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# Study status and progress of the cisplatin resistance mechanism of cervical cancer cells

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***Abstract:*** **The prevalence and mortality of cervical cancer ranked first in the malignancies of the female reproductive system, and the incidence is increasing in recent years, especially in developing countries. Clinical treatment of cervical cancer mainly takes the combination of surgery, radiotherapy and chemotherapy method. At present, cisplatin is still the preferred drug for chemotherapy, but its drug resistance has seriously hampered its treatment of cervical cancer.To improve the therapeutic effect of cisplatin on cervical cancer patients, and improve the sensitivity of cervical cancer cells to cisplatin, we investigated the cisplatin resistance mechanism of cervical cancer cells and reviewed them, to provide a scientific basis for better clinical effect of cisplatin.**

***Keywords:*** Cervical cancer; Cisplatin; Drug resistance; Chemotherapy; Molecular mechanism

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## 1. Introduction

Cervical cancer is the fourth most common malignancy among women, and is one of the leading causes of cancer death in women. Worldwide, approximately 85% of cervical cancer deaths occur in underdeveloped or developing countries [1]. Clinical treatment of cervical cancer mainly take the combination of surgery and radiotherapy and chemotherapy method. At present, cisplatin is still the preferred drug for chemotherapy, but its resistance has seriously hampered its treatment of cervical cancer [2].

Cisplatin can bind to DNA and cause DNA cross-linking and induce DNA damage, it activating downstream signaling pathways, including ATR, p53, p73 and MAPK, eventually leading to cell cycle arrest or immediate activation of apoptosis and kill cancer cells [3]. But, cisplatin resistance is increasingly common and often leading to chemotherapy failure.

The main reasons of cisplatin resistance of cervical cancer cells can be divided into the following categories: (1) reduced in the intracellular accumulation of cisplatin; (2) autophagy and apoptosis; (3) DNA methylation; (4) the presence of cancer stem cells. Next we will described them separately.

## 2. Drug resistance mechanism

### *2.1. Reduced in the intracellular accumulation of cisplatin*

Actually, it is often found that the accumulation of cisplatin is reduced in cisplatin-resistant cells, either by impaired uptake or increased efflux. This is considered to be one of the most consistent features of cisplatin-resistant cells [4]. There are many factors to affect cisplatin uptake and efflux.

#### *2.1.1. P-glycoprotein*

Multidrug resistance (MDR) refers to the malignant tumor tissue on antitumor drugs have cross-tolerance, it is considered a major cause of malignant tumor chemotherapy failure [5]. P-glycoprotein (P-gp) is a product of MDR genes and it is also a transmembrane glycoprotein encoded by the MDR gene. The expression of P-gp in normal tissues is low, but overexpressed in tumor cells of MDR phenotype. P-gp has ATP energy-dependent drug pump function, which can transfer the chemotherapeutic drugs from the intracellular to the extracellular by means of active transport to reduce the accumulation of intracellular chemotherapeutic drugs. P-gp also protects cancer cells from damage and reduce apoptosis, which expression level is proportional to the degree of drug resistance [6-7].

Studies have shown that P-gp is overexpressed in cervical cancer cells, and down-regulation of P-gp levels can enhance the sensitivity of cervical cancer cells to cisplatin [8].

#### *2.1.2. Copper transporter 1*

The main copper uptake transporter in human cells is copper transporter 1 ( CTR1 ), a 190-amino acid protein of 28 kDa with three transmembrane domains that forms a stable homotrimer in membranes. Early studies have shown that CTR1 is the primary protein that controls the uptake of cisplatin in yeast and mice and can promote cisplatin uptake [9]. CTR1 can indirectly alter the accumulation of cisplatin by influencing intracellular copper levels [10]. Studies have shown that both copper and cisplatin are substrates of CTR1, and CTR1 transports via a series of transchelation reactions suggest that cisplatin may

 

be distributed to various cellular compartments through chaperones and transchelation reactions in a manner similar to copper transport [11]. Kelland et al. showed that knockout CTR1 will significantly reduce the uptake of cisplatin in yeast and mammalian cells [12]. Researches showed that the level of CTR1 was downregulated in cervical cancer cell lines [13], whereas overexpression of CTR1 in cells can increase the accumulation of cisplatin [14].

### *2.2. Apoptosis and Autophagy*

Apoptosis and autophagy share regulatory mechanisms which play an important roles not only under normal physiological conditions, but also in disease states such as cancer [15].

#### *2.2.1. Bcl-2 and Beclin-1*

The interaction between Bcl-2 and Beclin-1 proteins is an important point between apoptosis and autophagy pathways.Beclin-1 is a tumor suppressor protein, and its function can be inhibited by Bcl-2, an autophagy gene that participates in apoptosis by caspase-9 signaling, and then contributing to the carcinogenic potential of Bcl-2 [16]. Studies have shown that cisplatin treatment significantly increases the level of Bcl-2 protein in cervical cancer cell lines. However, when Bcl-2 was silenced, the apoptosis may occur, and the sensitivity of cervical cancer cell lines to cisplatin can be greatly improved. The analysis of apoptosis death markers showed that Bcl-2 played a role in delaying the onset of apoptosis, thereby conferring resistance to cisplatin treatment [17,18]. Thus, inhibition of Bcl-2 expression levels can be used to increase the sensitivity of cervical cancer to cisplatin.

#### *2.2.2. NF-κB*

NF-κB is an anti-apoptotic or pro-apoptotic molecule and depends on the cell type and stress properties, and the level of NF-κB activity is associated with the resistance of most tumor cells [19].

Several nuclear proteins have been found to modulate NF-κB activity. It has been reported that protein phosphatase X [20], DNA-PK [21] and ATM [22] have increased NF-κB activity and it has been reported that ERK2 negatively regulates NF-κB activity. The mechanism of activation of NF-κB induced by cisplatin can also be further enhanced by inhibition of MEK-ERK signaling pathway. However, how DNA damage signals depend on the MEK-ERK pathway and the crosstalk between the MEK-ERK pathway and NF-κB need further study [23,24].

Early studies have shown that the higher inducibility of NF-κB activity in cervical cancer cells lines was the major mechanism responsible for their resistance to cisplatin [25]. Therefore, we can downregulated the level of NF-κB and enhance the sensitivity of cervical cancer cells to cisplatin from the above mechanisms.

#### *2.2.3. Metadherin*

Metadherin (MTDH), also named as Astrocyte Elevated Gene-1 (AEG-1) or LYsine-RIch CEACAM1 co-isolated (LYRIC), has become a new oncogene, which is overexpressed in various solid tumors [26]. The study results showed that the expression of MTDH in cervical cancer tissues was higher than normal cervical tissues, and the expression level of MTDH was positively correlated with the resistance of cisplatin. On the one hand, MTDH increased the accumulation of LC3II and decreased the cleavage of Caspase-3, thereby inducing autophagy of cervical cancer cells and reducing apoptosis. On the other hand, MTDH inhibits chemotherapy-induced apoptosis of cervical cancer cells by activating ERK/NF-κB pathway and promotes cell survival [27]. Therefore, MTDH can be used as a therapeutic target to overcome the resistance of cervical cancer to cisplatin.

#### *2.2.4. mTOR*

Studies have shown that cisplatin reduces the expression of mTOR protein, increases the autophagy of cervical cancer cells, and inhibits apoptosis and changes the cell cycle [28].

Researchers used rapamycin and RNA silencing to achieve mTOR inhibition [29]. The data suggest that the use of lower doses of cisplatin in combination with mTOR inhibition is a viable treatment option and addresses the challenge of cisplatin dose-dependent toxicity, whereas future studies need to be confirmed in clinical settings.

#### *2.2.5. Protein reversionless 3-like*

Protein reversionless 3-like (REV3L) is a catalytic subunit of DNA polymerase ζ, which plays a key role in DNA damage during the translesion synthesis [30]. The overexpression of REV3L promotes the transition from G1 phase to S phase in cervical cancer cells, and promotes cell proliferation and colony formation.REV3L also confers resistance to cisplatin in cervical cancer cells by regulating cell apoptosis and anti-apoptotic proteins, such as Bcl-2, Mcl-1, Bcl-xL, etc. Studies have shown that REV3L is highly expressed in cervical cancer. Inhibition of REV3L expression helps to improve the sensitivity of cervical cancer cells to cisplatin. Therefore, it can be used as a potential therapeutic target in the treatment of cervical cancer [31].

### *2.3. DNA methylation*

After the tumor formation, metastasis and the development of drug resistance, accumulation of abnormal DNA methylation can be observed [32].

Chen et al. found that DNA methylation can lead to the development of drug resistance in different cervical cancer cell lines by establishing a two-component

system for monitoring targeted DNA methylation and quantifying the degree of methylation [33]. Thus, methylation changes may serve as biomarkers and therapeutic targets for drug resistance of cervical cancer cell, and demethylation may reverse drug resistance phenotype. But its mechanism of action is not yet clear.

### *2.4. Cancer stem cells*

Cancer stem cells (CSCs) refer to cancer cells with stem cell properties, which have the abilities of self-renewal, infnite proliferation and multiple differentiation potentials [34].

The relationship between CSCs and drug resistance of cervical cancer cells was studied by Liu et al. [35]. They enriched CSCs through the suspended sphere culture of CaSki cells and measured using MTS. The results shown that the CaSki sphere-forming cells were more resistant to chemotherapeutic drugs than the control CaSki cells. It is proved that the presence of CSCs affects the drug resistance of cervical cancer cells.

## 3. Conclusion and outlook

Cisplatin as an effective chemotherapy drug for treat cervical cancer, its drug resistance has seriously hampered its treatment of cervical cancer. We do a review to explain the reasons and mechanism for resistance of cervical cancer cells to cisplatin, although the content is not comprehensive enough.The mechanism of cisplatin resistance of cervical cancer cells is complex and is the result of the interaction of many factors.Further research is necessary in order to give a more comprehensive explanation that the reasons of drug resistance of cervical cancer cells. At present, we can take some appropriate measures to enhance the sensitivity of cervical cancer cells to cisplatin based on the existing research results. For example, modifying the drug structure of cisplatin; developing new drugs; combine cisplatin with other drugs and so on. At present, many studies have shown that cisplatin in combination with other drugs can increase the drug sensitivity [36,37]. Therefore, we need study the molecular mechanism of drug resistance of cervical cancer cells more deeply, and provide more effective treatment to cervical cancer patients.

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