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Chemotherapy-resistant TNBC: Molecular Mechanisms, Biomarkers and Emerging Therapies

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Introduction

Chemotherapy-resistant Triple-Negative Breast Cancer (TNBC) represents a significant challenge in oncology. TNBC is characterized by the absence of Estrogen Receptors (ER), Progesterone Receptors (PR), and Human Epidermal Growth Factor Receptor 2 (HER2), making it unresponsive to hormonal therapies and HER2-targeted treatments. This distinct lack of receptor targets necessitates reliance on chemotherapy, yet resistance to such treatment poses a formidable obstacle. Understanding the molecular mechanisms underlying this resistance, identifying relevant biomarkers, and developing emerging therapies are critical steps in improving patient outcomes. TNBC accounts for approximately 10-20% of all breast cancers and tends to be more aggressive and have a poorer prognosis compared to other subtypes. Its aggressive nature is partly due to its high heterogeneity and the propensity for early metastasis. Standard chemotherapy, including anthracyclines and taxanes, remains the cornerstone of treatment. However, many patients either do not respond to initial chemotherapy or develop resistance over time, leading to disease progression [1].

Chemotherapy resistance in TNBC can be attributed to several molecular mechanisms. One significant factor is the role of drug efflux pumps, particularly the ATP-Binding Cassette (ABC) transporters. These transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), actively pump chemotherapeutic agents out of cancer cells, reducing their intracellular concentrations and thereby diminishing their efficacy. Overexpression of these transporters is frequently observed in TNBC and is associated with poor response to chemotherapy. Another critical mechanism is the alteration of drug targets. For instance, mutations in the gene encoding topoisomerase II alpha (TOP2A) can render cells less sensitive to anthracyclines, which target this enzyme. Similarly, alterations in microtubule dynamics, often due to mutations or changes in expression of tubulin isotypes, can lead to resistance to taxanes, which disrupt microtubule function [2].

Description

The DNA Damage Response (DDR) pathway is also implicated in chemotherapy resistance. Defects in DDR, particularly in the homologous recombination repair (HRR) pathway, can lead to genomic instability and an increased ability to survive DNA damage induced by chemotherapy. BRCA1 and BRCA2 mutations are well-known contributors to impaired HRR. However, paradoxically, while these mutations can initially sensitize cells to DNA-damaging agents, they can also lead to the development of resistance through mechanisms such as the restoration of HRR function or activation of alternative repair pathways. Cancer Stem Cells (CSCs) are another factor contributing to chemotherapy resistance. These cells possess self-renewal capabilities and are often more resistant to conventional therapies due to their quiescent state and enhanced DNA repair mechanisms [3].

CSCs can repopulate the tumor after chemotherapy, leading to relapse and metastasis. Identifying and targeting CSCs is therefore crucial for overcoming resistance. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, play a role in regulating gene expression and can contribute to chemotherapy resistance. For example, hypermethylation of the promoter regions of tumor suppressor genes can lead to their silencing, while histone modifications can alter chromatin structure and gene accessibility. Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), can also modulate the expression of genes involved in drug resistance [4].

Emerging therapies aim to tackle these resistance mechanisms through various strategies. One promising approach is the use of poly (ADP-ribose) polymerase (PARP) inhibitors, particularly in patients with BRCA mutations. PARP inhibitors exploit the concept of synthetic lethality, where the inhibition of PARP in HRR-deficient cells leads to the accumulation of DNA damage and cell death. Several PARP inhibitors, such as olaparib and talazoparib, have shown efficacy in TNBC and are approved for clinical use. Immunotherapy, especially immune checkpoint inhibitors, has also emerged as a potential treatment for TNBC. Immune checkpoints, such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1), play a role in maintaining immune tolerance and preventing autoimmunity. Tumors often exploit these checkpoints to evade immune detection [5].

Conclusion

Clinical trials remain essential for advancing the treatment of chemotherapy-resistant TNBC. Participation in clinical trials provides patients with access to innovative therapies and contributes to the generation of knowledge that can benefit future patients. It is important to design trials that not only test new drugs but also investigate combination strategies, biomarker-driven approaches, and adaptive treatment regimens.

In conclusion, chemotherapy-resistant TNBC is a complex and challenging disease that requires a multifaceted approach to improve outcomes. Understanding the molecular mechanisms underlying resistance, identifying relevant biomarkers, and developing emerging therapies are critical steps in this endeavor. Advances in genomics, immunotherapy, and targeted therapies offer hope for more effective and personalized treatments. Collaborative efforts among researchers, clinicians, and patients are essential to overcome the obstacles posed by chemotherapy resistance and ultimately improve the prognosis for individuals with TNBC. The journey towards conquering TNBC is ongoing, but with continued research and innovation, there is optimism for a future where resistance is no longer a barrier to effective treatment.

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Conflict of Interest

None.

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