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Altered microglial genome structure and transcription in HIVE impact HIV integration

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In CD4⁺ T-cells there is evidence for a vicious cycle model of HIV infection, whereby infection causes activation of T-cells, which is associated with broad changes to 3D-genome architecture and gene expression that in turn enhance HIV integration and replication. HIV also infects microglia, leading to HIV-associated neurocognitive disorder in 20-50% of people living with HIV; however, it is not known if microglia also undergo remodeling of genome architecture and gene expression in the setting of HIV infection and how these changes impact infection. We studied primary human microglia in the setting of HIV encephalitis (HIVE) to understand how active viral replication alters microglial transcription, 3D-genome architecture, and viral integration. HIVE microglia underwent 3D restructuring of >6% of the genome. Regions that switched to a more open conformation contained genes relating to the immune response and had significantly higher expression in HIVE microglia by single-nucleus RNA-sequencing. HIVE microglia overall showed increased expression of microglial activation and immune markers, driven by a subset of microglia with active HIV transcription. Viral integration sites were found in highly expressed microglia genes and >75% were in regions of open chromatin defined by Hi-C. Furthermore, integration sites were enriched in regions that underwent changes in transcription, chromatin compartment, and cis-chromosomal 3D contacts. These findings link HIVE to changes in microglial gene expression and spatial genome organization that influence viral integration, providing important insights as to how HIV infection impacts microglial function and contributes to disease development and viral persistence. Funded by R61DA048207, R01DA054526, and U24MH100931.