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Commentary

Mechanisms of Altered Drug Transport and Multidrug Resistance in Cancer Therapy

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DESCRIPTION

Chemoresistance remains one of the major challenges in effective cancer treatment and is a leading cause of therapy failure and disease recurrence. Despite advances in chemotherapy and targeted therapies, many cancers either fail to respond initially or develop resistance over time. The molecular basis of chemoresistance is complex and multifactorial, involving genetic, epigenetic, cellular and microenvironmental factors. Understanding these molecular mechanisms is essential for improving therapeutic outcomes and developing strategies to overcome resistance.

One of the primary molecular causes of chemoresistance is genetic alteration within cancer cells. Mutations in oncogenes and tumor suppressor genes can alter drug sensitivity by modifying key signaling pathways. For example, mutations in the Tumor Protein p53 *(TP53)* impair apoptosis, allowing cancer cells to survive despite chemotherapy-induced Deoxyribonucleic Acid (DNA) damage. Similarly, amplification or mutation of genes involved in cell survival pathways, such as Mitogen Activated Protein Kinase *(MAPK)*, promotes resistance by enhancing proliferation and inhibiting programmed cell death. These genetic changes may be present before treatment (intrinsic resistance) or acquired as a result of selective pressure during chemotherapy.

Another important mechanism of chemoresistance involves altered drug transport within cancer cells. Many chemotherapeutic agents rely on intracellular accumulation to exert their cytotoxic effects. Overexpression of Atp-Binding Cassette (ABC) transporter proteins, such as P-glycoprotein, leads to increased efflux of drugs from cancer cells. As a result, intracellular drug concentrations fall below therapeutic levels, rendering treatment ineffective. This phenomenon, known as multidrug resistance, is a major obstacle in the treatment of various cancers, including leukemia, breast cancer and ovarian cancer.

Enhanced DNA damage repair capacity also plays a major role in chemoresistance. Chemotherapeutic agents such as alkylating agents and platinum-based drugs function by inducing DNA damage. Cancer cells that upregulate DNA repair mechanisms, including homologous recombination and nucleotide excision repair pathways, can efficiently repair this damage and survive treatment. Overexpression of DNA repair proteins like Breast Cancer Gene *1(BRCA1)*, Excision Repair Cross Complementation Group *1(ERCC1)* and Poly (ADP-Ribose) Polymerase *(PARP)* contributes to resistance by maintaining genomic integrity despite chemotherapy-induced stress.

Epigenetic modifications further contribute to the molecular basis of chemoresistance. Changes in DNA methylation, histone modification and non-coding Ribonucleic Acid (RNA) expression can alter gene expression without changing the DNA sequence. Hypermethylation of tumor suppressor genes can silence pathways involved in drug sensitivity, while histone modifications may activate genes associated with survival and resistance. MicroRNAs also play a regulatory role by modulating the expression of genes involved in apoptosis, drug transport and cell cycle control, thereby influencing the response to chemotherapy.

The tumor microenvironment is another critical factor in the development of chemoresistance. Cancer cells interact dynamically with surrounding stromal cells, immune cells, blood vessels and extracellular matrix components. Hypoxic conditions within tumors can activate Hypoxia-Inducible Factors (HIFs), which promote angiogenesis, metabolic adaptation and resistance to chemotherapy. Additionally, cytokines and growth factors released by stromal cells can activate survival pathways in cancer cells, reducing drug efficacy.

Cancer Stem Cells (CSCs) represent a distinct subpopulation of tumor cells that significantly contribute to chemoresistance. These cells possess self-renewal capacity and are often quiescent, making them less susceptible to drugs that target rapidly dividing cells. CSCs exhibit high expression of drug efflux transporters, enhanced DNA repair mechanisms and resistance to apoptosis. Following chemotherapy, surviving CSCs can repopulate the tumor, leading to relapse and metastasis.

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CONCLUSION

In conclusion, the molecular basis of chemoresistance in cancer involves a complex interplay of genetic mutations, altered drug transport, enhanced DNA repair, epigenetic regulation, tumor microenvironment influences and cancer stem cell biology. These mechanisms allow cancer cells to evade the cytotoxic effects of chemotherapy and continue to survive and proliferate. A deeper understanding of these molecular processes is important for the development of novel therapeutic strategies, including combination therapies, targeted inhibitors and personalized treatment approaches aimed at overcoming chemoresistance and improving patient outcomes.