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Paired-Tag Single-Cell Joint Profiling of H3k27me3-H3k4me1 and Transcriptome Revealed Prenatal E-Cigarette Induced Abnormal Neuronal Lineage Development in Rat Neonatal Prefrontal Cortex

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We have demonstrated that prenatal electronic-cigarette (e-cig) exposure led to a disruption in the ratio of excitatory vs. inhibitory neurons, i.e., E/I imbalance in the postnatal day 7 (P7) rat brain. We hypothesize that this E/I imbalance is caused by prenatal e-cig induced epigenomic reprogramming that alters the differentiation of neuronal progenitors during the early brain development. Histone modifications vary greatly in different cells and directly correlating cell type specific gene expression with histone modifications at single-cell level remained challenging. Here we performed single-nucleus joint profiling of transcriptome and histone modifications, namely H3K27me3 and H3K4me1, in P7 rat prefrontal cortex. We found that e-cig induced unique H3K27me3-H3K4me1 modifications and differential expression as the consequence in many cell type-specific genes. We demonstrated that H3K27me3-H3K4me1 bivalency regulated the neuronal lineage differentiation by controlling the accessibility of promoter regions in genes responsible for cell specifications. In addition, H3K27me3-H3K4me1 methylations also altered the expression of circadian genes involved in circadian entrainment including calcium signaling genes Cacna1c, Camk2b, Ryr2, and genes in cAMP and protein kinase signaling transduction, as well as synaptic transmission. These results suggested that nicotine addiction could be epigenetically imprinted at a very early stage of brain development. Our study showed a profound effect of epigenomic regulation of histone marks by prenatal e-cig exposure on neuronal lineage development and highlighted a new underlying epigenetic mechanism of nicotine addiction.