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Altered Microglial Genome Structure and Transcription in HIVE Impact HIV Integration

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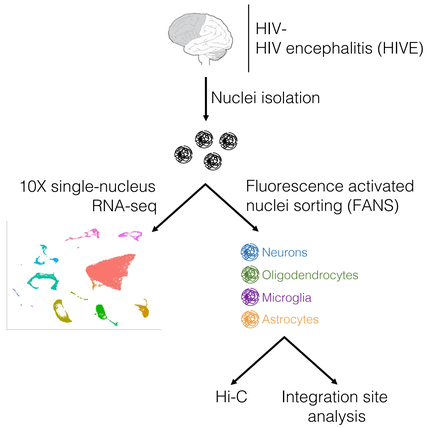
Background

- HIV readily infects microglia in the brain, where it persists despite antiretroviral therapy and causes neurologic disease, including HIV-associated neurocognitive disorder and HIV encephalitis (HIVE).
- The mechanisms by which HIV persists in microglia and causes disease are unknown.
- Here we study microglia from HIVE brain tissue in order to understand how active viremia impacts microglial function and viral persistence through viral integration.

Methods

Nuclei were isolated from human postmortem frontal cortex brain tissue from the Manhattan HIV Brain Bank from HIV negative controls (HIV-) and HIV positive cases with encephalitis (HIVE). Nuclei were submitted to integration site (IS) analysis, Hi-C, and 10X Chromium single-nucleus RNA-seq (snRNA-seq).



Conclusions

- HIVE leads to widespread 3D-genome restructuring in microglia , including at immune loci, which is associated with transcriptional upregulation of these genes. Some of this restructuring may be mediated by YY1 and CTCF.
- Regions of the genome that undergo 3D-genomic and transcriptional changes in HIVE are targeted for viral integration.

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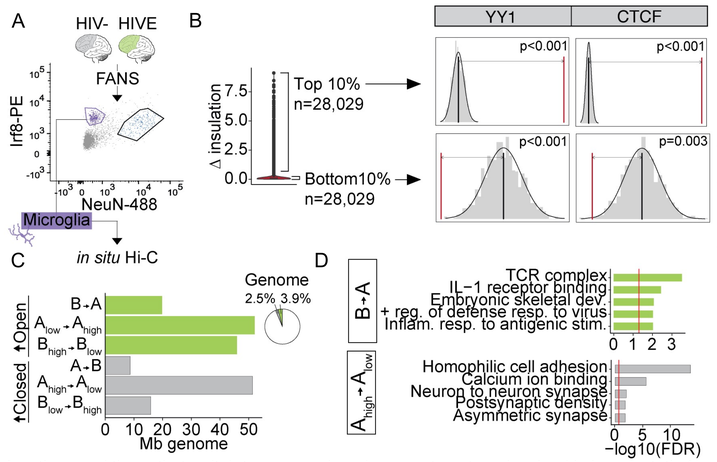
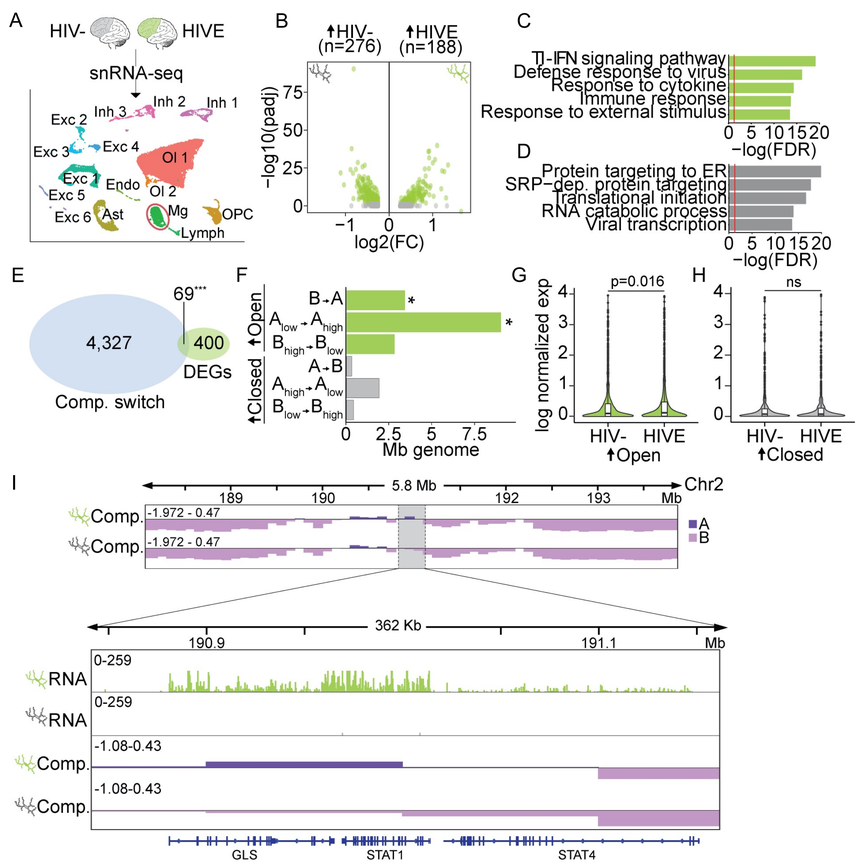
Results

1 Microglia in HIV encephalitis undergo 3D-genomic restructuring at immune loci



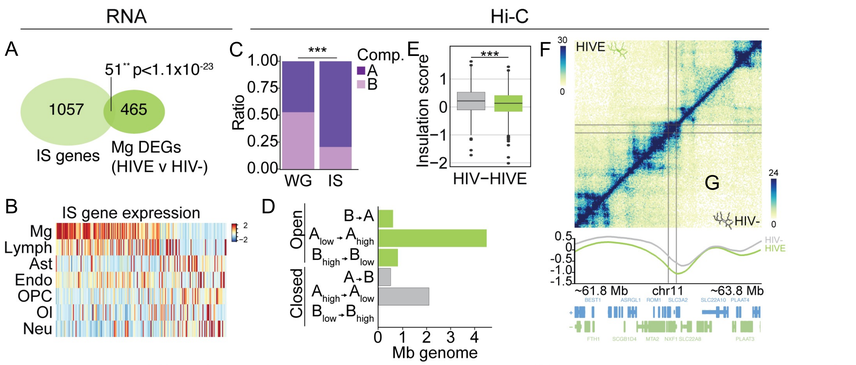
HIVE microglia undergo changes in 3D domain and looping structure as measure by insulation score in regions bound by the chromatin structuring proteins YY1 and CTCF (**B**). HIVE microglia also undergo changes to chromatin compartments, defined as open/A or closed/B compartments, of >6% of the genome (**C**). Genes switching to a more open compartment are involved in immune functions and those that switch to a more closed compartment are involved in homeostatic functions related to neurons (**D**).

2 3D restructuring drives increased expression of a subset of genes in HIVE microglia



Differential expression of HIVE vs. HIV- microglia reveals 188 upregulated genes, related to the immune response (**B, C**) and 276 downregulated genes related to pathways downregulated as part of the antiviral response (transcription, translation, **D**). 69 of the DEGs are found in regions that undergo compartment switching in HIVE, significantly higher overlap than expected by chance (**E**). Of these, the majority are switching to a more open compartment (**F**) and are significantly more highly expressed in HIVE microglia as compared to HIV- (**G**). An example of this is shown for a region of Chr2 that contains STAT1 and STAT4, transcription factors that are involved in mediating the IFN response (**I**). This region switches from the B (closed) in HIV- to A (active) compartment in HIVE and is significantly more highly expressed in HIVE microglia as well.

3 HIV integration sites (IS) are found in regions of 3D-genomic and transcriptomic alterations in HIVE



HIV integration sites (IS) are found in highly expressed microglial genes (**B**) and are overrepresented among DEGs in HIVE microglia (**A**). When looking at Hi-C data, we see that IS are very highly enriched in the A compartment relative to the whole genome (WG) (**C**) and that IS that undergo a compartment switch in HIVE are mostly in the A compartment (**D**). We also see evidence for preferential integration at regions that undergo changes in domain and looping structure as measured by insulation score. IS have a significant lower insulation score in HIVE (**E**), shown for an example locus on chr11 that contains two IS (gray lines, **F**).