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Commentary

Epigenetic Modifications Driving Resistance to Chemotherapy in Lung Cancer

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DESCRIPTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, with chemotherapy serving as a cornerstone treatment modality for many patients. Despite initial responses, the emergence of chemotherapy resistance often leads to treatment failure and disease progression. A growing body of evidence points toward epigenetic modifications as critical drivers of this resistance, offering novel insights into the molecular mechanisms underlying therapeutic failure and potential avenues for overcoming it. Epigenetics refers to heritable changes in gene expression that do not involve alterations to the underlying DNA sequence. These modifications include DNA methylation, histone modifications and non-coding RNA regulation, all of which orchestrate chromatin architecture and gene transcription. In lung cancer, aberrant epigenetic landscapes contribute significantly to the acquisition of drug resistance by modulating genes involved in drug metabolism, apoptosis, DNA repair and cellular survival pathways.

One of the most well-characterized epigenetic mechanisms driving chemotherapy resistance is DNA hypermethylation of tumor suppressor gene promoters. Hypermethylation of genes such as *p16INK4a*, *RASSF1A* and *MLH1* leads to their transcriptional silencing, allowing lung cancer cells to evade cell cycle arrest and apoptosis induced by chemotherapeutic agents like cisplatin and paclitaxel. Notably, methylation of *MLH1*, a key mismatch repair gene, impairs DNA damage recognition, resulting in resistance to platinum-based chemotherapy. Histone modifications also play a pivotal role. Altered patterns of histone acetylation and methylation can modify chromatin accessibility, thereby influencing gene expression profiles associated with drug resistance. For example, increased activity of Histone Deacetylases (HDACs) has been observed in resistant lung cancer cells, leading to repression of pro-apoptotic genes. This epigenetic silencing contributes to enhanced survival following chemotherapy exposure. Consequently, HDAC inhibitors are under clinical investigation as agents that can reverse resistance and sensitize tumors to standard treatments.

Moreover, non-coding RNAs, especially microRNAs (miRNAs),modulate chemotherapy responses by targeting messenger RNAs involved in resistance pathways. Dysregulated miRNAs such as miR-21, miR-200c and miR-155 have been implicated in promoting Epithelial-to-Mesenchymal Transition (EMT), a process associated with resistance and metastatic potential. By suppressing genes that regulate apoptosis and drug uptake, these miRNAs enhance the chemoresistant phenotype in lung cancer cells. Epigenetic plasticity also facilitates reversible transitions between drug-sensitive and drug-tolerant states, allowing subpopulations of lung cancer cells to survive chemotherapy. These “drug-tolerant persister” cells can evade cell death through epigenetic remodeling, only to repopulate the tumor once therapy pressure is relieved. Targeting the epigenetic regulators responsible for maintaining this transient state may be key to preventing relapse.

In addition to intrinsic tumor cell changes, the Tumor Microenvironment (TME) influenced by epigenetic modifications can contribute to chemotherapy resistance. Epigenetic alterations regulate the expression of cytokines and growth factors that modulate immune cell infiltration and extracellular matrix remodeling, creating a protective niche for resistant cells. This highlights the importance of considering epigenetic therapy not only as a tumor cell-directed approach but also as a means to modulate the TME. The therapeutic implications of these insights are profound. Epigenetic drugs such as DNA methyltransferase inhibitors (e.g., azacitidine, decitabine) and HDAC inhibitors (e.g., vorinostat, romidepsin) have shown promise in preclinical lung cancer models by restoring chemosensitivity. Combination strategies pairing epigenetic agents with conventional chemotherapy or targeted therapies are currently under clinical evaluation and represent a promising frontier in overcoming resistance.

Despite these advances, challenges remain. The heterogeneity of epigenetic alterations across lung cancer subtypes and individual patients necessitates personalized approaches. Moreover, off-target effects and toxicity associated with epigenetic drugs require careful consideration. Future research should focus on identifying predictive biomarkers to guide patient selection and optimize therapeutic regimens.

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CONCLUSION

Epigenetic modifications are central to the development of chemotherapy resistance in lung cancer, influencing multiple pathways that enable tumor cells to evade drug-induced cytotoxicity. The reversible nature of epigenetic changes provides a unique therapeutic opportunity to re-sensitize resistant tumors and improve clinical outcomes. Targeting aberrant DNA methylation, histone modifications and non-coding RNA dysregulation holds promise in disrupting resistance mechanisms. The integration of epigenetic therapies into standard treatment paradigms could transform the management of lung cancer by overcoming one of the most formidable obstacles chemotherapy resistance.

Advancing this field will require comprehensive characterization of epigenetic landscapes in patient tumors, development of precise biomarkers and refinement of combination strategies to maximize efficacy while minimizing toxicity. As we deepen our understanding of epigenetic regulation in lung cancer, the prospect of durable, effective therapies that circumvent resistance becomes increasingly attainable.