Title: Identification of Crucial Drug Targets and Pathways to Reprogram Drug Resistance Through Epigenetic Modulation in Advanced Lung Cancer Using Integrated Bioinformatics Approach

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Abstract: Resistance to chemotherapy, which is demonstrated in almost every patient with advanced-stage lung cancer (ALC), underscores an urgent need to unravel the underlying molecular mechanisms and identify novel strategies to overcome drug resistance. In the present study, an attempt was made to identify epigenetic targets and modulators that can be exploited to reverse chemotherapeutic resistance in ALC. We performed an integrative analysis to identify epigenetically regulated key genes involved in drug resistance using clinical data from the "TCGA-LUAD" project. Transcriptomic and epigenetic analysis of 71 advanced-stage samples, compared with normal samples, revealed 8532 unique differentially expressed genes (DEGs) in ALC (5752 upregulated and 2779 downregulated genes) and 8313 differentially methylated genes (DMGs) (5816 hypermethylated and 2497 hypomethylated). A total of 143 methylation-driven drug resistance-related genes (mDRGs) were identified through the intersection of DEGs, DMGs, and drug-resistant genes in cancer. By correlating DMGs observed in ALC with crucial genes responsible for drug resistance, 10 hub genes, namely, FGFR2, BDNF, GFRA1, AGTR1, ENO1, GATA2, NTRK3, CXCL12, MSX1, and FGF2, were identified, which are supposed to be associated with the development of lung cancer and therapeutic resistance as well. Functional enrichment analysis revealed that mDRGs were mainly involved in the MAPK signaling pathway, Ras signaling pathway, chemokine signaling pathway, ErbB signaling pathway, and GPCR downstream signaling. Finally, the study identified three key genes, namely, AGTR1, NTRK3, and GFRA1, which can predict the survival of lung cancer patients as well as provide novel mechanisms of drug resistance in ALC. The findings were further validated using GEO datasets (GSE81089 and GSE66836) and were found to be consistent.

Key words: bioinformatics, drug resistance, epigenetics , GFRA1, GTR1, lung cancer, NTRK3

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