

Epigenetic and Spatial Transcriptomic Reprogramming of the Developing Brain Following Prenatal E-Cigarette Vapor Exposure

Maternal smoking is a well-established risk factor for adverse neurodevelopmental outcomes. Emerging evidence suggests that prenatal exposure to e-cigarette vapor (PeCV) similarly perturbs brain development; however, the underlying epigenetic mechanisms remain poorly defined. Using a rat PeCV model, we implemented an integrated multiomic strategy combining single-nucleus RNA sequencing (snRNA-seq), single-nucleus ATAC-seq (snATAC-seq), single-cell joint profiling (Paired-Tag) of H3K27me3–H3K4me1 epigenome and transcriptome, and spatial transcriptomics to delineate molecular reprogramming in the neonatal brain. We found that PeCV disrupted excitatory–inhibitory (E/I) balance, the relative abundance of excitatory and inhibitory neuronal populations in the prefrontal cortex and hippocampus. Our single-cell joint epigenomic and transcriptomic profiling revealed PeCV-induced remodeling of H3K27me3–H3K4me1 bivalent chromatin states within gene bodies of cell type–specific genes, accompanied by concordant differential gene expression. We also found that PeCV induced a H3K27me3–H3K4me1 bivalent epigenetic regulation on genes preferentially governing neuronal differentiation and cell fate specification. Our spatial transcriptomic analysis identified region-specific vulnerability, with the caudate putamen exhibiting the highest number of differentially expressed genes. Gene set enrichment analysis demonstrated significant downregulation of dendrite morphogenesis pathways in the caudate putamen and impaired synaptic structural programs in the medial prefrontal cortex. Functionally, PeCV induced global hyperexcitability and sensitized dopaminergic signaling in the neonatal brain. Collectively, these findings demonstrate that prenatal e-cigarette vapor exposure induces coordinated epigenetic and spatial transcriptomic reprogramming during early brain development, providing mechanistic insight into molecular pathways that may contribute to increased susceptibility to neurodevelopmental disorders.

Authors:

Submitter: Charles Wang, Professor & Director, Loma Linda University Center for Genomics, Loma Linda

Wanqiu Chen, PhD, Loma Linda University Center for Genomics

Zhong Chen, PhD, Loma Linda University Center for Genomics