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Research Progress of c-Kit in Platinum-Resistant Ovarian Cancer

Shiwei Li, Xiaolan Ke, Ning Hu, Xiaowen Wang*

Department of Obstetrics and Gynecology, First Affiliated Hospital, Yangtze University, Jingzhou, China
Email: *1142380494@qq.com

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Abstract

c-Kit (CD117) is a type IIIa receptor tyrosine kinase (RTK) that plays a key role in regulating the normal physiological processes of cells. In addition, the activation of c-Kit activates the tyrosine kinase signal transduction pathway, which is closely related to the occurrence and development of gynecological tumors, especially ovarian cancer. This article reviews the mechanisms of platinum resistance in ovarian cancer and the research progress of c-Kit in ovarian cancer.

Keywords

Ovarian Cancer, Platinum Resistance, c-Kit

1. Background

According to the date from Chinese Center for Disease Control and Prevention, in 2020, the number of cancer-related deaths in China increased by 21.6% compared to 2005, and the incidence of cancer in China is similar to the world average. Among them, the number of new cases and deaths of gynecological malignancies in China is on the rise [1]. Ovarian cancer is one of the most common malignant tumors in the female reproductive system, ranking first in mortality among gynecological malignancies. Its early symptoms are often atypical, and there is a lack of effective screening methods, leading to most patients being diagnosed at an advanced stage, which is unfavorable for the prognosis of the disease. Currently, the first-line treatment for ovarian cancer is based on multi-disciplinary cytoreductive surgery, plus paclitaxel, platinum and other chemotherapy drugs. However, patients with ovarian cancer often respond significantly to initial treatment, but with time, the increasing of platinum resistance in ovarian cancer is increasing,

*Corresponding author.

affecting the patient's survival rate and leading to death. Therefore, improving the sensitivity of patients to platinum-based chemotherapeutic agents is a major difficulty to overcome in clinical research, and it is also a major hotspot in ovarian cancer treatment research.

2. Mechanism of Platinum Resistance in Ovarian Cancer

The molecular mechanisms of platinum-based chemotherapy drug resistance in ovarian cancer are very complex and involve mechanisms such as DNA damage repair, imbalance of platinum-based chemotherapy drugs inside and outside tumor cells, inhibition of tumor cell apoptosis, oxidative stress, and tumor microenvironment. There are also complex interactions among these mechanisms.

DNA Damage Repair

DNA is the target of platinum-based drugs, and tumor cells recognize and repair chemotherapy induced DNA damage, which affects drug sensitivity. Platinum-based chemotherapeutic drugs bind to DNA, forming DNA monoadducts, leading to the inter-strand cross-linking of DNA, inhibiting DNA synthesis and transcription, and ultimately leading to the death of tumor cells. However, this DNA damage response persists and induces DNA damage repair, thereby enhancing its repair capacity and ultimately leading to platinum resistance [2].

Imbalance of platinum-based chemotherapeutic agents inside and outside tumor cells

Platinum-based drugs are highly polar molecules that do not pass directly through the lipid membrane of the bilayer and rely on transporters to move in and out of the cell. Among them, copper transporters (COPTs) belong to the copper transport family (CTR/COPT) and are involved in regulating the homeostasis of copper. Copper transporter 1 (CTR-1) is a transmembrane transport protein involved in copper homeostasis. Research has shown that knocking out CTR-1 in mouse cell lines leads to a decrease in intracellular platinum drug concentration, resulting in platinum resistance [3]. Conversely, up-regulation of CTR-1 expression can increase the intracellular accumulation of platinum drugs, increasing the sensitivity of ovarian cancer cells to platinum drugs [4]. In addition, copper transporter 2 (CTR-2) acts as a platinum efflux transporter and is also involved in the regulation of intracellular platinum levels, which is associated with platinum resistance in ovarian cancer [5]. Platinum drugs reduce CTR1, at which point resistance occurs [2]. The adenosine triphosphate-binding cassette (ABC) superfamily of transporters associated with drug efflux is significantly associated with platinum resistance. Among them, ABCB1 is a unidirectional membrane-bound protein that can reduce the concentration of platinum-based chemotherapeutic agents in tumor cells. Research has shown that ABCB1 is overexpressed in platinum-resistant ovarian cancer cells [6], and overexpression of ABCB1 can lead to increased excretion of chemotherapy drugs, resulting in platinum resistance.

Apoptosis inhibition

The action of chemotherapy drugs causes DNA damage and activates the p53-

dependent pathway, which in turn leads to cell death. Apoptosis is a tightly regulated cell death, and impaired regulatory ability can lead to drug resistance in cells. Studies have found that the main cause of chemoresistance is the imbalance between pro-apoptotic and anti-apoptotic pathways. The B-cell lymphoma-2 (Bcl-2) family is involved in the intrinsic apoptosis pathway [7]. The balance between pro-apoptotic and anti-apoptotic proteins in the Bcl-2 family maintains chemotherapy sensitivity, and once this balance is disrupted, it can lead to chemotherapy resistance [8].

Others

In addition, tumor microenvironment, oxidative stress, and abnormal PI3K/Akt signaling pathway are also one of the mechanisms of platinum resistance in ovarian cancer.

The tumor microenvironment refers to the components around tumor cells, which are closely related to the occurrence and development of tumors. Studies have shown that tumor-associated macrophage (TAM) density is closely related to poor prognosis and treatment resistance in ovarian cancer patients [9].

Induction of oxidative stress determines the effectiveness of chemotherapy. Platinum drugs induce cells to produce reactive oxygen species (ROS), which leads to oxidative DNA damage and promotes apoptosis, senescence, and autophagy [10].

The regulation of the PI3K/Akt signaling pathway is also an important approach to improve chemoresistance in ovarian cancer. Studies have shown that inhibition of PI3K can disrupt ovarian cancer cell proliferation and trigger cell death, while activation of PI3K/Akt/mTOR signaling pathway can cause the expression of cancer stem cell markers and participate in the chemoresistance of epithelial ovarian cancer [11].

3. Research on the Expression of c-Kit in Ovarian Cancer

c-Kit (CD117) is an allele of the white spot dominant gene located on human chromosome 4q12 - 13. It is a type IIIa receptor tyrosine kinase (RTK) belonging to the protein kinase superfamily, the Tyr protein kinase family, and the CSF-1/PDGF receptor subfamily [12] [13]. It plays a key role in regulating physiological processes in normal cells. Binding of CD117 to SCF activates multiple signaling pathways critical for embryonic development, cell proliferation, survival, hematopoiesis, gamete formation, mast cell development and migration [13], and plays a catalytic role in the maintenance of stem cells in the prostate, liver and heart [14]. In addition, c-Kit is a classic proto-oncogene. Current studies have found that c-Kit is associated with the occurrence, proliferation, invasion and metastasis of a variety of malignant tumors. Tonary *et al.* [15] pointed out that there was no c-Kit immunoreactivity in normal ovarian surface epithelium, and c-Kit expression was found to be positive in 76% of serous cancer tissues. Research by Yi Cunjian *et al.* [16] showed that the positive rate of c-Kit expression in epithelial ovarian cancer (50.7%) was higher than that in normal ovarian tissue (10.0%) and benign ovarian tumors (20.0%). This suggests that the overexpression of c-Kit is related to tumor proliferation and can therefore be used as a proliferation marker

of ovarian tumors. And the expression rate of c-Kit (+) increased with the progression of FIGO stage [17]. Research by the same research group showed [18] that c-Kit expression was higher in stage III - IV epithelial ovarian cancer than in stage I - II epithelial ovarian cancer. And the expression of c-Kit in well-differentiated epithelial ovarian carcinoma was lower than that in poorly differentiated epithelial ovarian carcinoma. The positive expression rate of c-Kit in the group with lymph node metastasis was significantly higher than that in the group without lymph node metastasis ($P < 0.05$). Maybe they are also related to tumor invasion and metastasis [19]. These results indicate that the expression of c-Kit gradually increases with the progression of grade and stage in epithelial ovarian cancer. This means that patients with positive c-Kit expression should have a worse prognosis than those with negative c-Kit expression. An Yuan [20] *et al.* followed up 58 patients with epithelial ovarian cancer for 3 years. The 3-year survival rate was 45.96% for c-Kit positive patients and 76.19% for c-Kit negative patients. The survival time of c-Kit positive patients was shorter than that of c-Kit negative patients, and there was a significant difference ($P < 0.05$). Tornary *et al.* [15] followed up 34 cases of malignant ovarian tumors for 4 years and found that 8 (89%) of the 9 c-Kit negative patients died, and the remaining 1 case recurred; while 56% of the 25 c-Kit positive patients survived, and 8 of them had no disease symptoms. Statistical analysis showed that patients with c-Kit negative in epithelial ovarian tumors had shorter survival than patients with c-Kit positive ($P < 0.05$). The Brustmann [21] study also demonstrated that patients with negative c-Kit expression in serous ovarian cancer have a worse prognosis. However, Tornary *et al.* [15]. found that among patients with positive c-Kit expression, c-Kit was mainly expressed in the cytoplasm of patients with better prognosis, while c-Kit was mainly expressed on the cell membrane with worse prognosis. Therefore, they concluded that c-Kit positive expression was stained on the cytoplasm in patients with good prognosis. Some scholars believe [22] that increased expression of c-Kit in the cytoplasm can inhibit the proliferation of ovarian epithelial cells by stimulating cyclo-adenosine phosphate (C-AMP). This may be one of the reasons why some scholars have contradictory conclusions on the prognosis of ovarian cancer patients. In a retrospective analysis of patients undergoing post-surgical chemotherapy, Raspollini *et al.* [23] found that patients with positive c-Kit expression were less sensitive to first-line chemotherapy drugs and progressed faster after the use of chemotherapy drugs. Research by Peng Guangcai *et al.* [17] showed that the positive rate of c-Kit expression in platinum-resistant ovarian cancer was higher than that in platinum-sensitive group. Yi Cunjian *et al.* [24] successfully established an orthotopic tumor transplantation model in nude mice. After identification, the c-Kit gene was expressed in both cell lines and was significantly highly expressed in DDP-resistant SKOV3/DDP cells. This suggests that positive expression of c-Kit is related to platinum resistance to chemotherapy in epithelial ovarian cancer. These studies provide us with good guidance in studying ovarian tumors and judging the prognosis.

In the study of the molecular mechanism related to c-Kit and platinum resistance in ovarian cancer, scholars generally believe that ovarian cancer stem cells (CSC) are an important factor leading to platinum resistance, and c-Kit is the most common marker of ovarian cancer stem cells (SCS), there is a clear correlation with platinum resistance in ovarian cancer. CSCs are responsible for self-renewal, differentiation and proliferation potential, tumor initiation ability, its progression, drug resistance, and metastasis and spread. Studies by Mazzoldi [25] *et al.* have shown that c-Kit-positive CSCs can survive and promote classic dryness under selective culture conditions with the help of their ligand stem cell factor (SCF), indicating that there may be a near secretory/paracrine circuit in EOC, which can promote the survival of cancer stem cells in epithelial ovarian cancer, leading to drug resistance in ovarian cancer cells. The ligand for c-Kit is stem cell factor (SCF). Inactive c-Kit exists as a monomer on the cell surface, while SCF exists outside the cell as a dimer. When c-Kit binds to its ligand SCF, it induces a change in the conformation of its extracellular region, causing the receptor to migrate and accumulate on the cell membrane, forming a dimer, and activation of c-Kit occurs. Causes autophosphorylation of specific tyrosine residues in the catalytic domain within cells. These phosphorylated tyrosine sites provide recognition, anchoring and binding sites for intracellular substrates, allowing the substrates to be further phosphorylated in turn, triggering a cascade chain reaction of intercellular signals, and ultimately activating transcription factors in the cytosol. c-Kit phosphorylation triggers multiple signal transduction pathways, regulates gene expression in tumor cells, controls cell growth, proliferation and differentiation. In addition, Fang *et al.* [26] showed that the binding of c-Kit to PHB upregulated phosphorylated PHB^{Y259} in the lipid raft domain, leading to subsequent activation of the Notch3-PBX1 and β-catenin-ABCG2 signaling pathways to increase the dryness, tumorigenicity and drug resistance of ovarian cancer.

4. Application of Drugs Inhibiting c-Kit in Improving Chemotherapy Resistance of Ovarian Cancer

Because the activation of c-Kit activates the tyrosine kinase signal transduction pathway, it is closely related to the occurrence and development of gynecological tumors. Among them, it is particularly closely related to ovarian cancer. Studies [27] have shown that most epithelial serous ovarian tumors express one or more tyrosinases, suggesting that they play a regulatory role in ovarian epithelial growth and epithelial cancer development. Therefore, the use of tyrosine kinase inhibitors to inhibit abnormal signal transduction at the cellular level may provide a new way to treat tumors. Imatinib mesylate is a specific inhibitor of tyrosine kinase receptors such as c-Kit, C-abl, and PDEFRα. By blocking the tyrosine kinase receptor pathway, it inhibits cell differentiation and proliferation and promotes cell apoptosis. Sachin *et al.* [28] found that there were no significant changes in tumors after treating mice transfected with ovarian cancer cells with imatinib alone, but after it was combined with paclitaxel, the tumor volume shrank compared with

before, and the recurrence rate was significantly reduced. Compared with paclitaxel alone, the difference was statistically significant. This suggests that imatinib alone has poor efficacy, and combination with other chemotherapeutic drugs may improve chemotherapy efficacy. Foreign scholars have also conducted a lot of research [29] [30] and found that if imatinib was used alone in patients with recurrent ovarian cancer who expressed at least one of the target receptors of imatinib, these patients were well tolerated imatinib, but there was no obvious clinical efficacy. Zhang Kuo *et al.* [31] compared the proliferation inhibition of imatinib mesylate, cisplatin and combinations on the cisplatin-resistant human ovarian cancer cell line SKOV3/DDP. The results showed that different drug concentrations of imatinib mesylate showed an inhibitory effect on SKOV3/DDP cells, and the inhibitory rate of imatinib mesylate combined with cisplatin was higher than that of the cisplatin alone group. There was a statistically significant difference between the two groups ($P < 0.05$). After co-administration of imatinib mesylate and cisplatin, the early apoptosis rate increased from 1.25% to 12.31% ($P < 0.05$). This suggests that imatinib mesylate and cisplatin have a synergistic effect, promoting apoptosis and increasing sensitivity to DDP. Imatinib mesylate alone is not effective in treating ovarian cancer. Some scholars believe that the low expression of c-Kit in ovarian cancer stromal cells may be one of the reasons [16].

5. Discussion

As one of the most common gynecological malignancies, ovarian cancer seriously endangers women's health. The incidence of drug resistance in ovarian cancer is increasing day by day, and the chemotherapy mechanism of ovarian cancer cells is quite complex. c-Kit is a tyrosine kinase and a proto-oncogene, associated with the occurrence, proliferation, invasion and metastasis of ovarian cancer. c-Kit can be used as an important marker for clinical assessment of ovarian cancer staging and grading. However, whether it can provide a more accurate assessment of prognosis remains to be discussed. As a tyrosine kinase inhibitor, imatinib mesylate can effectively inhibit the proliferation of ovarian cancer cells. However, there is some controversy in laboratory studies and phase II clinical studies on ovarian cancer. Although imatinib alone is not effective in the treatment of advanced recurrent ovarian cancer, whether it can prolong patient survival for early cancer, initial treatment, and as a sensitizer for other chemotherapeutic drugs still requires a lot of clinical verification. The mechanism of ovarian cancer development is very complex, and the molecular mechanism is the result of multiple genes and multiple steps. Further research and analysis are needed for the expression of c-Kit in different parts of ovarian cancer cells, or its combined effect with other molecules, on patient prognosis, the development of platinum resistance, and the application effect of tyrosine kinase inhibitors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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