NLRP3 inflammasome signaling pathway is up-regulated in brains of people with HIV-1.

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BACKGROUND

Human immunodeficiency virus type 1 (HIV-1) causes a chronic disease that may be associated with neuroinflammation. In the setting of neuroinflammation, people with HIV-1 (PWH) can develop cognitive impairment. With active brain viral replication, this reflects HIV encephalitis (HIVE). In the absence of replicating HIV, mechanisms underlying brain inflammation despite viral suppression on antiretroviral therapies (ART) are unclear. One hypothesis is that HIV-1 latent reservoir in the brain give rise to chronic inflammation and cognitive impairment. The molecular mechanisms of this neuroinflammation have not been well characterized and the data for HIV-1 latency in the central nervous system are lacking. Here, we present data from single nuclei RNA transcriptome sequencing analyses on post-mortem brains of PWH.

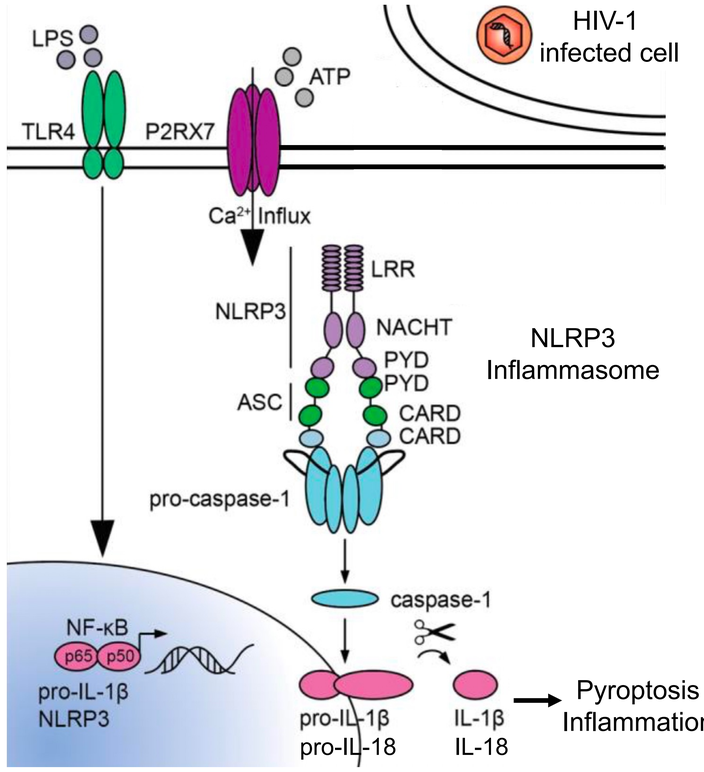
METHODS

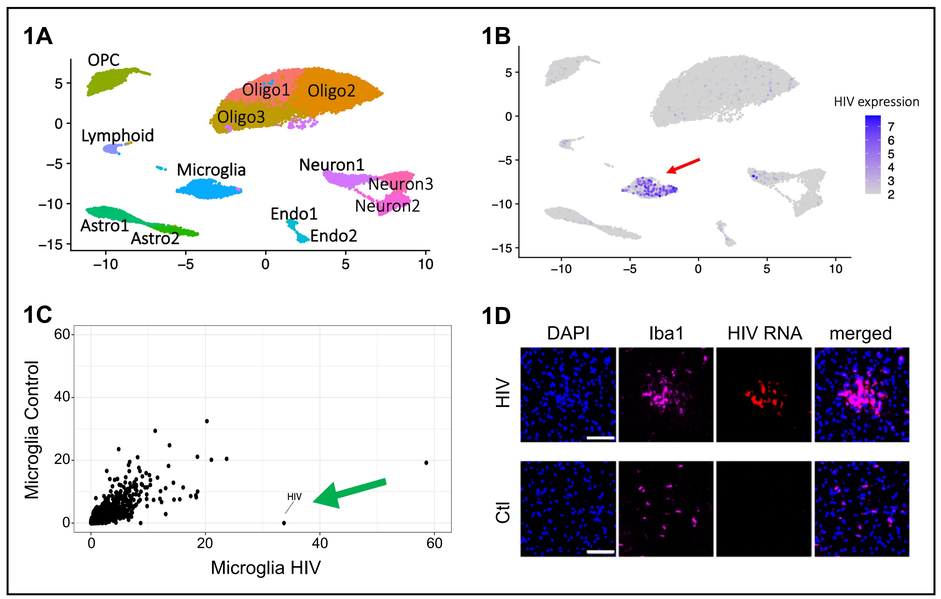
Using 10x Genomics Chromium platform, we performed high-throughput single nucleus RNA sequencing (snRNA-seq) on post-mortem frontal cortex brain tissue of three different groups: 1) control subjects (n=2), 2) PWH without HIVE (-HIVE, n=3), 3) PWH with HIVE (+HIVE, n=3). The HIV -HIVE group had an average CD4 T lymphocyte count of 516 and viral load (VL) of 440. The HIV +HIVE group had an average CD4 T lymphocyte count of 11 and VL of 623,068.

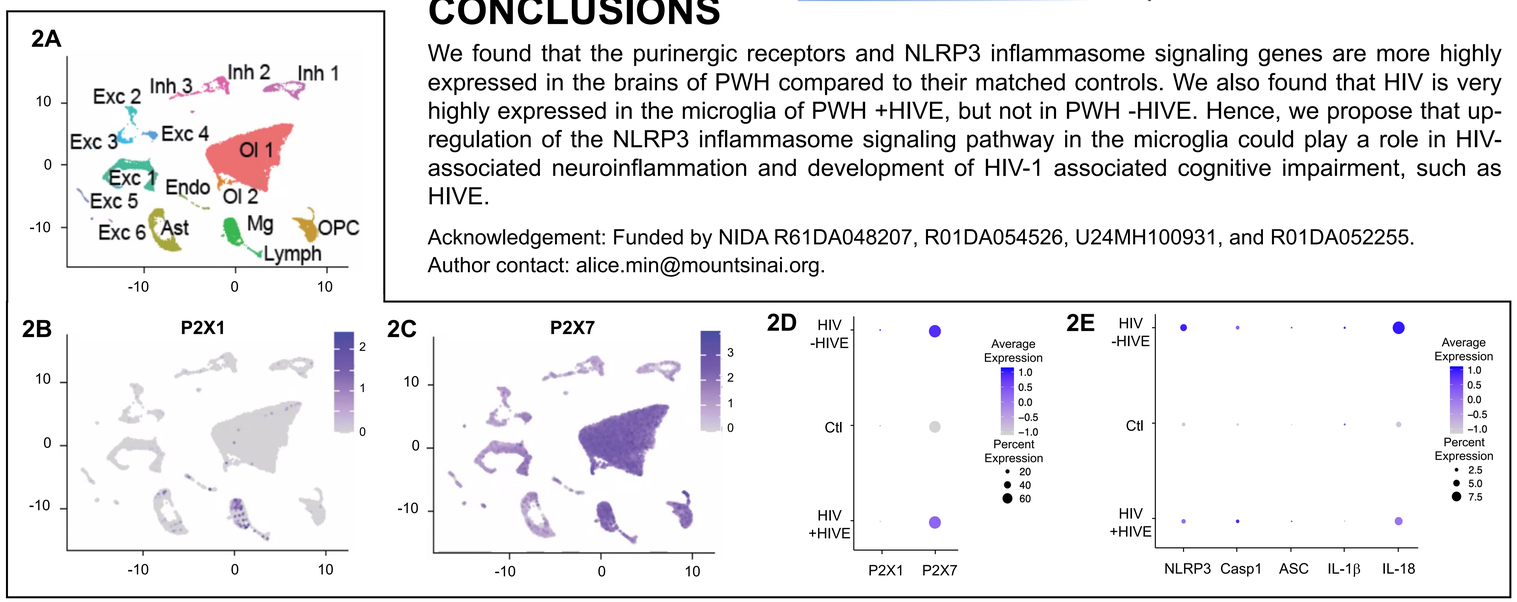
Etiology of HIV-1 associated cognitive impairment has been attributed to neuroinflammation as a result of latent cellular reservoir. There is growing evidence that microglia constitute a major reservoir of HIV-1. We found that **microglia express one of the highest levels of HIV-1 transcript in post-mortem brains of PWH**. In addition, **genes of the NLRP3 inflammasome signaling pathway are up-regulated in the brains of PWH** that could contribute to HIV-associated neuroinflammation and development of HIV-1 associated cognitive impairment.

RESULTS

Cell-type specific clustering resulted in separation of the major cell types (oligodendrocyte precursors, myeloid cells, endothelial cells, microglia, multiple subtypes of astrocytes and oligodendrocytes, and neurons) (Fig 1A). HIV transcript level was significantly elevated in a subset of microglia in post-mortem brains of HIV +HIVE group (Fig 1B,C), but not in post-mortem brains of HIV -HIVE group. Dual RNA-FISH assays with probes complementary to Iba1 microglial marker and HIV RNA confirmed microglial cells expressing high level of HIV RNA (Fig 1D). In PWH +HIVE, HIV transcripts represented the top 0.3% of the most highly expressed transcript in the microglial transcriptome. There was elevated transcription of pro-inflammatory signaling genes in the PWH compared to their matched controls. These genes included the purinergic receptors (P2X1, P2X7), NLRP3 inflammasome signaling components (NLRP3, Casp1, ASC), and pro-inflammatory cytokines (IL-1β, IL-18) (Fig 2A-E).







CONCLUSIONS

We found that the purinergic receptors and NLRP3 inflammasome signaling genes are more highly expressed in the brains of PWH compared to their matched controls. We also found that HIV is very highly expressed in the microglia of PWH +HIVE, but not in PWH -HIVE. Hence, we propose that up-regulation of the NLRP3 inflammasome signaling pathway in the microglia could play a role in HIV-associated neuroinflammation and development of HIV-1 associated cognitive impairment, such as HIVE.

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