Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ30635

Drug Resistance Mechanisms in Ovarian Cancer

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Abstract. Ovarian cancer, as the leading cause of mortality among gynecological malignancies, mainly relies on platinum-based drugs and taxanes for chemotherapy. The drug resistance that develops during the treatment process is the core bottleneck leading to treatment failure, tumor recurrence, and a significant decline in survival rate for patients. The mechanism of drug resistance involves multiple aspects. Abnormal drug transport is mainly due to the overexpression of P-glycoprotein in the ABCB1 gene, which enhances excretion through gene amplification, variation or promoter alteration, leading to the pumping of taxus and PARP inhibitors out of the cells. Dysregulation of drug activation is manifested as insufficient reduction of platinum-based prodrugs and accelerated metabolism of paclitaxel by CYP3A4, which is influenced by variations in metabolic enzymes, concomitant medications, and the tumor microenvironment. Target alterations include upregulation of the tubulin subtype TUBB3, which reduces paclitaxel binding, and PARP1 mutations that weaken the efficacy of PARP inhibitors. Enhanced DNA damage repair rapidly eliminates platinum-DNA adions through high expression of nucleotide excision repair proteins (XPA, ERRCC1), while mismatch repair defects prevent apoptotic signal transduction. Apoptosis evasion is achieved through p53 inactivation, inhibition of the mitochondrial pathway by overexpression of Bcl-2/Bcl-XL and blocking of the caspase cascade by IAPs proteins. These mechanisms form a closed loop of drug resistance from injury repair to apoptosis inhibition, jointly leading to chemotherapy failure.

Keywords: Ovarian cancer, Drug resistance, Mechanisms.

1. Introduction

Ovarian cancer is the gynecological malignancy with the highest fatality rate worldwide. In China, the situation of its prevention and treatment is equally severe. Due to the insidious and non-specific symptoms in the early stage of the disease, most patients are diagnosed at an advanced stage, making early diagnosis and treatment extremely difficult. Moreover, the treatment outcome for advanced patients is poor, with an overall 5-year survival rate of less than 50% [1,2]. At present, the standard treatment for ovarian cancer is mainly surgery, supplemented by platinum-based chemotherapy regimens combined with taxanes (such as carboplatin and paclitaxel). Although chemotherapy drugs have been continuously advancing and widely used in clinical practice in recent

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years, the emergence of chemotherapy resistance remains one of the main causes of treatment failure and patient death. Therefore, thoroughly clarifying the drug resistance mechanism of ovarian cancer is the key to developing effective strategies to reverse drug resistance and shift the management model of ovarian cancer from an "acute disease" to a "chronic disease" for long-term control. This article aims to conduct a comprehensive review of the research progress on the drug resistance mechanism of ovarian cancer [1].

2. Abnormal drug transport

The treatment of ovarian cancer mainly relies on platinum-based drugs and taxane drugs. Platinum-based drugs are represented by cisplatin and carboplatin. After entering the cell, they combine with water and form intrachain/interchain cross-links with the guanine N7 site of DNA, thereby blocking DNA replication and transcription. They are the basis of chemotherapy for epithelial ovarian tumors. Taxane drugs, represented by paclitaxel and docetaxel, directly bind to the β subunit of microtubules and stabilize them, inhibiting their depolymerization and causing tumor cells to stagnate at the G_2/M phase. Although their target sites are different, both types of drugs are affected by the common resistance axis of insufficient transmembrane entry and excessive transmembrane effusion in recurrent ovarian cancer. Among them, the P-glycoprotein (P-gp) efflux pump encoded by the ABCB1 gene is highly correlated with taxus resistance. P-gp is a typical transporter protein, consisting of two transmembrane domains (responsible for recognizing and transporting hydrophobic chemotherapy drugs, including paclitaxel and docetaxel) and two nucleotide-binding domains (responsible for hydrolyzing ATP and providing excretion energy). In various acquired drug resistance models of ovarian cancer, both paclitaxel-resistant cell lines and PARP inhibitors (such as Olaparib) resistant cell lines show significant upregulation of ABCB1. These cells then possess the ability to exhalate multiple drugs with different structures, but all recognized by P-gp, and exhibit cross-resistance [2,3]. The molecular basis for the overexpression of ABCB1 mainly includes four points. Firstly, copy number variation or gene amplification increases the transcriptional template of ABCB1, directly leading to an increase in the number of P-gp on the cell membrane; Second, functional single-nucleotide variations may enhance the stability or transport activity of P-gp, resulting in higher excretion efficiency. Thirdly, gene fusion events can link the coding region of ABCB1 with highly active promoters or upstream regulatory sequences, thereby transforming the otherwise poorly expressed effector pump into a constructively highly expressed one. Fourth, mutations in the promoter or distal regulatory region can alter the binding of key transcription factors, causing ABCB1 to be over-induced in chemotherapy stress, inflammation, or hypoxic microenvironments. Yew species are the most sensitive to this kind of exhalation because they themselves are high-affinity substrates of P-gp. The commonly used platinum types (cisplatin, carboplatin) primarily rely on copper-transportation-related pathways, such as CTR1, ATP7A, or ATP7B, to enter and exit cells, and are relatively indirectly affected by P-gp. However, within the same tumor cell, when ABCB1 is highly activated, it is often accompanied by the synergistic upregulation of other ABC families (such as ABCC, ABCG). Ultimately, it leads to overall resistance of cells to platinum-based drugs [2-4].

3. Dysregulation of drug activation and inhibition

To improve the solubility, oral accessibility, and toxicity spectrum of platinum drugs, oral or highly stable platinum compounds with Pt (IV) as the skeleton were further developed in the research. These compounds are in a relatively inert and less toxic high-valent platinum state when

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administered and thus are classified as prodrugs. It needs to be reduced to a Pt (II) species with true DNA cross-linking activity after entering the body or tumor to exert anti-tumor effects. Its transformation mainly relies on reducing small molecules within tumor cells, such as glutathione and ascorbic acid, as well as cytochrome P450 reductase and other enzyme systems involved in REDOX reactions. Once the local reducing capacity of the tumor is insufficient or unevenly distributed, functional resistance will occur where prodrugs enter but fail to fully generate active Pt (II) [3,4]. In contrast, paclitaxel and docetaxel are themselves active anti-microtubule drugs that can block mitosis by binding to the microtubule β subunit without metabolic activation. However, the exposure in vivo and effective concentration are highly regulated by CYP3A4, a drug-metabolizing enzyme. When CYP3A4 expression or activity increases, taxanes will be metabolized and cleared more quickly. As a result, it is difficult to maintain sufficient time and concentration within cells, which is clinically manifested as a decrease in sensitivity to the same dose of the drug. The alterations of CYP3A4 or related metabolic and activation pathways have multiple sources. First, the polymorphism or functional variation of the CYP3A4 gene itself can directly affect the transcriptional level of the enzyme, protein stability, or catalytic efficiency. Secondly, if the combined medication includes strong suppressants or strong inducers of CYP3A4, it will significantly alter the metabolic rate of Taxus or other chemotherapy drugs, resulting in either too low efficacy or too high toxicity. Thirdly, systemic disease conditions such as liver function impairment and renal insufficiency can secondarily alter the expression and activity of CYP3A4 by affecting the ability of drug-metabolizing organs. Fourth, tumor-related inflammation, systemic inflammation, and the cytokines released thereby can inhibit the expression of various drug-metabolizing enzymes, altering the actual exposure to chemotherapy drugs. Fifth, physiological variables such as age, gender and endocrine status have also been proven to cause individual differences in CYP3A4 levels; Sixth, the unique tumor microenvironment factors of ovarian cancer, including hypoxia, acidic pH, increased interstitial components, poor drug permeability in the surrounding tissues of the tumor, and unbalanced expression of local metabolic enzymes, all cause the same drug to exhibit different metabolic and activation degrees in different lesions and at different time points Ultimately, it is manifested as acquired drug resistance or unstable efficacy under seemingly the same protocol [5,6].

4. Changes in drug targets

In ovarian epithelial tumors, mainly characterized by high-grade serous ovarian cancer (HGSOC), the first-line chemotherapy regimen is usually platinum-containing, combined with taxanes. Therefore, this group of people often develops acquired resistance to taxus drugs after recurrence. One of the important mechanisms is that the expression profile or isotype of the microtubule β subunit, the direct target of the drug, changes, making it difficult for taxus drugs to stabilize the microtubules again. The direct target of taxanes (docetaxel) is the β subunit of microtubules, which blocks mitosis through "steady-stabilized microtubules". When the tumor replaces the composition of microtubules with more TUBB3 (βIII-tubulin, an isotype of the β subunit), the microtubule dynamics and the drug binding interface change accordingly, manifested as more difficulty for drugs to stabilize microtubules, a decrease in clinical response rate, and a poorer prognosis (the same target, but drug binding). Under stress conditions such as hypoxia or hypoglycemia, post-transcriptional regulation mediated by HuR can further upregulate TUBB3. TUBB3 is an isoform of β-tubulin, which is not highly expressed in normal ovarian epithelium but can be screened out in tumors that have undergone tax-like treatment. After TUBB3 participates in the assembly of microtubules, it alters the dynamic characteristics of the microtubules and the drug binding

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interface, making it more difficult to maintain the stable state of the microtubules with the same dose of paclitaxel or docetaxel. Eventually, the cells can still partially complete mitosis, and clinically, it is observed that the response rate decreases, the progression-free survival period shortens, and the overall prognosis deteriorates. This is more evident in HGSOC, as these tumors have been screened by high-intensity microtubule inhibitors from the very beginning, and those that remain are often the clones of TUBB3-high. In addition, the direct target of PARP inhibitors (such as olaparib) is PARP1. The efficacy of this drug depends on the so-called PARP target. When the drug is fixed at the DNA damage site, a stable drug-protein-DNA complex is formed. If the cell cannot repair this damage, it will undergo apoptosis. However, if tumor cells acquire functional mutations or deletions of PARP1, or reduce the amount of target proteins that can be trapped by down-regulating expression, then even if the drug remains at the site, it is difficult to form stable complexes, and eventually clinical resistance is manifested [4,7].

5. Cancer cells enhance the ability to repair DNA damage

The logic by which platinum-based drugs kill cancer cells is that when such drugs enter tumor cells, they first combine with DNA bases through platinum atoms to form DNA adducts, directly destroying the normal structure of DNA, blocking DNA replication and transcription, and further activating the apoptosis signaling pathways within the cells, triggering programmed death in tumor cells, and ultimately preventing the division and proliferation of cancer cells. Ovarian cancer cells have developed two major levels of drug resistance mechanisms in response to the series of action processes of chemotherapy drugs. Firstly, it enhances the DNA damage repair capacity of ovarian cancer cells, thereby increasing their drug resistance. This is equivalent to the "first line of defense", directly weakening the effect of chemotherapy drugs from the source. The specific mechanism is: First, the high expression of XPA, which is involved in nucleotide excision repair (responsible for identifying damage sites), and ERRCC1, which is responsible for cutting DNA damage repair, significantly enhances the nucleotide repair capacity responsible for large-scale DNA damage repair. This enables rapid clearance of DNA adions caused by platinum-based drugs, preventing the accumulation of DNA damage. Reduce the possibility of indirectly entering the apoptotic pathway due to large-scale DNA damage and forming initial drug resistance [7,8]. Second, the loss of the mismatch repair system function. Since MMR is responsible for repairing minor errors in DNA replication such as base mismatches and small fragment deletions, and most crucially, identifying damage and actively transmitting apoptotic signals, therefore, Ovarian cancer cells prevent the transmission of apoptotic signals by under expressing two proteins, hMsH2 (responsible for identifying base mismatches) and hMLH1 (responsible for mediating the excision of erroneous fragments), which are involved in mismatch repair. Meanwhile, as it does not enter apoptosis, the defect of MMR may also promote the initiation of replication bypass mechanisms, activating special DNA polymerases that can bypass the damage site and continue to synthesize the DNA strands of cancer cells downstream. As a result, the resistance of ovarian cancer cells to platinum-based drugs is further enhanced [9].

6. Apoptosis evasion mechanism of ovarian cancer cells

Due to the DNA repair capacity of ovarian cancer cells is not unlimited and they may still activate apoptosis, ovarian cancer cells have formed a "second line of defense", causing the chain from the initiation to the execution of the apoptotic pathway to fail: First, the inactivation of p53. p53 is a key tumor suppressor protein within human cells, responsible for receiving damage signals within the

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cells and determining whether to activate cell cycle arrest genes to pause cell division and allow time for repair, or to activate apoptotic genes to activate the mitochondrial apoptotic pathway based on the degree of damage. Ovarian cancer cells inhibit the activity of p53 by mutating the gene sequence of p53 or overexpressing MDM2, the main negative regulatory factor of p53. Thereby preventing p53 from receiving apoptotic signals [10]. Second, inhibiting mitochondrial pathways blocks the execution of apoptosis. The mitochondrial pathway is the core executive pathway that induces apoptosis in cancer cells. When p53 is activated, the pro-apoptotic proteins Bax and PUMA will aggregate in the mitochondria and compete with the anti-apoptotic proteins Bcl-2 and Bcl-XL on the mitochondrial membrane for binding. When the pro-apoptotic proteins are dominant, the "permeability" of the mitochondrial membrane will be disrupted. Cytochrome C (a key molecule for apoptosis) within the membrane leaks into the cytoplasm, activating caspase 9 and further activating executive enzymes such as caspase 3 and 7. These "molecular scissors" will cut key proteins such as cytoskeletal proteins and DNA repair enzymes, ultimately leading to the disintegration and death of cancer cells. Ovarian cancer cells express a large amount of anti-apoptotic proteins such as "Bcl-2 and Bcl-XL". These proteins act like "guards" and attach to the outer mitochondrial membrane, preventing pro-apoptotic proteins from approaching and damaging the mitochondrial membrane. Eventually, this leads to the inability of cytochrome C to be released and exert its function. Furthermore, even if cytochrome C can be released, ovarian cancer cells will precisely bind and degrade caspase by up-regulating the IAPs family proteins (apoptosis inhibitory proteins, among which X-IAP is the main one), thereby preventing its disassembly of cells from the executive end [8]. Ovarian cancer cells precisely complement each other through the synergy of two lines of defense and double insurance: DNA damage repair enhancement and apoptosis evasion of cancer cells. The former reduces the generation of apoptotic signals from the source, while the latter guarantees to prevent the execution of apoptotic signals. This interlocking drug resistance loop ultimately leads to the inability of platinum-based drugs used to effectively kill them.

7. Conclusion

Drug resistance in ovarian cancer is the main challenge leading to treatment failure and recurrence. It is caused by abnormal transmembrane transport of drugs (such as ABCB1/P-gp mediated excretion), imbalance in drug activation and metabolism (insufficient reduction of Pt(IV) prodrug, excessive metabolism of CYP3A4), alteration of direct target configuration or expression profile (TUBB3, PARP1, etc.), and remodeling of DNA damage repair ability (NER) Drug resistance is composed of enhanced, MMR deficiency and multi-level apoptotic evasion networks (p53 inactivation, Bcl-2 family and IAPs upregulation). The limitation of current research lies in that most of the mechanism cognition is derived from in vitro cell models or xenograft models, which are difficult to fully simulate the complex tumor microenvironment and the overall drug metabolism in the human body. Meanwhile, targeted drugs targeting a single pathway often have limited efficacy in clinical application due to compensatory activation of tumors and dose-limiting toxicity, and there is a lack of safe and effective strategies that can simultaneously target multiple drug resistance links in a coordinated manner. Looking ahead, the breakthrough point for overcoming drug resistance lies in developing precision medicine based on multi-omics maps to identify the dominant drug resistance pathways in each patient. Based on this, innovative combined treatment regimens are designed, such as the intelligent combination of P-gp inhibitors, BH3 mimics, PARP inhibitors and traditional chemotherapy drugs. Meanwhile, developing new drugs targeting "undruppable" targets (such as mutant p53) and using nanotechnology to achieve tumor-specific targeted delivery to

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reduce systemic toxicity will be the key directions for reversing drug resistance and improving the long-term survival prospects of ovarian cancer.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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