**Transcriptomics Profiling of Peripheral Blood Mononuclear Cells in Mustard Lung: A Systems Biology Approach**

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**Introduction:** Sulfur mustard (SM) is a substance that causes blisters and has been repeatedly used by Iraq in chemical warfare against more than 100,000 Iranians. The main issue for these people is various pulmonary problems similar to chronic obstructive pulmonary disease (COPD).

**Materials and Methods:** Our study analyzed the total RNA profile extracted using the RNA-seq technique from peripheral blood mononuclear cells (PBMCs) isolated from Mustard Lung (ML) patients of all three groups (Severe, Moderate, and Mild) in terms of disease in healthy control (HC) subjects on the BGISEQ platform (Paired-end, 7GB data, and rRNA depletion). However, given the severe group's importance in clinical problems, we prioritized studying this group. Differentially expressed genes (DEGs) of the severe group versus HC were obtained using the limma package. DEGs were analyzed through bioinformatics tools, and their gene ontology (GO) and enrichment analysis (EA) were evaluated. Then, String-db and Cytoscape tools were used to search for the most important functional genes.

**Results:** We identified *SERPINA1*, *MAPK3*, *MMP9*, *FOXO3*, *SLC4A1*, *FCGR3B*, *CXCR2*, *PTGS2*, *HBA2*, *GPX1*, *IL1RN*, *IFNG*, *RPS29*, *CXCL1*, *FPR1*, and *RPS9* genes using hub and bottleneck criteria. Based on the analysis of important genes, several biological pathways were identified, including innate immunity, inflammatory response, and activation of neutrophils, cellular response to cytokines, and cellular response to oxidative stress, lipoxygenase pathway, and macrophage differentiation.

**Conclusion:** Innate immunity and neutrophils play a crucial role in the pathogenesis of these individuals. The signaling pathways of interleukins 4, 10, and 13 stimulate the differentiation of lung macrophages (MQs) into M2, essential for repair, remodeling, and inflammation. Additionally, reactive oxygen species (ROS) activate Protein kinase B (PKB), also known as AKT, through Phosphoinositide 3-kinases (PI3K) and increase the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which results in decreased histone deacetylase 2 (HDAC2) being one of the important pathways of pathophysiology in these patients.

**Keywords:** Mustard Lung, Systems Biology, Transcriptomics, RNA-Seq, Bioinformatics Analysis