Single-nucleus multi-omics reveals dysfunction in multiple glial cell types in brain tissue of PWH

606

Kriti Agrawal[*1], Junchen Yang[*1], Jay Stanley[1], Chang Lu[1], Nicholas Jacobs[1], Haowei Wang[1], Declan Clarke[1], Le Zhang[1], Anita Huttner[1], Mark Gerstein[1], Yuval Kluger[1], Serena Spudich[1], on behalf of the Y-SCORCH study team.
[1]Yale University, New Haven, CT, USA

BACKGROUND

- What are the key cell populations and pathways affected by HIV that may be targeted in therapies for HIV-associated CNS dysfunction in the insular cortex (INS), prefrontal cortex (PFC), and ventral striatum (VST)?

HIV infection has widespread effects on the central nervous system (CNS), yet its localized impact on distinct brain regions and cell types remains unclear.

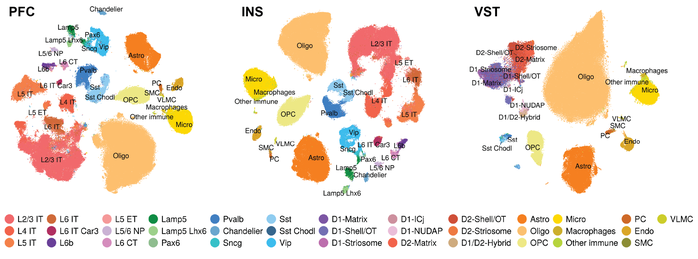
METHODS

Nuclei from frozen post-mortem INS, PFC, and VST of 20 PWH and 13 PWoH were profiled using 10x Genomics Multiome. Reference atlases identified major cell types. EdgeR performed pseudobulk DE analysis between PWH and PWoH within cell types and regions.



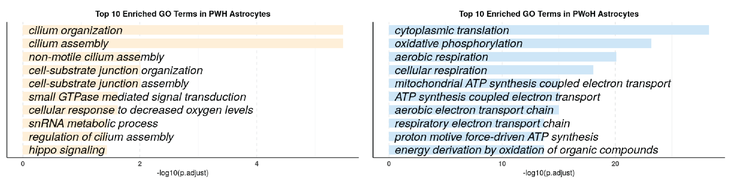
RESULTS

We found large populations of neuronal and glial cells across each region- and region-specific cell types.



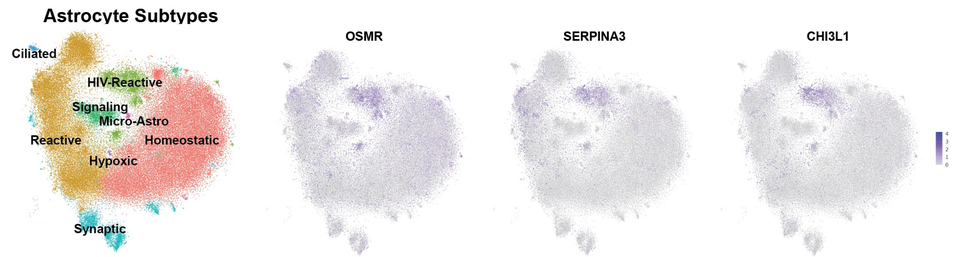
Astrocytes

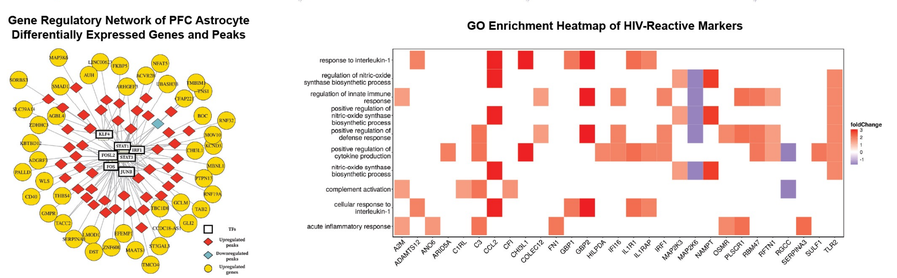
Pathway analysis of astrocytes exhibits an increase in reactive signatures with many cilium related pathways and possible metabolic dysfunction shown by downregulation of metabolic genes.



PWH have signatures of dysfunction in multiple glial cell types which are most pronounced in microglia and astrocytes. Microglia from PWH have upregulation of pathways and genes related to *immune activation* and *metabolic dysfunction*. Astrocytes from PWH have a unique population of reactive cells marked by expression of *SERPINA3*, *CHI3L1*, and *OSMR* and exhibit signatures of *metabolic dysfunction*.

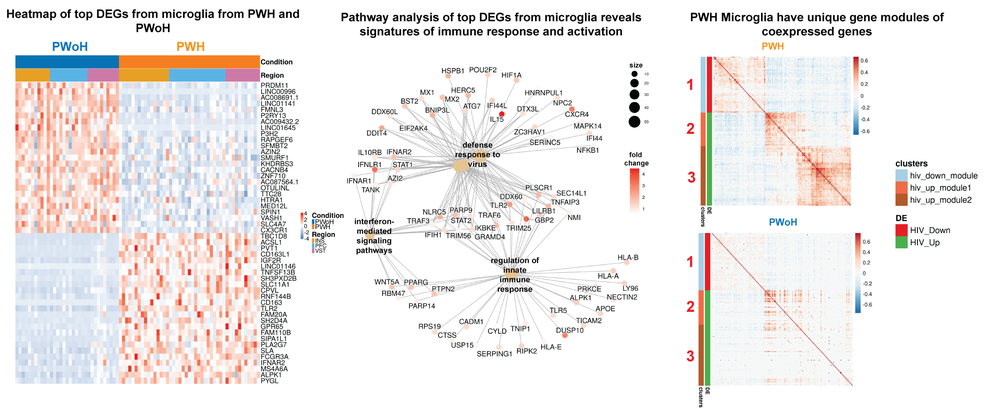
We found unique subtypes of astrocytes including one specific to PWH (HIV-Reactive). Gene regulatory network analysis revealed transcriptional and epigenetic networks related to astrocyte reactivity increased in HIV. The unique HIV-Reactive population has upregulation of several genes related to complement activation and interleukin signaling.



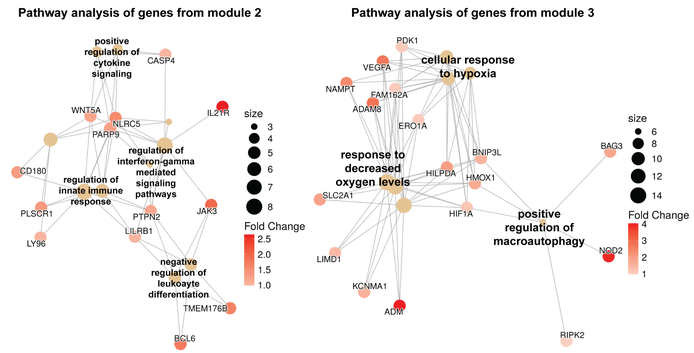


Microglia

Top differentially expressed genes from microglia are related to immune response and activation, Microglia from PWH have 2 unique modules of co-expressed genes that are upregulated.



Genes from modules 2 and 3 have unique function, with module 2 co-expressing genes that are primarily related to cytokine signaling and immune response and module 3 co-expressing genes related to hypoxia



CONCLUSIONS

Our study reveals broad glial dysfunction in PWH suggesting a persistent glial response to HIV. Moreover, these changes appear to mostly be associated to immune activation and metabolic dysfunction, suggesting alterations in key glial function in PWH. Some of the changes that we found were both transcriptional and epigenetic and understanding these changes helps to elucidate disease etiology and suggests potential targets for therapeutics to suppress these dysfunctional and activated glial cells.

ADDITIONAL KEY INFORMATION

Preprint:
https://www.biorxiv.org/content/10.1101/2025.02.05.636707v1

Author Contact Information:
Kriti Agrawal, kriti.agrawal@yale.edu,
Serena Spudich, serena.spudich@yale.edu

Acknowledgements:
Generous tissue donors and their families
NIH/NIDA: UM1DA051410
NIH/National NeuroHIV Tissue Consortium
Tissue bank of Dr. Deborah Mash

National Institute on Drug Abuse
Yale University School of Medicine
SCORCH Single Cell Opioid Responses in the Context of HIV