

Molecular mechanisms of platinum-based chemotherapy resistance in ovarian cancer (Review)

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Abstract. Cisplatin is one of the most effective chemotherapy drugs for ovarian cancer, but resistance is common. The initial response to platinum-based chemotherapy is as high as 80%, but in most advanced patients, final relapse and death are caused by acquired drug resistance. The development of resistance to therapy in ovarian cancer is a significant hindrance to therapeutic efficacy. The resistance of ovarian cancer cells to chemotherapeutic mechanisms is rather complex and includes multidrug resistance, DNA damage repair, cell metabolism, oxidative stress, cell cycle regulation, cancer stem cells, immunity, apoptotic pathways, autophagy and abnormal signaling pathways. The present review provided an update of recent developments in our understanding of the mechanisms of ovarian cancer platinum-based chemotherapy resistance, discussed current and emerging approaches for targeting these patients and presented challenges associated with these approaches, with a focus on development and overcoming resistance.

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1. Introduction

Ovarian cancer is one of the most common malignant tumors of the reproductive organs and has the highest mortality rate among all gynecological malignancies. At diagnosis, ~70% of patients present with advanced disease and most are resistant to platinum-based chemotherapy, resulting in a low five-year survival rate (1,2). Ovarian cancer can be subdivided into two main histological subtypes: Epithelial ovarian cancers (EOCs), which account for ~90% of ovarian cancers, and non-EOCs, which account for ~10% of ovarian cancers (3). Epithelial cancers include serous [high-grade serous carcinoma (HGSC) and low-grade serous carcinoma (LGSC)], endometrioid (high-grade endometrioid carcinoma and low-grade endometrioid carcinoma), clear-cell and mucinous carcinomas (2,4). LGSCs usually contain KRAS and BRAF mutations (5,6), whereas most HGSCs have TP53 mutations and exhibit severe aneuploidy genome aberrations. Clear cell carcinoma is characterized by mutations in the ARID1A, PIK3CA, PTEN and KRAS genes, while endometrioid carcinoma, similar to its uterine counterpart, has mutations in ARID1A, CTNNB1, and PTEN, as well as microsatellite instability (7,8).

Approximately 80% of patients with ovarian cancer are treated with cytoreductive surgery followed by adjuvant chemotherapy with carboplatin and paclitaxel or cisplatin and paclitaxel (2,9). However, ~70% of patients with this treatment regimen will relapse (10) and the recurring cancer is often resistant to standard platinum-based chemotherapy. In patients with advanced cancer, mortality is usually due to acquisition of drug resistance. Cisplatin is one of the most effective chemotherapy drugs for ovarian cancer, but resistance to cisplatin is common. Patient recurrence more than 6 months after front-line platinum-based therapy is considered platinum-sensitive, whereas platinum-resistant recurrence occurs after less than 6 months (2,11,12). During the six months after the completion of major platinum-based chemotherapy, disease progression is usually closely related to platinum resistance. Due to its significant impact on patient survival time and quality, improving the response to platinum is an important challenge. At present, the standard treatment for platinum-resistant or refractory ovarian cancer is pegylated liposomal adriamycin, weekly paclitaxel and topotecan, but the efficacy of this regimen is limited (13).

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To provide a thorough understanding of the mechanism of drug resistance, in the present review, the important molecular mechanisms involved in the response of ovarian cancer patients to platinum-based chemotherapy, as well as methods to circumvent these mechanisms that have been studied extensively by clinical and laboratory researchers are explored (Fig. 1).

2. Literature review methods

A systematic literature search was conducted via electronic search engine PubMed for eligible studies published until December 31, 2021. The keywords for searches were as follows: 'Ovarian cancer', 'chemotherapy resistance', 'chemo-resistance'. Furthermore, the references in retrieved articles were also manually reviewed for potentially relevant studies.

3. Molecular mechanisms of platinum-based chemotherapy resistance in ovarian cancer

Multidrug resistance (MDR). Since the ovary is deep in the pelvic cavity and small in size, it is difficult to detect early ovarian cancer due to a lack of typical symptoms. Upon surgery, the tumor is confined to the ovary in less than 30% of patients with ovarian cancer (14); in most patients, the tumor has spread to the pelvic and abdominal organs. Although progress has been made in surgical techniques and chemotherapy drugs in recent years, the mortality rate of ovarian cancer has not decreased significantly. Chemotherapy MDR is the main cause of treatment failure (15). MDR is a drug-resistant phenotype in which cancer cells are simultaneously resistant to multiple drugs with different molecular targets and without obvious structural similarities (16). Overcoming MDR is a top priority in clinical and research oncology but remains elusive. In the present study, the latest literature on the main mechanisms of MDR were summarized and several new MDR reversal strategies were evaluated, including more effective and specific P-glycoprotein (P-gp) inhibitors.

Membrane-bound adenosine triphosphate (ATP)-dependent active drug efflux pumps can significantly decrease the intracellular concentration of the drug and thus the efficacy of treatment. P-gp uses the energy of ATP hydrolysis to transport various structural and functional drugs out of the cell. P-gp and multidrug-resistance-associated protein (MRP) are two main membrane proteins known to cause MDR in cancer. Inhibiting these proteins is a strategy to sensitize cancer cells to chemotherapy (17). Overexpression of P-gp can also lead to the development of MDR in human tumors (including ovarian cancer). Therefore, many years of extensive research have focused on overcoming P-gp-based MDR. To date, three generations of P-gp modulators have been developed. The second-generation P-gp modulator, valspodar, has exhibited the capacity to modulate ovarian cancer resistance in phase I, II and III clinical trials (18).

DNA damage repair (DDR). As MDR is one of the most studied mechanisms of ovarian cancer drug resistance in the early stages of the research process, DDR is one of the most important mechanisms of ovarian cancer drug resistance. At present, the standard treatment for advanced ovarian cancer is surgical

cytoreduction, followed by platinum and taxane-based chemotherapy. Current research focuses on new agents, particularly those that target the DDR pathway (19,20). A comprehensive understanding of the process of DDR in ovarian cancer and its working principle may promote future research on treatments and drug resistance.

Studies have revealed that more than 50% of HGSCs have homologous recombination repair (HR) pathway defects (21-23), which are mainly related to genetic and epigenetic changes in HR pathway genes. The tumor suppressors BRCA1 and BRCA2, which encode proteins involved in DDR via homologous recombination, have been associated with an increased risk of ovarian cancer (24). Mutations in BRCA1/2 are associated with high sensitivity to DNA-damaging agents, including poly-(ADP-ribose) polymerase (PARP) inhibitors and platinum (25-27). Patients with BRCA mutations have an improved overall response to platinum therapy, which is associated with a longer survival rate for ovarian cancer (28,29). Compared with patients who do not carry the mutation, patients with the mutation are less likely to have disease progression within 6 months after the end of the main treatment (28). Therefore, patients with BRCA1/2 mutations are more likely to have longer progression-free survival (PFS) than patients without mutations.

Concurrently, the study found that upon the first relapse of platinum-sensitive or platinum-resistant patients, the response rates for second-line platinum-based or nonplatinum-based chemotherapy were higher in patients carrying mutations than in those who did not (28). In BRCA-mutant cancers, BRCA reversion mutations that restore protein function are the key resistance mechanism of platinum-based chemotherapy (30).

Reversion mutations that may be caused by DNA-damaging chemotherapy or genome instability are base substitutions or insertions/deletions. Such mutations are usually close to the main protein truncation mutation and restore the open reading frame (ORF) of the gene to allow the production of functional protein, transforming tumor cells from HR defective to proficient. A total of 18% of platinum-refractory cancers and 13% of platinum-resistant cancers have BRCA mutations in circulating cell-free DNA (cfDNA) before treatment, compared with 2% of platinum-sensitive cancers (31). Before treatment, patients with no BRCA reversion mutations in cfDNA had significantly longer PFS after treatment with rucaparib compared with patients with reversion mutations (32).

In cancer, the restoration of HR function promotes drug resistance by repairing DNA damage induced by PARP inhibitors and/or platinum-based chemotherapy, destroying the basis of synthetic lethality and ultimately promoting cell survival (33). Reversion mutations in multiple HR pathway genes, including BRCA1, BRCA2, RAD51C, RAD51D (34) and PALB2, cause acquired resistance to platinum-based chemotherapies and PARP inhibitors (32).

Limited DNA end resection is the key to impaired HR in BRCA1-mutant cells. A loss-of-function CRISPR screen identified dynein light chain 1 protein (DYNLL1) as a factor responsible for platinum resistance in BRCA-defective patients with HGSC by facilitating DNA end resection (35). After platinum-based chemotherapy for BRCA1 mutant ovarian cancer, low expression of DYNLL1 was significantly associated with poor PFS.

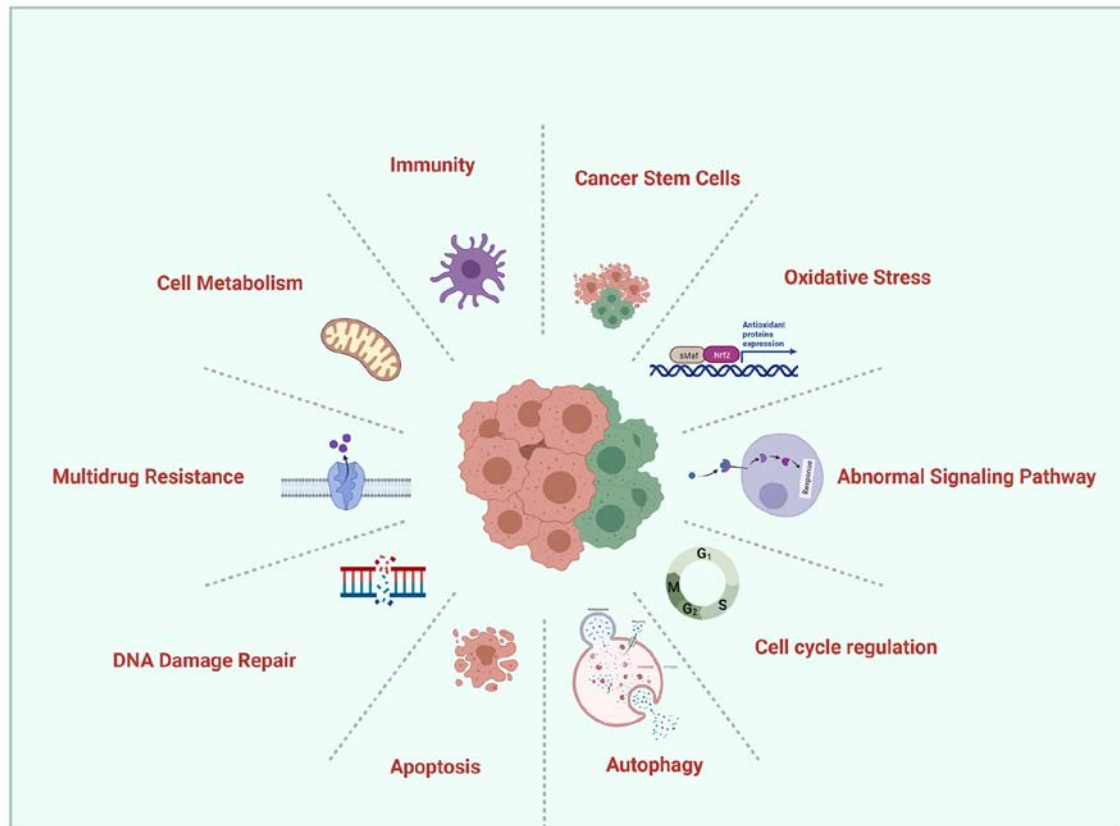


Figure 1. Schematic overview of the mechanisms of platinum-based chemotherapy resistance in ovarian cancer.

Strengthening DNA repair pathways is one of the ways that cancer cells resist the DNA-damaging effects of platinum (Fig. 2). Inhibiting these DNA repair pathways may restore the sensitivity of cancer cells to platinum. This is precisely the objective of several drugs under development. PARP inhibitors disrupt the mechanism by which damaged parts of DNA are removed and the drug trabectedin binds directly to and damages DNA (36). TOP1 initiates the DNA relaxation by cleaving one DNA strand. This in turn generates TOP1 cleavage complexes (TOP1ccs). The selective trapping of TOP1ccs by topotecan stabilizes TOP1ccs which covalently attach to the 3'-end of the breaks. These stalled TOP1ccs lead to lethal DNA double-strand breaks when they produce collisions with DNA replication (37). The drug topotecan blocks the action of the enzyme TOP1, thereby helping to cause DNA damage, improving the sensitivity of chemotherapy and is already licensed to treat recurrent ovarian cancer (38). As apical kinases, ATM (recruited to double-strand breaks) and ATR (recruited to single-stranded DNA) regulate the DNA damage response, and ATR inhibitors may restore platinum sensitivity for the treatment of patients with recurrent BRCA1/2 mutant ovarian cancer (39,40).

Cell cycle regulation. More than 50% of HGSCs are defective in the HR pathway (21). For HGSCs with intact HR, the expansion of cyclin E1 (CCNE1), which encodes the cell cycle regulator cyclin E1, is the best-characterized driving factor. Amplification or gain of CCNE1 is observed in 20% of HGSC tumors and is related to main treatment resistance and decreased overall survival (OS) (41). Patients with CCNE1

amplification are unlikely to benefit from PARP inhibitors and are unlikely to respond to platinum drugs due to the mutual exclusivity of CCNE1 amplification and BRCA1/2 mutations (42,43).

Cyclin-dependent kinase (CDKs) are proteins required for appropriate progression of the cell cycle and also play a central role in regulating DDR (44). CCNE1 is essential for CDK2 activation and its overexpression can lead to premature entry into the S phase, abrogating DNA repair during the G1 phase and leading to increased levels of replication stress. Checkpoint kinase 1 and 2 (CHK1 and CHK2) are responsible for regulating DNA replication and DNA damage response (45). Thus, CCNE1 overexpression may increase sensitivity to CHK1 inhibition (46). Promising targeted strategies using WEE1 kinase inhibitors, CHK1 inhibitors and CDK2 inhibitors are under review in clinical trials examining biomarkers (47). The combination of the CDK2 inhibitor dinaciclib and the AKT inhibitor MK2206 exhibited a selective synergistic effect in a CCNE1-expanded cell line in a xenograft model (42). Approximately 60% of patients with platinum-resistant or refractory diseases receive clinical benefit from the CHK1 and CHK2 inhibitor, prexasertib (LY2606368) (48). Recently, a study reported that the CCNE1-overexpressing HGSC model is markedly sensitive to combinations of cell cycle checkpoint kinase and immune checkpoint inhibitors (29).

CCNE1 and RB1 are cyclins related to cell cycle transition in the G1-S phase. Tumors with increased CCNE1 copy number are more resistant to platinum therapy, while RB1 loss is associated with high sensitivity to platinum therapy (49,50).

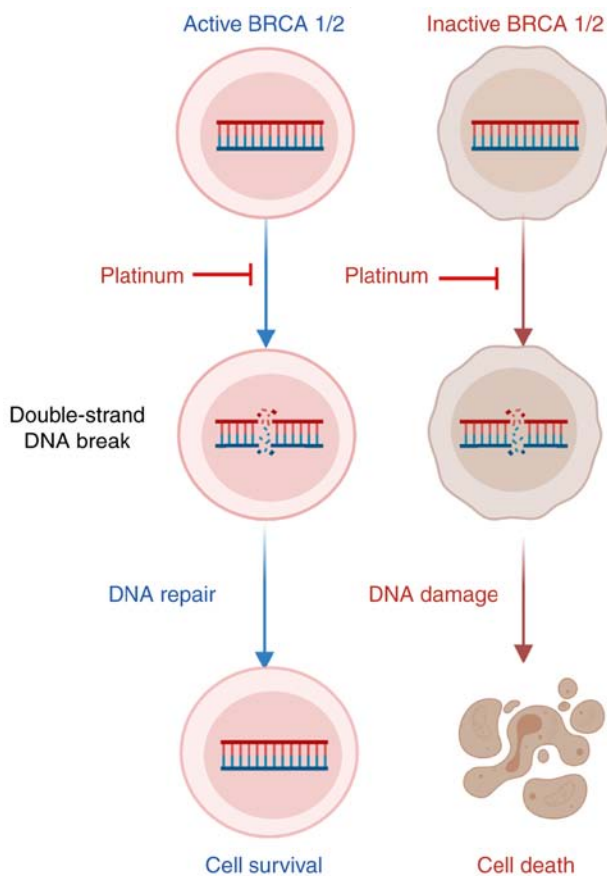


Figure 2. BRCA1/2 activity in ovarian cancer is associated with the response to platinum chemotherapy. BRCA1/2 functions in activating the repair of double-strand breaks and initiating homologous recombination, linking the maintenance of genomic integrity to tumor suppression. BRCA1/2 active cells can repair the platinum drug-caused double-strand DNA damage by homologous recombination, while BRCA1/2 inactive cells cannot, thus tumor cells with BRCA gene mutation are more sensitive to platinum drugs.

Studies have shown that loss of RB1 protein expression is associated with longer OS and PFS (47,50,51).

ATM/ATR kinases play a central role in coordinating the DDR. Blocking the activity of key CDKs can signal DNA damage and cause cell cycle arrest. The combination of ATR inhibitor and PARP inhibitor (PARPi) has a synergistic effect in reducing the survival rate and colony formation in BRCA1/2 mutant PARPi/platinum-resistant cell models that are resistant to PARPi and platinum or exhibit *de novo* resistance (46).

CDK6 can bind to and phosphorylate FOXO3, thereby inducing the expression of ATR. CDK6 regulates ATR through FOXO3 to control platinum-induced cell death (52). In a model of advanced platinum-resistant tumors, silencing or pharmacological inhibition of CDK6 increased the sensitivity of EOC cells to platinum without affecting RB1 phosphorylation but increased platinum-induced DNA damage by increasing apoptosis (52). Notably, compared with other models, CDK6 is less involved in regulating G1-S transition and proliferation in EOC. When platinum and CDK6 inhibitor PD0332991 are combined, platinum induces significant cell cycle arrest in the S phase (52), while CDK6 inhibition induces more apoptosis (Fig. 3).

Cell metabolism. Metabolic reprogramming is emerging as a proposed molecular mechanism of cisplatin resistance (53).

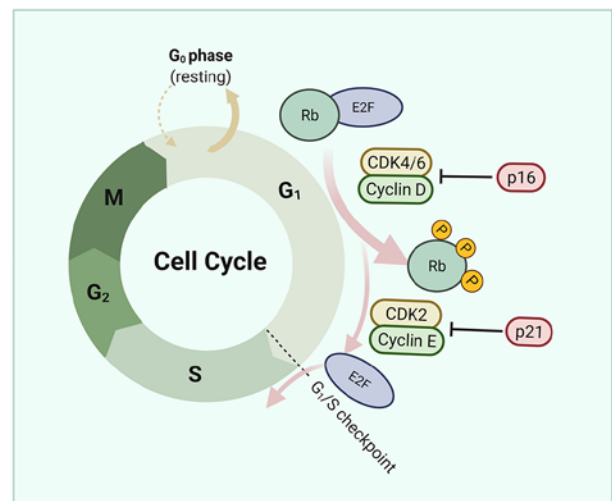


Figure 3. Regulation of the cell cycle by platinum treatment in ovarian cancer. CCNE1 and RB are cyclins associated to cell cycle transition in the G1-S phase. CCNE1 is essential for CDK2 activation and its overexpression can lead to premature entry into the S phase, abrogating DNA repair during the G1 phase and leading to increased levels of replication stress. Inhibition of CDK6 increases the sensitivity of epithelial ovarian cancers cells to platinum by increasing apoptosis.

Accumulating evidence has suggested that the metabolism of tumor tissues differs from that of matched normal tissues and metabolic reprogramming is likely to be an important cause of treatment resistance (54,55). Metabolic reprogramming involves a series of metabolic alterations involving all major pathways from glucose metabolism to glutamine and lipids as well as mitochondrial (mt) alterations (56). The pentose phosphate pathway (PPP) is an important component of glucose metabolism that uses glucose-6-phosphate as the primary substrate (57). The products of PPP biosynthesis are ribonucleotides and nicotinamide adenine dinucleotide phosphate; the latter is essential for reductive biosynthesis (57).

Overexpression and higher enzyme activity of glucose-6-phosphate dehydrogenase (G6PD) can increase cisplatin resistance. G6PD and transketolase have been identified as possible targets to overcome cisplatin resistance (53). The enzymes that regulate glycolysis flow are transcriptionally regulated by three major transcription factors: p53, hypoxia-inducible factor-1 (HIF-1) and Myc (58). HIF-1, a major hypoxia-induced transcription factor, promotes a dissociation of glycolysis and the tricarboxylic acid cycle (59). HIF-1 allows adaptation to hypoxia by increasing glucose transport, glycolysis and lactate production. In addition to stimulating glycolysis, HIF-1 inhibits the function of the mt respiratory chain in a variety of ways. Inhibition of HIF-1 may redirect aerobic glycolysis toward mt oxidative phosphorylation, which can sensitize cells to cisplatin through overproduction of reactive oxygen species (ROS), leading to apoptosis; the cisplatin response in ovarian cancer cells can be improved by targeting HIF-1-regulated cancer metabolism (60). Studies have demonstrated that metformin can modulate cell growth and metabolism by inhibiting mt activity, AMP/ATP balance disturbance and AMPK activation and can partially reverse platinum resistance in the PDX model (61-63). This provides a new direction for reducing resistance.

Oxidative stress. Cell metabolism induces the production of ROS; a variety of chemotherapeutic drugs, including cisplatin, also induce the production of large amounts of ROS in tumor cells. The effectiveness of chemotherapy depends on the induction of oxidative stress. Increased ROS can cause oxidative DNA damage, leading to genomic instability and promoting cellular apoptosis, senescence or autophagy. To withstand oxidative stress, cells activate the transcription factor Nrf2, the major regulator of antioxidant responsive element-mediated genes (64).

Activation of the Nrf2 pathway is involved in the development of ovarian cancer and platinum resistance (65). Thus, targeting redox regulation is a promising strategy to overcome drug resistance (66). In line with this, Nrf2 inhibition is expected to increase chemotherapy sensitivity. Combining Nrf2 inhibition with chemotherapy enhances cytotoxic effects but produces side effects such as chemotherapy-induced myelosuppression (67). Additionally, Nrf2 inhibition results in enhanced sensitivity toward ROS-induced DNA damage, whereas PARP inhibitors inhibit this DNA repair pathway (68). Furthermore, PARP inhibitors increase not only DNA damage but also ROS (69). Studies have revealed that combined treatment with Nrf2 inhibitors and PARP inhibitors improves therapeutic efficacy, particularly in BRCA1 mutant cancer cells and no severe side effects are expected (68,69).

Mitochondria are important sites of redox activity. Notably, compared with cisplatin-sensitive HGSC cells, cisplatin-resistant HGSC cells have a lower mt content and lower levels of mtROS, which induce cell death (70). The principle of anticancer treatment with chemotherapeutic drugs is usually to disrupt cell integrity by destroying nuclear DNA (nDNA) to induce cell death. In addition, mtDNA, similar to nDNA, is greatly affected by cisplatin. Therefore, mtDNA damage is evident in cisplatin-treated cells (71,72). Furthermore, the ATP synthase inhibitor oligomycin A can block mt function and prevent the induction of mtROS during cisplatin treatment, thereby reducing cisplatin-induced apoptosis (70).

In fact, several oxidative stress-related genes, such as ARHGEF6, TXNRD1, GLA, GSTZ1 (73), thioredoxin (12), E26 oncogene homolog 1 (74,75) and ALDH (76), have been linked to chemoresistance in ovarian cancer. Increasing ROS through pharmacological methods may render ovarian cancer cells sensitive to cisplatin and overcome drug resistance. An ALDH inhibitor named CM37, has been revealed to increase intracellular ROS levels in ovarian cancer cells, leading to DNA damage and inhibition of cell survival and proliferation (76).

Cancer stem cells (CSCs). The current oncology hypothesis proposes that only a small percentage of cancer cells can spread into the tumor. These cells are called tumor promoter cells or CSCs and have pluripotent properties similar to those of normal stem cells (77,78). Previous studies have revealed that CSCs are a unique cell population that causes tumor recurrence and metastasis, leading to the formation of new tumors (79,80). CSCs also exist in ovarian tumors and are resistant to chemotherapy (81,82). Therefore, the development of new therapies for CSCs aims to improve the lives of patients with cancer, particularly those with metastatic disease, and to avoid the recurrence of chemotherapy-resistant tumors.

One understudied mechanism of chemoresistance is the persistence of quiescent cancer cells that are not eliminated by

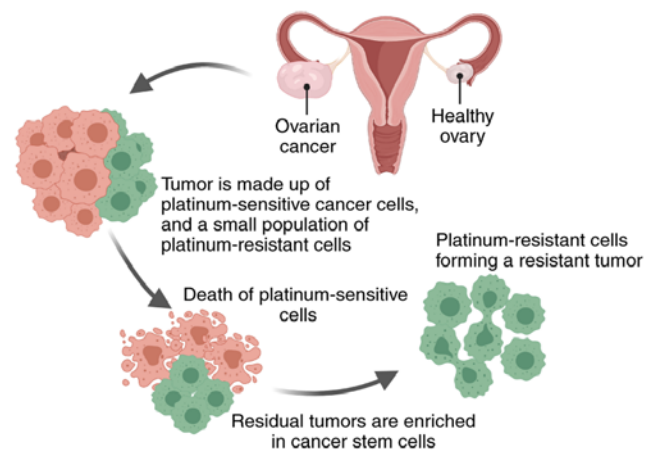


Figure 4. CSCs are more resistant to chemotherapy. The persistence of quiescent cancer cells that are hard to be eliminated by chemotherapy and these residual tumors are enriched in CSCs, which are more resistant to chemotherapy. CSCs are a unique cell population that causes tumor recurrence and metastasis, leading to the formation of new tumors. CSCs, cancer stem cells.

chemotherapy. According to previous studies, these residual tumors are enriched in CSCs (83), which are more resistant to chemotherapy (Fig. 4) (74,84,85). There are already several surface markers for ovarian CSC identification, including MyoD, CD44, CD117 (86), CD133 (87), ALDH (76) and nuclear factor of activated T cells, cytoplasmic 4 (NFATC4) (88,89).

CD44 is a cell-surface glycoprotein of the hyaluronate receptor that plays a role in tumor stemness, recurrence and drug resistance in ovarian cancer. Compared with cells cultured under differentiation conditions, isolated CD44⁺/CD117⁺ ovarian CSCs could completely regenerate the original tumor phenotype in mice and were more resistant to cisplatin and paclitaxel (90). The presence of ALDH⁺CD133⁺ CSC-like cells in primary ovarian tumors is associated with shorter disease-free survival and OS. In addition, compared with parental cells, these cells exhibit enhanced chemoresistance to the human primary ovarian tumor phenotype (89,91). The aforementioned studies revealed that CSCs are closely related to the chemoresistance of ovarian cancer. Metformin treatment significantly reduces the stemness of cancer by reducing ALDH⁺CD133⁺ CSCs in patients with ovarian cancer (92). Phase III clinical trials have shown that metformin is a favorable adjunct in the treatment of EOC.

Studies have demonstrated that activating the PI3K/Akt/mTOR signaling pathway can enhance the expression of epithelial-mesenchymal transition (EMT) and CSC markers in chemoresistant EOC cells. Accordingly, the PI3K inhibitor BEZ235 renders EOC cells sensitive to cisplatin by inhibiting the expression of EMT and CSC markers (91). NFATC4 is enriched in ovarian CSC-like cells, which leads to chemotherapy resistance by downregulating MYC at an early stage, helping cells enter a quiescent state (88). The aforementioned studies revealed that NFATC4 is a significant therapeutic target for ovarian cancer that is worthy of in-depth study.

Immunity. There is increasing evidence that the immune response may affect the prognosis of patients with ovarian cancer. For patients with recurrent ovarian cancer, the immune

system can be activated to identify and attack cancer cells to prevent recurrence. The tumor microenvironment is a potential factor for recurrence and chemotherapy resistance (93). Among them, the presence of tumor-infiltrating lymphocytes, particularly CD8⁺ tumor-infiltrating lymphocytes, often indicates an improved prognosis (94). In a study of patients receiving platinum-based chemotherapy, the 5-year OS rate of patients whose tumors contained significant T-cell infiltration was 38%, but the 5-year OS rate of patients whose tumors contained very few T cells was only 4.5% (95). CXCL9, CCL21 and CCL22 were more highly expressed in tumors with significant T-cell infiltrates than in tumors with few T cells (96,97).

Several studies have shown that high tumor-associated macrophage (TAM) density is closely related to poor prognosis and resistance to treatment in patients with ovarian cancer (98,99). The mechanism of drug resistance is as follows: i) Macrophages promote tumor polarization; ii) macrophages affect the pro-survival signaling pathways; and iii) macrophages upregulate MDR genes in cancer cells (10). In various ovarian cancer cell lines treated with cisplatin or carboplatin, macrophages are induced to differentiate into M2 macrophages through increased IL-10 production and enhanced activation of the STAT3 signaling factor (100,101). The understanding of the involvement of TAMs in tumor progression and chemoresistance provided by these studies has revealed new opportunities for the development of ovarian cancer therapies (10,99).

In addition, the immune checkpoint protein programmed death ligand (PD-L1) is often expressed by ovarian tumor cells, and PD-1 is a receptor often expressed by tumor-infiltrating lymphocytes. Studies have found that the interaction between PD-1 and PD-L1 is a key therapeutic target for reactivating the immune response against a variety of cancers. Therefore, blocking the PD-1/PD-L1 interaction with an antibody against the PD-L1 molecule is a new therapeutic opportunity for patients with advanced platinum-resistant ovarian cancer (102-104). The human immunoglobulin G1 monoclonal antibody avelumab has a wild-type Fc region that blocks PD-L1. Avelumab has shown antitumor activity in patients with relapsed or refractory ovarian cancer who have progressed after platinum-based chemotherapy (13).

Apoptotic pathways. The effectiveness of chemotherapy strongly depends on the ability of ovarian cancer cells to undergo drug-induced apoptosis (Fig. 5) (105-107). Platinum-based chemotherapeutics, such as carboplatin and cisplatin, are alkylating agents that bind to DNA to produce intra- and interstrand crosslinks, thereby inducing DNA damage that culminates in mitochondria-mediated apoptosis (108,109). The mt apoptotic pathway is controlled by proapoptotic (e.g., PUMA, Bim, Bid, Bad, Bik, Bax, Noxa and Bmf) and antiapoptotic (e.g., Bcl-2 Bcl-w, Mcl-1, Bfl-1 and Bcl-xL) proteins of the Bcl-2 family (110). Inhibition of apoptosis-related proteins in ovarian cancer cells increases cisplatin resistance and PI3K/mTOR inhibits the induction of pro-apoptotic and anti-apoptotic Bcl-2 family proteins, which are associated with treatment fragility in ovarian cancer cells (111).

Approximately 40-80% of patients with EOC have TP53 mutations (112,113). In addition, a few cases of HGSCs lacking

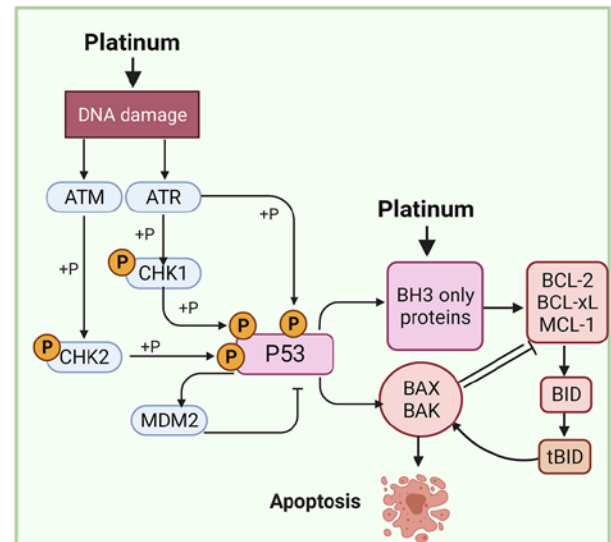


Figure 5. Effectiveness of chemotherapy strongly depends on the ability of ovarian cancer cells to undergo drug-induced apoptosis. Inactivation of p53 increase resistance to platinum-based chemotherapy by reducing the sensitivity of cells to activate apoptotic responses. The balance of proapoptotic and antiapoptotic proteins of the Bcl-2 family is a key factor to promote the sensitivity of platinum-based chemotherapy.

TP53 mutations have been reported with amplification of MDM2, which is a known alternative mechanism for inactivation of p53 (114). Mutations in the p53 gene can increase resistance to various DNA-damaging agents (including cisplatin) by reducing the sensitivity of cells to activate apoptotic responses (115). The introduction of wild-type p53 protein into A2780/CP cisplatin-resistant cells by adenovirus gene transfer renders these cells significantly sensitive to platinum-based cytotoxicity and further supports the participation of p53 in cisplatin resistance (112).

ARID1A mutation is a known genetic driver of ovarian cancer. Notably, ARID1A mutations are found in more than 50% of ovarian clear cell carcinomas and 30% of ovarian endometrioid carcinomas (116,117). ARID1A and TP53 mutations are typically mutually exclusive in ovarian cancer (118). ARID1A mutations lead to upregulation of HDAC6, which in turn inactivates the apoptosis-promoting function of p53, indicating that drug inhibition of HDAC6 is an effective treatment strategy for cancers with ARID1A mutations (119).

Autophagy. On the one hand, autophagy protects cells from genotoxic stress to prevent tumorigenesis and carcinogenic transformation. On the other hand, autophagy can be used as a survival strategy for cancer cells to overcome the stress caused by chemotherapy, radiotherapy or other treatments (120,121). Previous studies have demonstrated that autophagy in ovarian cancer cells can be induced by cisplatin through ubiquitin-binding protein p62 (SQSTM1) or HMGB1 (122,123). Autophagic flux in cisplatin-resistant ovarian cancer cells is caused by cisplatin. At present, the cytoprotective function of autophagy in cancer cells is considered a potential chemotherapy resistance mechanism.

Most studies have suggested that targeting autophagy-related molecules may increase the chemosensitivity of cancer cells (124,125). Knockdown of ATG7 and ATG14 can inhibit

basic autophagy in ovarian cancer cells and promote cell death induced by cisplatin (126). As a negative regulator of autophagy, mTOR inhibitors are used in combination with cisplatin to make cancer cells sensitive to chemotherapy. However, certain studies have suggested that chemosensitivity can be promoted by autophagy (127,128). The enhanced sensitivity of autophagy to cisplatin depends on different mechanisms, and dormant autophagic cancer cells are still susceptible to cisplatin-based chemotherapy.

Abnormal signaling pathways. A total of 10% of serous ovarian cancer is LGSC, which is characterized by early onset (median age 46 years), slow growth and poor response to chemotherapy (4,129). BRAF and KRAS hotspot mutations are found in ~2/3 of patients with LGSC. Furthermore, almost all patients with LGSC harbor a mutation predicted to induce ERK activation (5). Notably, RAS and PI3K participate in intensive cross-talk to regulate each other and coregulate downstream functions (130). Therefore, blocking only one pathway will induce compensatory signaling in the other pathway, ultimately leading to treatment failure and relapse (131).

PI3K/Akt/mTOR signaling plays an important role in regulating the cell cycle, quiescence and proliferation. Various somatic mutations in PTEN, Akt1 and mTOR have been identified in ovarian cancer and can induce enhanced PI3K/Akt/mTOR signaling (132,133). Excessive activation of PI3K/Akt/mTOR signaling is associated to chemoresistance and cancer metastasis and inhibition of PI3K/Akt/mTOR signaling can restore the sensitivity of chemotherapy-resistant ovarian cancer cells to chemotherapy drugs (134). Furthermore, combination treatment using RAS and PI3K inhibitors in ovarian cancer cell lines carrying activated oncogenic KRAS^{G12D} and deletion of two copies of the PTEN gene is a promising strategy for tumors that are rapidly resistant to targeted therapy alone (135). In addition, Wnt receptor Frizzled 7 (FZD7) is expressed in tumors and platinum-resistant cells. Knockdown of FZD7 reduces spheroid formation, increases sensitivity to platinum, and delays tumor occurrence (83).

As a cell surface transmembrane glycoprotein, the folate receptor (FR) promotes the unidirectional transport of folates into the cell. FR has limited distribution, and aberrant overexpression of FR is a characteristic of numerous epithelial tumors, including non-small cell lung, endometrial and ovarian cancer. Specifically, ~80% of EOC tumors constitutively express FR (136). In addition, the increase in receptor expression may be a negative prognostic factor for the chemotherapy response of this malignant tumor (137). Preclinical studies have revealed that folate-conjugated vintafolide (EC145) (138) and mirvetuximab soravtansine (IMGN853) (139) are well tolerated and active against platinum-resistant ovarian cancer, and response rates and PFS are encouraging.

4. Conclusions

Despite advances in chemotherapy, the 5-year survival rate of patients with ovarian cancer remains less than 50%, mainly due to chemotherapy resistance (22). Both primary resistance (patients do not respond at all to treatment and the

disease progresses) and acquired resistance (patients eventually develop acquired resistance after an initial response) to platinum are associated with a severely negative prognosis for EOC patients. For these patients, a thorough understanding of their resistance mechanisms and active drugs is an urgent unmet clinical need (140). The resistance of ovarian cancer cells to chemotherapeutic mechanisms is rather complex and includes MDR, DDR, cell metabolism, oxidative stress, cell cycle regulation, CSCs, immunity, apoptotic pathways, autophagy and abnormal signaling pathways. Therefore, a single mechanism cannot fully explain the resistance of ovarian cancer cells to treatment.

Numerous new strategies are being studied to try to overcome this chemical resistance, including combining platinum-based chemotherapy with new molecularly targeted drugs, such as bevacizumab or olaparib. Combining the vascular endothelial growth factor A-neutralizing antibody bevacizumab with chemotherapy has been revealed to reduce or slow the growth of advanced EOC, but this combination does not appear to extend survival (11). Olaparib is a PARP inhibitor that is only used for cancer patients with BRCA gene mutations since the drug only works on cells where the BRCA pathway is blocked (36). However, only a small percentage of patients with ovarian cancer have mutations in the BRCA gene (141). More detailed mechanistic insights and the development of biomarkers, particularly non-invasive biomarkers, are required to accurately select patients for therapy and facilitate the evaluation of therapeutic efficacy in real time.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

JM designed the review and edited the manuscript. LY and HJX wrote the manuscript. HJX, YYL, XXL, and XW collected and analyzed data. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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