Name: Jason Hammonds
PI Name: Paul Spearman

Email: jason.hammonds@cchmc.org
PI Email: paul.spearman@cchmc.org

HIV Infection Induces Rapid Activation of HAND-Associated Inflammatory Signatures in Microglia

Jason E. Hammonds[1], Roy Moscona[1], Omer Donmez[2], Andrew VonHandorf[2], Matthew Weirauch[2], Leah Kottyan[2], Thomas Hagan[1] and Paul Spearman[1]

[1]Division of Infectious Diseases, [2]Division of Human Genetics, Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital and University of Cincinnati, Cincinnati, OH, USA

HIV-associated neurocognitive disorders (HAND) continue to be a significant burden to people living with HIV-1 (PLWH) despite antiretroviral therapy (ART). Microglia within the central nervous system (CNS) are targeted by HIV-1 early and persists during chronic infection. Microglia play a central role in promoting neuroinflammation and HAND symptoms seen in PLWH. Exploring the transcriptional changes in microglia following HIV-1 infection may reveal mechanisms underlying the development of HAND.

iPSC-derived microglia (iMG) were infected with HIV-1 BaL and samples on days 1, 2, 4, 6 and 8 post-infection were collected for bulk RNA-sequencing. Chromatin accessibility by ATAC-seq was performed on infected samples from days 1 and 4 post-infection. HIV-infected monocyte-derived macrophages (MDMs) were sampled in parallel as a comparator in our analyses.

The integration of RNA-seq-derived differentially expressed genes (DEGs) with ATAC-seq-identified differentially accessible regions (DARs) uncovered a subset of genes demonstrating simultaneous changes in transcript levels and promoter accessibility. Inflammatory pathways were triggered early following infection of microglia, in a pattern that differed from MDMs. Genes identified as both DARs and DEGs were significantly enriched in key biological pathways, including TNFα signaling via NFκB, IL6/JAK/STAT3 signaling, interferon-alpha responses, and apoptosis. DiffTF analysis identified NFκB family members as key regulators of the responses, with significant contributions from AP-1 family members FOS, JUNB, and additionally the interferon regulatory factor (IRF) transcription factors IRF1, IRF8, IRF 7 and IRF9.

In summary, HIV infection of microglia triggered the rapid onset of inflammatory profiles similar to those observed in studies of patients diagnosed with HAND.