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Understanding the Molecular Mechanisms of Ovarian Cancer Drug Resistance to Provide Effective Treatment Alternatives

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INTRODUCTION

Ovarian cancer remains one of the most lethal gynecological malignancies, with high mortality rates largely attributed to late-stage diagnosis and the development of drug resistance. While initial responses to chemotherapy, particularly platinum-based compounds, are often favorable, the majority of patients eventually experience relapse and resistance, rendering subsequent treatments less effective. Understanding the molecular mechanisms underlying drug resistance in ovarian cancer is crucial for developing effective treatment alternatives and improving patient outcomes. This article explores the various molecular mechanisms contributing to drug resistance in ovarian cancer, including genetic and epigenetic alterations, cellular adaptive responses, and tumor microenvironment factors. Additionally, it discusses current and emerging strategies to overcome resistance and provide more effective treatment options for patients [1].

DESCRIPTION

The TP53 gene, which encodes the tumor suppressor protein p53, is mutated in a majority of high-grade serous ovarian cancers (HGSOCs). These mutations can lead to loss of p53 function, impairing the cell's ability to undergo apoptosis in response to DNA damage caused by chemotherapy. Although BRCA1/2 mutations initially make ovarian cancer cells more sensitive to platinum-based chemotherapy and PARP inhibitors, secondary mutations can restore BRCA function, leading to resistance. The amplification of genes such as MDR1 (multidrug resistance gene 1) and its product, P-glycoprotein, can lead to increased efflux of chemotherapeutic drugs from cancer cells, reducing their efficacy. Epigenetic changes, such as DNA methylation and histone modifications, can alter gene expression without changing the DNA sequence, contributing to drug resistance. Hypermethylation of promoter regions of tumor suppressor genes can lead to their silencing. For instance, methylation of the MLH1 gene, a key player in DNA mismatch repair, can result in resistance to platinum-based therapies. Alterations in histone acetylation and methylation can affect the expression of genes involved in drug response. For example, histone deacetylases (HDACs) can repress the expression of genes necessary for apoptosis, contributing to resistance. The interaction between cancer cells and surrounding stromal cells can modulate drug response. For instance, fibroblasts in the TME can secrete growth factors that activate survival pathways in cancer cells. The ECM can act as a physical barrier, impeding drug penetration. Additionally, components of the ECM, such as collagen and integrins, can activate signaling pathways that confer resistance. For patients with BRCA1/2 mutations, PARP inhibitors like olaparib have shown efficacy by exploiting the concept of synthetic lethality [2,3]. However, overcoming secondary BRCA mutations requires combination therapies or novel inhibitors. These agents can reverse histone modifications and restore the expression of genes involved in apoptosis. Combining HDAC inhibitors with traditional chemotherapy has shown promise in preclinical models. Drugs such as bevacizumab target VEGF and disrupt the formation of new blood vessels, thereby reducing hypoxia and improving drug delivery. Targeting stromal cells or disrupting the ECM can enhance the efficacy of chemotherapeutic agents. For instance, inhibitors of fibroblast activation protein (FAP) can reduce stromal support for cancer cells. Compounds that inhibit ABC transporters can increase the intracellular concentration of chemotherapeutic drugs. However, the development of selective and non-toxic inhibitors remains a challenge. Targeting key proteins in DNA repair pathways, such as ATR or CHK1, can sensitize cancer cells to chemotherapy by preventing the repair of DNA damage. Agents like chloroquine,

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which inhibit autophagy, can enhance the effectiveness of chemotherapy by promoting apoptotic cell death [4,5].

CONCLUSION

Understanding the molecular mechanisms of drug resistance in ovarian cancer is essential for developing effective treatment alternatives. Genetic and epigenetic alterations, microenvironmental factors, and intrinsic cellular mechanisms all contribute to the complexity of drug resistance. By targeting these pathways and integrating emerging therapies, we can improve the efficacy of treatment and offer better outcomes for ovarian cancer patients. Continued research and personalized medicine approaches hold the promise of overcoming drug resistance and enhancing the quality of life for those affected by this challenging disease. Immune checkpoint inhibitors, such as pembrolizumab, have shown promise in treating ovarian cancer by unleashing the immune system to target cancer cells. Combining these agents with other therapies may overcome resistance mechanisms. This approach involves the infusion of genetically modified immune cells, such as CAR-T cells, that are designed to target and kill cancer cells. TKIs that target specific oncogenic drivers, such as HER2 or VEGFR, can be effective in subsets of ovarian cancer patients. These agents combine a monoclonal antibody specific to a cancer antigen with a cytotoxic drug, allowing for targeted delivery of the chemotherapeutic agent. The integration of genomics and proteomics into clinical practice enables the tailoring of treatment strategies based on the molecular profile of the individual's tumor. This approach can help identify the most effective therapies and overcome resistance.

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CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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