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Cell-type specific genomics and transcriptomics of HIV in the brain

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Characterization of organ-specific reservoirs is critical as we look toward a functional cure for HIV, yet in depth molecular studies of the brain reservoir are lacking. Genomic integration is a key step in establishing the reservoir. In T-cells, HIV preferentially integrates into active, highly expressed regions of the genome; however, integration and its effects have not been studied in the brain. We sequenced integration sites (IS) from sorted neurons and glia from frontal cortex of HIV+ donors. We identified 1,279 IS, predominantly from the glial cell fraction of HIVE encephalitis (HIVE) cases. Glial IS are found preferentially in active, gene dense regions. As compared to T-cells, there is significantly less clonal and recurrent integration. Single nucleus RNA-sequencing of HIV- and HIVE brains revealed that IS are preferentially found in highly expressed microglial genes and genes that are differentially expressed in HIVE vs. HIV- microglia. Furthermore, microglia with active viral transcription have elevated expression of core markers of microglial activation and decreased expression of markers of proliferation. Notably, changes in gene expression in HIVE microglia were accompanied by rewiring of the 3D-genomic landscape as assessed by Hi-C chromosome conformation capture, and IS were found in sites that had undergone changes in cis-chromosomal contacts. Taken together, these findings link HIVE to changes in microglial gene expression and spatial genome organization that influence integration site selection. Integration and viral transcription in turn enhance microglial activation. Neuroinflammatory mechanisms play a critical role in promoting the spread of HIV in HIVE. Supported by NIDA *R61DA048207*.