NEUROINFLAMMATION ASSOCIATED WITH INTACT AND 5' DEFECTIVE PROVIRAL DNA PERSISTS IN THE BRAIN OF VIRALLY SUPPRESSED PEOPLE WITH HIV

Authors:
Byrnes SJ[1], Jamal Eddine J[1], Zhou J[1], Chalmers E[1], Wanicek E[1], Osman N[1], Jenkins TA[1], Roche M[1,2], Brew BJ[3], Estes JD[1,4], Angelovich TA[1,2,5*], Churchill MJ[1,2,6*]

[1] RMIT University, [2] Peter Doherty Institute for Infection and Immunity, [3] St Vincent's Hospital, University of New South Wales and University of Notre Dame, [4] Vaccine & Gene Therapy Institute, Oregon Health & Science University, [5] Burnet Institute, [6] Monash University

Background:
Despite viral suppression with antiretroviral therapy (ART), people with HIV (PWH) continue to exhibit brain pathology and ~20% of ART-suppressed PWH develop a form of neurocognitive impairment. However, the state of cellular activation in the brain of ART-suppressed PWH, and the impact of HIV reservoirs in the brain on cellular activation are unclear.

Methods:
Formalin-fixed paraffin embedded frontal cortex tissue from non-virally suppressed (nVS; n=17) and ART-suppressed PWH (n=18) was assessed by multiplex immunofluorescence imaging to quantify levels of resident brain cells (CD68+ myeloid cells or GFAP+ astrocytes) co-expressing cell activation markers TNFα, TGF-β1 or Mx1). Findings in PWH were compared to those from HIV-seronegative individuals (n=6). Levels of intact, 3' defective or 5' defective HIV proviral DNA was measured in matched frozen tissue by intact proviral DNA assay and correlated with levels of cell activation.

Results:
Non-virally suppressed (nVS; n=17) and ART-suppressed PWH (n=18) had higher frequencies of astrocytes and myeloid cells expressing interferon-inducible Mx-1 and proinflammatory TNFα in grey matter relative to HIV-seronegative individuals ($P<0.05$ for all), demonstrating persistent cell activation in the brain that is not resolved by ART. The frequency of TGF-β1+ cells were also elevated in brain tissue from both nVS and ART-suppressed PWH, which may support active immunoregulatory responses despite viral suppression. Importantly, the frequency of Mx1+ myeloid cells correlated with levels of total HIV DNA, intact and 5' defective HIV proviral DNA ($P<0.05$ for all) in the brain of ART-suppressed PWH.

Conclusion:
These findings demonstrate that cell activation persists in the brain of ART-suppressed PWH that is not resolved by ART. Furthermore, we demonstrate a relationship exists between both intact, and importantly, 5' defective HIV proviral DNA and cell activation in the brain that must be considered as a possible cause of ongoing neuropathology in ART-suppressed PWH.

Disclosure of Interest Statement:
No conflicts to declare.