECM remodeling and TGF-β signaling pathways have been implicated in EMT. Apoptosis, metabolism, cell proliferation, angiogenesis, and cell growth are the key components of the EMT process.[58]

## Biomarkers associated with platinum resistance in ovarian cancer

### Function of DNA methylation in enhancing or re-sensitizing platinum resistance

Abnormal DNA methylation is closely associated with human cancer occurrence and development, especially OC.[59]

Studies have revealed an important association between DNA methylation and cisplatin resistance in OC. Cisplatin-resistance has been associated with hypermethylation loss in a group of CpG sites that are localized in the intergenic regions of the genome. They include CYP24A1 that regulates the processing of vitamin D and is an anticancer agent; IL6 that regulates KLF4 which enhances cisplatin-resistance and is a biomarker for poor prognosis in OC patients.[60] Promoter CpG island hypermethylation-associated silencing of the putative DNA/RNA helicase Schlafen-11 (SLFN11) has been implicated in increased platinum-

resistance.[61] Moreover, 9 highly methylated genes (FZD10, FAM83A, MYO18B, MKX, GLI3, TMIG2, TMEM40, NEUROG3, and HOMER3) have been reported to be highly expressed in OC, of which FZD10 was significant. Downregulation of FZD10 promotes cisplatin-induced inhibition of cell proliferation and enhances OC cell apoptosis.[62] In addition, elevated TMEM88 protein expression levels are associated with DNA hypomethylation in platinum-resistant OC cells. TMEM88 knockdown up-regulates cisplatin sensitivity through the Wnt signaling pathway.[63] Hypomethylation of multiple CpG sites at the MSX1 region in OC has been positively correlated with free survival outcomes. By promoting apoptosis, MSX1 methylation and expression can sensitize OC cells to cisplatin.[64]

Furthermore, BRCA1 methylation loss in OC exposed to chemotherapy showed the significance of real-time pre-treatment biopsies to assess methylation as a predictor of therapeutic responses in patients with recurrent OC.[65] Hypomethylation of the SERPINE1 promoter enhances the expression of SERPINE1 and EMT processes in OC cells. These outcomes are consistent with the findings that showed that carboplatin treated cancer cells exhibited high DNA damage levels.[66] Cisplatin induced DNA damage in OC cells can be enhanced by SGI-110 (a DNA hypomethylator). Hypomethylating agents can re-sensitize OC cells to cisplatin.[67] Guadecitabine induced DNA hypomethylation (a hypomethylating agent) affects metabolism, immune responses and reactivates TSGs. This led to positive platinum sensitivity responses in OC.[68]

Among the 12 differently methylated probes identified[69], ZNF671 depletion contributed to more metastatic OC phenotypes. This indicates that ZNF671 is an OC tumor suppressor and its DNA methylation is a potential OC biomarker and recurrence predictor after platinum-based chemotherapy. In addition, chemotherapy induced DNA methylation in blood provides a non-invasive means of monitoring a patients' epigenetic responses to therapy.[70]

These results show that DNA methylation is closely associated with platinum-resistance in OC. Strengthened or re-sensitized platinum-resistance is an indispensable therapeutic biomarker or recurrence predictor for platinum-resistant OC.

## Functions of histone deacetylases in platinum-resistant OC therapy

Histone acetylation is a critical epigenetic regulator that is associated with multiple cancers. Histone deacetylase (HDAC) modulates histone deacetylation structures that are implicated in various cancer-related pathophysiological processes. In addition, it plays crucial roles in chromatin remodelling and gene transcription. HDAC inhibitors (HDACi) are among the most potent targets for platinum-resistant OC therapies due to their key roles in the mediation of cellular functions such as cell proliferation, migration and apoptosis.[71,72]

HDACi is a novel class of anti-cancer compounds. It has a unique complementary mode of action that make it a valuable agent for enhancing the cytotoxicity of chemotherapeutics. Vorinosta is a HDACi drug that if combined with platinum therapy, exhibits synergistic effects when killing cancer cells in recurrent or persistent OC.[73] The HDACi belinostat exhibited significant anti-cancer effects in pre-clinical OC models with elevated PFS and OS after belinostat therapy.[74] Valproic acid is a HDACi that binds Pt (II) centres through the carboxylato functionality and in a monodentate manner that promotes cytotoxicity against cisplatin-resistant OC cells.[75,76] In addition, HDACi induced different pH2AX expression levels and high pH2AX levels in HDACi-treated OC cell lines have been closely associated with increased apoptosis and decreased cell viability.[77] M344 HDACi inhibits BRCA1 expression. Up-regulated cisplatin cytotoxicity and down-regulated BRCA1 protein levels have been documented in cisplatin-resistant OC cell lines.[78] Elevated apoptosis levels have been documented in platinum-resistant OC cells treated with a combination of cisplatin and SAHA (a novel HDACi) when compared to either drugs alone.[79] The p53 mutant platinum-resistant OC cell lines exhibited a synergistic interaction between the HDACi ST2782 and the proteasome inhibitor bortezomib, that was correlated with increased apoptosis.[80]

These results indicate that HDACi exerts critical effects on the biological processes involved in the treatment of platinum resistant OC. In addition, there is a unique interaction between HDACi and platinum chemotherapeutic drugs that have promising clinical efficacies.

## DNA repair functions in the treatment of platinum-resistant OC

### Homologous recombination repair

Platinum resistance in OC is, to an extent, attributed to homologous recombination repair (HRR).[81] Through homologous recombination (HR), most OCs have shown defective DNA repair. These defective repair mechanisms result from the epigenetic and genetic regulation of HR pathway genes. Defective DNA repair through HR regulation is a key OC therapeutic target. Targeting defective HR provides a promising approach for utilizing molecular differences between cancer and normal cells to mediate cancer-specific synthetic lethality.[82] Triapine is a small molecule inhibitor that promotes the clinical efficacy of platinum-resistant OC by disrupting HRR while sensitizing wild-type BRCA OC cells to platinum-based combination treatment.[83] Homologous recombination deficiency (HRD) is closely correlated with platinum sensitivity in OC patients. It is an efficient clinical predictor of sensitivity to the PARP inhibitor and has exhibited the potential to become a common auxiliary diagnostic method in the management of OC patients.[84]

### BRCA mutations

The association between *BRCA1* and *BRCA2* germ-line mutations and platinum-resistance in OC has been documented. *BRCA1/2* gene germline mutations are predictors for platinum-sensitivity. In OC patients, *BRCA* mutations have been reported to lead to platinum-sensitivity.[85] Approximately 14.1% of OC patients with *BRCA*, *BRCA1* or *BRCA2* mutations are diagnosed during the advanced stages of the disease. In addition, *BRCA1/2* mutation-positive patients have longer OS and PFS when compared to *BRCA1/2* mutation-negative patients. This implies that *BRCA*

mutations exert key survival effects in OC patients and should be used as an additional risk prediction factor[86]

Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme with significant roles in DNA repair and transcription. It mediates DNA single-strand break repair through the base excision repair pathway. BRCA1/2 proteins are important in the DNA double-strand break repair process.[87,88] DNA repair pathway deficits have been attributed to *BRCA1/2* mutations that make them susceptible to DNA-damaging therapies such as PARP inhibitors.[89–91] Niraparib is a selective PARP-1 and PARP-2 inhibitor with favorable pharmacokinetics and anti-tumor roles in *BRCA1/2* mutations.[92] In patients with *BRCA* mutant or *BRCA* wild-type OC treated with rucaparib (a PARP inhibitor) as maintenance therapy after platinum-based therapy for patients of platinum-sensitive and recurrent OC, PFS and OS was longer than in patients without BRCA mutant OC.[93] cfDNA from platinum-resistant or -refractory OC has BRCA reversed mutations and is associated with suppressed clinical efficacies during rucaparib therapy.[94]

### BRCAness

The BRCAness phenotype concept is associated with defective HR. This phenotype is correlated with a series of mechanisms such as epigenetic hypermethylation of the BRCA1 promoter, somatic mutation of *BRCA*, *EMSY* amplification and lack of other functional mutations in HR pathway genes.[95] BRCAness is significantly correlated with platinum and PARPi susceptibilities. This indicates that this phenotype is a potential biomarker for predicting platinum and PARPi sensitivity.[96] PI3K pathway activation and BRCA function inactivation can be a therapeutic target in high-grade OC. OC platinum-sensitivity can be regulated by PARP and other molecules that mediate cell cycle regulation.[97] PARPi-olaparib is effective in both platinum-sensitive and platinum-resistant *BRCA* mutation OC patients. BRCA negative 'BRCAness' patients without *BRCA* mutations, but accompanied by dysfunctional HR pathway are more sensitive to anti-tumor drugs with double-strand DNA breaks.[98]

Patients with highly expressed PARP, FANCD2 and P53 (BRCAness Profile) proteins are positively correlated with the risk of early OC recurrence and platinum-resistance.[99] The second-DNA repair pathway and base excision repair inhibition induced by PARPi causes synthetic lethality in OC cell lines. BRCAness and PARPi have derived response rates of over 40% in OC with *BRCA1/2* mutations.[100]

### Nucleotide excision repair

Studies have documented the key genes or factors that are involved in the NER pathway. Mutations in these genes or factors contribute to NER dysfunction and elevate the susceptibility to OC. Several core genes/proteins (ERCC1, XPA, XPB, CSB, ERCC1, XPD) are involved in the biological processes of platinum-resistance or platinum-sensitivity in OC through two main NER sub-pathways (transcription coupled repair (TCR-NER) and global genome repair (GGR-NER)), that include at least five steps: DNA damage recognition, unwinding of DNA helix surrounding the lesion, dual incision of damaged DNA strand, excision and DNA synthesis, as well as DNA polymerization and ligation.[101] In TC-NER, the lesion was observed by lesion-stalling of RNA polymerase 2 (RNAP2) that promotes the recruitment of UVSSA, CSB and CSA proteins. These proteins are crucial downstream NER factors. In GGR-NER, the lesion was observed in the genome by the synergistic effects of UV-DDB and XPC/RAD23B/CETN2 complexes.[102]

NER pathway defects in OC are manifested by suppressed expressions of ERCC1 and DNA repair proteins. OC cell lines with intrinsic cisplatin resistance have shown increased sensitivity to cisplatin after ERCC1 inhibition. OC cell lines develop resistance by avoiding platinum-induced DNA damage after cisplatin-therapy. These findings are consistent with the results of elevated ERCCI expressions.[102,103] ERCC1 is significantly over-expressed in OC tissues after treatment with platinum drugs and is highly correlated with longer OS in OC patients.[104] TIE-1, exerts its inhibitory effects on cisplatin-induced apoptosis and activates the NER pathway through xeroderma pigmentosum complementation group C (XPC). TIE-1 inhibition sensitizes OC cells to DNA damaging anticancer agents such as platinum chemotherapy drugs.[105] These findings suggest that DNA repair (HRR, BRAC mutation, BRCAness and NER) proteins can be used as bio-markers to predict OC response to platinum-based chemotherapy.

## *eccDNA*

The majority of extrachromosomal circular DNAs (eccDNA) are derived from repetitive genomic sequences while the minority derived from unique (non-repetitive) DNA. Extrachromosomal circular DNAs are products of programmed genome rearrangements and are drivers of eukaryotic genome instability.[106–108] The majority of eccDNA are $<$500 bp and are referred to as polydisperse circular DNA (spcDNA).[109] Analysis of the changes in large eccDNAs, DMs, between cancerous and normal cells have shown that EGFR and myc are amplified in cancer cells after a few passages through the formation of eccDNA.[110,111] Moreover, oncogenes were significantly amplified through the eccDNA formation mechanism than the chromosomal amplification mechanism.[110] Kumar et al documented the presence of eccDNA in the nuclei of mammalian tissues and cell lines. They also established that eccDNA derived from uniquely mapped regions of the genome can be detected in plasma and serum.[112] Human-derived cfmicroDNA can be detected in the sera of mice harbouring human ovarian xenograft tumors. This implies that eccDNA from xenografted tumor cells are released into circulation and result in eccDNA being detected in plasma or serum to functions as OC biomarkers. Circular DNA is resistant to digestion by RNAses and exonucleases. This enhances its stability and survival when released from cells into the blood. Tumor-specific features of eccDNA can be used in the identification and prognosis of the disease.[113] When compared to normal tissues, human cancer cells release longer eccDNA into circulation. This eccDNA is also resistant to RNAse and exonuclease digestion. This property is advantageous when using eccDNA in blood for liquid biopsy experiments to identify OC and establish its prognosis.

## Current clinical outcomes corresponding to OC platinum resistance

### Biomaterial applications in platinum resistant OC

Biomaterials improve the half-lives of therapeutic agents.[114] The micellar nanopreparation, containing anti-surviving siRNA as siRNA-S-SPE conjugate and PXL, has been developed for the treatment of OC. It exhibits a system high colloidal stability and is highly efficient co-encapsulation of chemotherapeutic drugs and siRNA to parenteral administration with small particle sizes compatible.[115] He et al were pioneers in the establishment of an efficient vehicle that simultaneously delivers cisplatin and pooled siRNAs to cisplatin-resistant OC cells by utilizing the self-assembled nanoscale coordination polymers (NCPs). This delivery leads to NCP-1/siRNAs mediated effective gene silencing in cisplatin-resistant OC cells to overcome multi-drug resistance and re-sensitizes cells to cisplatin.[116] Biomaterials designed for the delivery of bioactive factors individually, or in combination minimize systemic exposure, reduce general toxicity and facilitate the delivery of a high dose of bioactive drug to the target site. Scientists have developed a gold nanocage covered by smart polymers for controlled drug release with near-infrared light.[117] Once drugs are covered by the gold nanocage, they enter the tumor tissue through the circulatory system and release the drugs in specific areas. Due to the plasticity of biomaterials, their composition, size, surface characteristics, shape, release kinetics and targeting agent can be adjusted. Pore sizes in the tumor vasculature vary from 100 to 780 nm,[118] while the biomaterial size can be modified to take advantage of enhanced permeability and retention effects that are unique features of tumor angiogenesis that can keep particles at the tumor site. Biomaterial carriers efficiently deliver the platinum compound by targeting cell-penetrating peptides, antibodies, aptamers, and other over-expressed receptors.[119] This targeted drug release enhances anti-tumor activities by improving the uptake of chemotherapeutic agents in resistant cells.[120–122] Instead of utilizing transport proteins, biomaterial carriers have the ability to enter cells through a proposed endosomolytic or passive diffusion pathway.[123,124] Current biomaterials increase the efficacy of platinum on OC by enhancing the efficacy and delivery of platinum-based therapy, or the delivery of non-platinum-based therapy.

### The applications of targeted agents in platinum resistant OC

Targeted therapies have provided new prospects in OC therapy. They have exhibited various unprecedented breakthroughs. In recurrent and resistant refractory OC, targeted therapies can prolong the PFS and OS thereby making up for the deficiency of platinum-based or other chemotherapies. In future, personalized medicine could be made possible through biomarker profiles in targeted therapy.

A high expression of MAL (myelin and lymphocyte protein) is involved in epigenetic regulation and has been associated with platinum-resistance and poor OC prognosis. Dysregulation of aberrant MAL expression can, therefore, re-sensitize platinum-based therapies and improve their clinical efficacies.[125] Aberrantly elevated Notch3 in OC cells has been attributed to the expansion of CSCs and increased platinum-resistance through the Notch pathway. $\gamma$-Secretase inhibitor (GSI) is a Notch pathway inhibitor that depletes CSCs and improves platinum sensitivity in OC. Studies have reported that the two main mechanisms for platinum resistance in OC are mutations of the tumor suppressor gene (*TP53*) and drug-induced elevations of intracellular glutathione concentration. APR-246 (PRIMA-1MET) is an agent that reactivates mutant *p53* and induces apoptosis. It decreases the intracellular free concentration of cysteine by binding it in glutathione. When used in combination with platinum, APR-246 enhances curative effects in refractory *p53* mutant OC through chemo-drugs re-sensitization and synergism.[126] Elevated c-MYC protein levels in cisplatin-resistant OC cells have been positively correlated with poor PFS and OS. In addition, siRNA-mediated *c-MYC* knockdown suppresses cell proliferation, viability, cell cycle arrest and promotes cell apoptosis.[127] There is a significant association between platinum-resistant OC cells and glutamine. In platinum-resistant OC cells, elevated glutamine transporter (ASCT2) and glutaminase lead to a higher oxygen consumption rate through the tricarboxylic acid cycle when compared to platinum-sensitive OC cells. The combination of BPTES (a glutaminase inhibitor) with platinum synergistically inhibits the growth of platinum-resistant OC cells. These findings indicate that glutamine metabolism is prospective avenue for the development of novel therapies.[128] Targeted XPO1 inhibition mediates cell apoptosis through both p53-dependent and p53-independent signal pathways that synergistically reverses platinum sensitivity.[129] Mirvetuximab soravtansine (IMGN853) is an antibody—drug conjugate that is made up of a humanized anti-FRa monoclonal antibody bound to the tubulin-disrupting maytansinoid DM4. In platinum-resistant OC, it has a good safety profile with anti-tumor activities.[130] The inhibition of high mobility group box 3 (HMGB3) proteins in cisplatin-resistant cell lines accounts for the transcriptional down-regulation of both ATR and CHK1 kinases that impair the ATR/CHK1/p-CHK1 DNA-damaging signal pathway. Therefore, targeting HMGB3 can resensitize cisplatin-resistant OC to cisplatin-susceptible OC.[131] HIF-1$\alpha$ mediated TGF-$\beta$1/ERK/PHD2 pathway is associated with poor prognoses in patients with platinum-resistant or platinum-refractory OC. Targeting TGF-$\beta$1, ERK, or HIF-1$\alpha$ inhibition is a potential therapeutic option for OC.[132]

In summary, both platinum-resistant and platinum-sensitive relapses could benefit from targeted agents.

### Applications of tyrosine kinase inhibitors in platinum resistant OC

Tyrosine-kinases are a group of enzymes that play key roles in signal transduction. They are relay points in numerous biological processes.[133] They activate the PI3K/AKT/mTOR pathway, the Ras/Raf MAPK pathway, the Raf/MEK/Erk

pathway and the PKC pathway. These pathways regulate cell proliferation, endothelial cell migration, apoptosis as well as increase vascular permeabilities that result in blood vessel formation. Inhibition of these pathways is essential in overcoming platinum-resistance.

Angiopoietin-2 (Ang-2) exhibits better PFS after anti-angiogenic treatment with sunitinib (a tyrosine kinase inhibitor (TKI)).[134] Sunitinib is an orally administered TKI that targets PDGF receptors, VEGF receptors, Flt3 and c-Kit. Sunitinib targets both tumor cells, endothelial cells and enhances inhibitory and regulatory effects on cell growth and angiogenesis. This implies that TKI treatment is efficacious for platinum-resistant ROC.[135,136] Vandetanib is a novel inhibitor that binds VEGFR-2 tyrosine kinase. It inhibits EGFR tyrosine kinase and RET kinase, suppresses two key pathways by targeting tumor growth indirectly through the inhibition of VEGF-dependent tumor angiogenesis and VEGF-dependent endothelial cell survival, as well as through the direct inhibition of EGFR-dependent cell proliferation and survival.[137] A combination of apatinib (an oral TKI that selectively inhibits VEGFR-2) and oral etoposide has been shown to be effective with minimal toxicities in platinum-resistant or platinum-refractory OC patients.[138,139] When the tyrosine kinase AXL receptor is activated by GAS6, it promotes OC proliferation and inhibits the apoptosis of OC cells through the PI3K/AKT and Ras/ERK pathways. BGB324 mediated inhibition of AXL expression re-sensitizes OC cells to carboplatin.[140] The over-expression of focal adhesion kinase (FAK) (a non-receptor tyrosine kinase) has been positively correlated with advanced tumor stages and shorter OS in OC patients. A combination of FAK inhibitors and platinum-based chemotherapies is a potential therapeutic option for platinum resistant OC.[141]

In summary, a combination of TKI inhibitors and platinum enhances positive clinical outcomes in platinum resistant OC cases. This shows the value of TKI inhibitors as therapeutic options.

## Applications of PARP inhibitors in platinum resistant OC

There are 17 members of poly (ADP-ribose) polymerase (PARP) superfamily of nuclear enzymes that are involved in a variety of biological functions. The most important members are PARP1, PARP2 and PARP3. They are involved in DNA damage, detection and repair. They are activated by DNA damage and are critical mediators in the repair of single-strand breaks. PARP1 and PARP2 inhibition enhances double-strand breaks and collapsed DNA replication forks that are repaired through the BRCA-mediated HRR pathway (Fig. 1). Defects in the HRR pathway, for instance, an adverse *BRCA1/2* mutation, can lead to a homologous recombination deficiency (HRD) that selectively sensitizes tumors to PARP inhibition through synthetic lethality.[90,142] The combination of platinum-based chemotherapies and PARP inhibitors is associated with good prognosis in BRCA-mutated OC patients.[143]

OC patients with defective *BRCA* genes are especially sensitive to treatment with PARP inhibitors. Reversed BRCA-mutations have been documented in cfDNA obtained from platinum-resistant or platinum-refractory OC. These reverse mutations were correlated with reduced clinical efficacies from rucaparib therapy.[94] Rucaparib is a potent PARP1/2/3 inhibitor in BRCA-mutated OC that exhibits its anti-cancer roles through synthetic lethality. It has a favorable toxicity profile.[144,145] Olaparib is an effective oral PARP inhibitor with

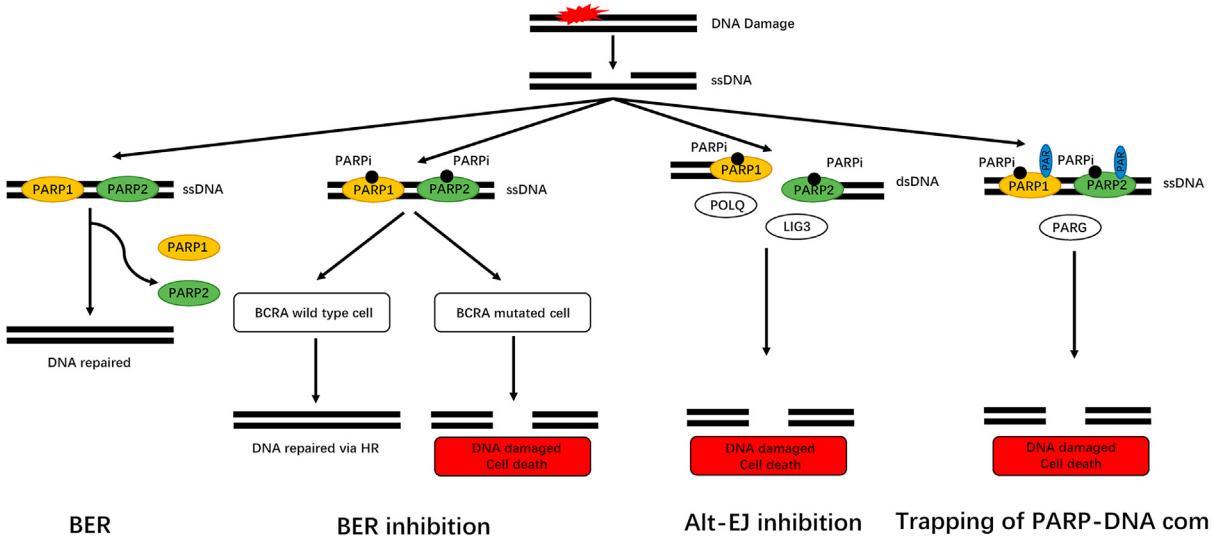


**Figure 1** Single stranded DNA breaks (ssDNA) can be repaired by PARP pathway. PARP inhibitor (PARPi) treatment restrain PARP repairing ssDNA and lead to double-stranded DNA (dsDNA) breaks which then undergo homologous recombination (HR). When coming to DNA repair via HR pathway, *BRCA* mutated cells are unable to undergo and lead to cell death. Both PARP inhibition and *BRCA* mutation are needed for cell death. In case of defects of both HR and NHEJ, inhibition of PARP restrains activation of alternative NHEJ (Alt-EJ) which contributes to dsDNA repairment when NHEJ components are missing. With the formation of PARP-DNA complexes PARP trapping may occur restraining DNA replication and transcription. But PARP inhibitors' trapping ability varies significantly.

good safety profiles. It also has a relatively high response rate in OCs associated with *BRCA* mutations. Clinical responses to PARP inhibition have not been associated with platinum sensitivity. Furthermore, platinum-resistant and platinum-refractory patients exhibit good clinical outcomes from olaparib administration (41.7% and 15.4% response rate respectively).[146,147] A combination of niraparib with pembrolizumab (a PD-1 inhibitor) showed promising anti-tumor activities in patients with platinum-resistant and platinum-refractory recurrent OC that has limited therapies, regardless of its platinum or biomarker status.[148]

## Conclusions

Chemotherapy is a common therapeutic option for OC. However, this therapeutic option is inhibited by platinum-based resistance. Platinum-resistance involves multiple molecular mechanisms. Studies evaluating these mechanisms are limited to small panels of OC cell lines. Due to differences in OC cells of distinct subtypes or high degrees of molecular heterogeneity, platinum-resistance studies should be performed using the full spectrum of well-defined primary cell lines, tissue samples and *in vivo* models.[149] Platinum resistance biomarkers should be used to evaluate the efficacy of approved cancer therapeutics with established safety and toxicity profiles. Studies have established the benefits of using biomaterials to enhance drug delivery, efficacy and to overcome drug resistance. This study provides an avenue for overcoming platinum-resistance and new therapeutic approaches for OC.

## Conflict of interests

The authors declare that they have no conflict of interest.

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