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A multi-omic analysis to characterize cigarette smoke induced molecular alterations in esophageal cells

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Abstract

Esophageal squamous cell carcinoma (ESCC) is one of the most common cancers with high mortality rate. Smoking is one of the established risk factors of ESCC. However, there is limited data on molecular alterations associated with cigarette smoke exposure in esophageal cells. Understanding the effects of cigarette smoke on esophageal squamous epithelial cells at a molecular level would lead to a better understanding of the pathobiology of ESCC which has implications for identification of early biomarkers and therapeutic targets. To investigate the effect of cigarette smoke exposure, we developed a cell line model where Het1A cells (non-neoplastic human esophageal epithelial cells) were chronically treated with cigarette smoke condensate (CSC) for 2 months, 4 months, 6 months and 8 months. We carried out comparative proteomic, phosphoproteomic and whole exome sequencing analyses on CSC treated and untreated cells. Increased cell proliferation, invasion and anchorage independent growth of Het1A cells was observed after chronic exposure to cigarette smoke. Using quantitative proteomic and phosphoproteomic analyses, we identified 35 proteins and 118 phosphoproteins that showed differential expression. Bioinformatics analysis of differentially expressed proteins and phosphoproteins showed enrichment of molecules involved in DNA damage response pathway. To further understand the mutational burden associated with cigarette smoke, we did whole exome sequencing of CSC treated and untreated cells which also revealed mutations and copy number alterations in genes associated with DNA damage response. By correlating WES, proteomic and phosphoproteomic results, we observed potential loss of function in HMGN2 and MED1 that were reported as potential tumor suppressors and are known to play important role in DNA damage response. We also observed decreased expression of HMGN2 in tissue section of ESCC. Overexpression of HMGN2 and MED1 lead to decreased proliferative and invasive ability of CSC treated cells. These findings suggest that cigarette smoke affects genes and proteins associated with DNA damage response pathways which might play a vital role in development of ESCC.