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Mechanisms of drug resistance: Molecular insights into transporters and signal transduction pathways.

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Introduction

Drug resistance remains a critical challenge in the treatment of numerous diseases, particularly cancer, infectious diseases, and chronic conditions requiring long-term therapy. The failure of drugs to exert their therapeutic effect not only complicates treatment protocols but also increases morbidity, mortality, and healthcare costs. A growing body of research has focused on the molecular underpinnings of drug resistance, particularly emphasizing the roles of efflux transporters and signal transduction pathways [1].

One of the most well-documented mechanisms of drug resistance is the overexpression of ATP-binding cassette (ABC) transporters. These membrane-bound proteins actively expel drugs from cells using ATP hydrolysis, thereby reducing intracellular drug concentrations below therapeutic levels. Among the most studied is P-glycoprotein (P-gp), encoded by the MDR1 (ABCB1) gene, which contributes to multidrug resistance (MDR) in various cancers. Other ABC transporters such as MRP1 (ABCC1) and BCRP (ABCG2) also play pivotal roles in pumping out chemotherapeutic agents, antibiotics, and antivirals [2].

Beyond physical drug efflux, alterations in drug targets themselves can lead to resistance. For example, mutations in kinases targeted by tyrosine kinase inhibitors (TKIs) in cancer—such as the T315I mutation in BCR-ABL or EGFR T790M—can reduce drug binding affinity, rendering treatments ineffective. This form of resistance emphasizes the evolutionary adaptability of disease-related proteins under therapeutic pressure [3].

Signal transduction pathways, which mediate cellular responses to environmental stimuli, are frequently rewired in drug-resistant cells. In cancer, aberrant activation of the PI3K/Akt/mTOR and RAS/RAF/MEK/ERK pathways contributes to survival and proliferation even in the presence of therapeutic agents. Feedback loops and cross-talk between these pathways often provide alternate routes for cell signaling, allowing the cell to bypass drug-induced inhibition [4].

Moreover, epigenetic modifications—such as DNA methylation, histone acetylation, and non-coding RNA regulation—can influence the expression of genes associated with drug metabolism, apoptosis, and transport. For instance, hypermethylation of tumor suppressor gene promoters may silence genes responsible for apoptosis, allowing cells to evade drug-induced death. Likewise, microRNAs (miRNAs) can regulate transporter and signaling protein expression, further contributing to resistance [5].

Conclusion

In conclusion, drug resistance is a multifactorial phenomenon involving a complex interplay of transporters, signaling pathways, genetic mutations, and epigenetic regulation. A deeper molecular understanding of these mechanisms not only elucidates how resistance arises but also guides the development of more effective, personalized therapeutic strategies. Continued research in this area is vital to preserving the efficacy of current treatments and discovering innovative solutions for drug-resistant diseases.

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