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Single Nucleus Transcriptome and Chromatin Analysis Identifies Basal Ganglia Differentially Expressed Genes for SIV Infection in Rhesus Macaques: Preliminary Findings

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Simian immunodeficiency virus (SIV) infected-rhesus macaque is a well-established model for understanding the complex pathology of HIV. We analyzed single-nucleus RNA sequencing (snRNA-seq) and single-nucleus ATAC sequencing (snATAC-seq) in three brain regions [frontal cortex (FC), basal ganglia (BG), and thalamus (TH)] between SIV-infected and non-infected rhesus macaques (N=6). After quality control, a total of 24,010 transcripts and 117,409 nuclei were analyzed (1,502/nucleus). Our preliminary analysis of snRNA-seq in BG from a subset of the samples revealed 5 major cell types, including microglia (13%) and astrocytes (4%). We identified 272 differentially expressed genes (DEGs) in microglia between the macaques with and without SIV (FDR < 0.05) [e.g., IFI44L (avg_diff = 1.61, padj= 5.76e-125), MX1 (avg_diff = 1.04, padj= 1.24e-60), HDAC9 (avg_diff = -0.56, padj =1.23e-46)]. These DEGs were enriched for multiple GO terms including neuron projection development and cell adherence. In astrocytes, 457 DEGs were significant, e.g., COX1 ((avg_diff = -1.25, padj = 2.29e-47), COX2 (avg_diff = -1.40, padj = 1.48e-58). Interestingly, snATAC-seq analysis identified differential chromatin accessibility peaks near IFI44L between the macaques with and without SIV across multiple cell types (e.g., microglia, FDR=5.76E-125), suggesting that SIV infection alters epigenetically regulated IFI44L expression, which plays a critical role in inflammation. These preliminary findings provide new insight into the region and cell-type specific transcriptomic alterations for SIV infection in the primate brain. Future study will explore the transcriptomic and epigenomic impacts of cocaine use in SIV infection.