

Presenting Author Name

Anam Ara

Phonetic spelling of your (full) name

Anam Ara

Presenting Author Category

PhD Student

Supervisor Name

Meaghan Jones

Research Category

Basic Science

Abstract Title

Primed for re-exposure: Early-life cannabis smoke exposure reshapes lung immune programming with implications for child respiratory health

Authors

Name	Role	Profession
Anam Ara	Presenting Author	Graduate
Doris Onuzulu	Co Author	Post Doc
Haziqa Kassim	Co Author	Lab Tech
Sujata Basu	Co Author	Lab tech
Meaghan Jones	Co Author	Associate Professor

Background

Children are exposed to cannabis smoke prenatally through maternal use and postnatally through secondhand exposure, coinciding with a critical window of lung and immune development. Whether this early-life exposure leaves a lasting imprint on the lung's response to future respiratory challenges is poorly understood.

Objective

This study aimed to determine whether early-life cannabis smoke exposure primes the lung immune system, altering its transcriptional and epigenetic response to adult re-exposure.

Methods

Female mice were exposed to cannabis smoke during mating, pregnancy, and weaning, modelling maternal and early postnatal exposure in offspring; controls remained unexposed. In adulthood, half of each group underwent a second exposure, separating early-life exposure alone, adult exposure alone, and their interaction (priming). Whole-lung DNA methylation and gene expression were profiled, focusing on

immune signalling, with integrative eQTM analysis testing whether methylation changes functionally underlie transcriptional shifts.

Results

Chemokine genes central to immune cell recruitment showed a striking, exposure-history-dependent reversal. *Ccl12* was upregulated after early-life exposure alone ($\log_2FC=1.72$, $p=3.30\times 10^{-6}$) and adult-only exposure ($\log_2FC=1.69$, $p=1.52\times 10^{-5}$), but repressed under combined exposure ($\log_2FC=-2.36$, $p=3.72\times 10^{-6}$). *Ccl25* showed the same pattern (early-life: $\log_2FC=0.66$, $p=1.11\times 10^{-4}$; adult-only: $\log_2FC=0.78$, $p=1.25\times 10^{-5}$; priming: $\log_2FC=-0.85$, $p=2.95\times 10^{-4}$). Candidate regulators were differentially methylated: a *Taf11* CpG (cg34887209, $db=0.075$, $p=4.78\times 10^{-6}$) in the long-lasting effect; a *Smad2*-associated CpG ($db=-0.051$, $p=1.94\times 10^{-4}$) in priming; and a *Gtf2ird1*-associated CpG ($db=-0.054$, $p=1.78\times 10^{-4}$) in the adulthood effect. However, eQTM and permutation testing showed no genome-wide enrichment between methylation and expression changes.

Conclusion

These findings support our hypothesis that early-life cannabis smoke exposure primes the lung immune system, reprogramming rather than simply exaggerating chemokine responses to re-exposure. The methylation-expression dissociation points to histone modification, now being tested via CUT&Tag, as the more likely carrier of early-life memory. Clinically, these results suggest children exposed prenatally or postnatally to cannabis smoke may carry a hidden, reactivatable vulnerability shaping their lung's response to future respiratory insults.

Table/Figure File

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