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Chemoresistance in Ovarian Cancer: Mechanisms and Therapeutic Strategies

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INTRODUCTION

Chemoresistance in ovarian cancer remains one of the greatest challenges in oncology, as it significantly limits the efficacy of conventional chemotherapy treatments and contributes to poor patient outcomes. Despite initial responsiveness to chemotherapy, many patients with ovarian cancer experience relapse due to the emergence of resistant cancer cells. This phenomenon is driven by various molecular mechanisms that allow the tumor cells to evade the cytotoxic effects of chemotherapeutic agents. Understanding these mechanisms is crucial for developing new therapeutic strategies aimed at overcoming chemoresistance and improving patient survival [1]. Ovarian cancer, often diagnosed at advanced stages, is primarily treated with a combination of surgery and chemotherapy, typically using platinum-based agents such as cisplatin or carboplatin, along with taxanes like paclitaxel. Although many patients initially respond well to these treatments, the majority eventually relapse due to the development of chemoresistance. This resistance can occur through several interrelated processes, including alterations in drug uptake, efflux mechanisms, alterations in the target sites and activation of cellular pathways that promote survival and repair [2].

DESCRIPTION

One of the primary mechanisms of chemoresistance is the overexpression of drug efflux pumps, such as P-glycoprotein (P-gp), which actively transport chemotherapeutic agents out of cancer cells, reducing their intracellular concentrations. The increased activity of these pumps is often associated with resistance to both platinum-based drugs and taxanes. In addition, alterations in the DNA repair mechanisms of ovarian cancer cells contribute to resistance. The repair of DNA damage caused by chemotherapy-induced stress is vital for tumor cell survival. Overexpression of repair enzymes like excision repair cross-complementation group 1 (ERCC1) is linked to reduced sensitivity to platinum-based therapies, as these enzymes counteract the DNA damage caused by the chemotherapy. Another important factor contributing to chemoresistance is the dysregulation of apoptotic pathways. Apoptosis, or programmed cell death, is a key mechanism by which chemotherapy exerts its therapeutic effects. However, ovarian cancer cells often develop resistance by evading apoptosis. Mutations in apoptotic regulators, such as p53, a tumor suppressor gene, can disrupt the normal apoptotic response to chemotherapy. Additionally, overexpression of anti-apoptotic proteins, such as Bcl-2, or the activation of survival pathways like the PI3K/Akt/mTOR pathway, enables ovarian cancer cells to resist the cytotoxic effects of chemotherapy [1].

The tumor microenvironment also plays a critical role in the development of chemoresistance. Factors such as hypoxia, inflammation and the presence of cancer-associated fibroblasts contribute to the creation of a protective niche that shields ovarian cancer cells from chemotherapy. Hypoxic conditions within tumors activate adaptive mechanisms, such as the stabilization of hypoxia-inducible factors (HIFs), which promote cell survival and angiogenesis, thereby enhancing the resistance to chemotherapeutic agents. Additionally, the secretion of various cytokines and growth factors in the microenvironment can alter the sensitivity of tumor cells to chemotherapy and contribute to the recruitment of immune cells that promote tumor growth and protect against drug-induced cell death. Epigenetic modifications also play a role in the development of chemoresistance in ovarian cancer. DNA methylation, histone modifications and non-coding RNA expression can influence the expression of genes involved in drug resistance and survival pathways. For instance, hypermethylation of tumor suppressor genes or alterations in microRNA profiles can

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modulate the expression of drug resistance-related proteins, further complicating the management of the disease [2]. In recent years, significant progress has been made in identifying potential therapeutic strategies to overcome chemoresistance in ovarian cancer. Targeted therapies aimed at inhibiting specific molecular drivers of resistance, such as the inhibition of P-gp or the use of DNA repair inhibitors like PARP inhibitors, have shown promise in preclinical studies and clinical trials. The use of combination therapies, such as combining chemotherapy with inhibitors of the PI3K/Akt/mTOR pathway or Bcl-2 inhibitors, is also being explored to enhance the efficacy of existing chemotherapeutic agents.

Immunotherapy is another promising approach that is being investigated for overcoming chemoresistance. By harnessing the body's immune system to target and eliminate cancer cells, immunotherapy offers a novel way to bypass the mechanisms of resistance that cancer cells have developed to evade chemotherapy. Immune checkpoint inhibitors, such as those targeting PD-1/PD-L1, are currently being studied in ovarian cancer to enhance immune-mediated tumor cell killing and overcome chemoresistance [2]. Furthermore, advancements in personalized medicine have allowed for a more tailored approach to ovarian cancer treatment. By profiling the molecular characteristics of individual tumors, clinicians can identify specific resistance mechanisms and select the most appropriate therapies for each patient. This approach holds the potential to significantly improve treatment outcomes by addressing the unique challenges posed by chemoresistance in each case.

CONCLUSION

Chemoresistance in ovarian cancer remains a major hurdle in the effective treatment of the disease. The complex interplay of genetic, epigenetic and microenvironmental factors that contribute to resistance requires a multifaceted approach to treatment. Continued research into the underlying mechanisms of chemoresistance, coupled with the development of targeted therapies, immunotherapies and personalized medicine, holds promise for improving the prognosis of ovarian cancer patients and overcoming the challenges of chemoresistance.

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