Presenting Author Name
Haziqa Kassim

Presenting Author Category
Non-Trainee

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Abstract Title
Smoke-Free? Not Quite: E-Cigarette Exposure Reshapes Lung DNA Methylation and Gene Expression

Background
The rising popularity of e-cigarettes among young adults has raised concerns about their long-term impact on lung health. We have previously shown e-cigarette use changes the gene expression profile of lungs but don't know whether these changes persist long term. We hypothesized that e-cigarette use also alters the regulation of lung gene expression that can lead to long-term changes.

Objective
We identified DNA methylation (DNAm) changes associated with e-cigarette use and performed an expression Quantitative Trait Methylation analysis to determine which alterations in DNAm patterns were linked to gene expression.

Methods
Samples of healthy tissue were obtained from lung resections in 21 individuals (18-53 years old) who underwent surgery for a primary spontaneous pneumothorax. We extracted both DNA and RNA from lung tissues, quantifying DNAm using the Infinium MethylationEPIC array. We performed an epigenome-wide association study to identify DNAm changes associated with e-cigarette use, and subsequently identified which DNAm patterns were associated with gene expression changes.

Results
We identified 525 DNA methylation sites significantly associated with changes in activity of 486 genes, which were mainly involved in immune response, inflammation and cell differentiation. Among these, 14 genes are associated with e-cigarette use, 12 of which contained differentially methylated regions (DMRs). However, the majority of differentially methylated sites ($n = 1243$, FDR < 0.05) and DMRs ($n = 484$, FDR < 0.05) did not overlap with acute gene abundance differences. These non-overlapping regions may represent sites of biological priming in lung tissue, reflecting longer-term epigenetic alterations beyond acute transcriptional responses.

Conclusion
E-cigarette use alters DNAm at specific loci, some of which acutely modulate gene expression, providing insight into potential mechanisms linking e-cigarette exposure to future disease risk. Beyond these immediate effects, long-term DNAm changes in e-cigarette users may reflect persistent biological reprogramming that primes lungs for heightened immune responses, increasing vulnerability to chronic disease.

Authors

Name	Role	Profession
Haziqa Kassim	Presenting Author	
Doris Onuzulu	Co Author	
Ola Salama	Co Author	
Shana Kahnamoui Zadeh	Co Author	
Dr. Biniam Kidane	Co Author	Associate Professor
Dr. Christopher D. Pascoe	Co Author	Associate Professor
Dr. Meaghan J. Jones	Co Author	Associate Professor