HIV-Tat protein in inflammatory infiltrates of CNS-IRIS and in CSF of patients on ART

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Background

Persistent low level inflammation is found in most patients with chronic human immunodeficiency virus (HIV) infection despite virological control on antiretroviral therapy (ART).

Some of these individuals develop immune reconstitution inflammatory syndrome of the central nervous system (CNS-IRIS), the pathophysiology of which is poorly understood.

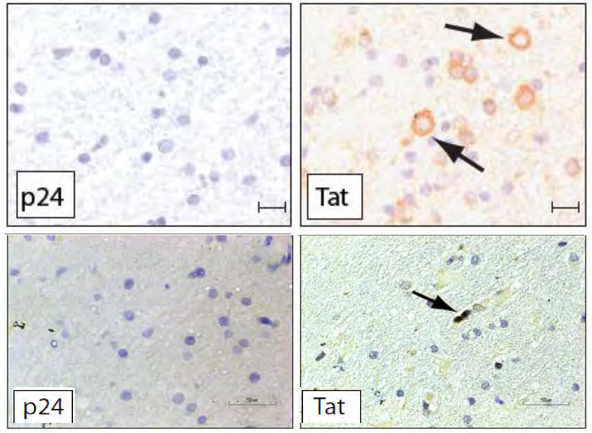
Methods

We immunostained brain biopsy and autopsy tissue and from HIV infected individuals on ART with CNS-IRIS, from virologically controlled HIV infected without IRIS as well as from patients with HIV encephalitis (HIVE). Tissue was stained for the HIV-proteins transactivator of transcription (Tat) and p24 antigen as well as for T cell markers.

We established an ELISA for the detection of Tat and examined in the cerebrospinal fluid (CSF) of HIV patients on ART (n=65).

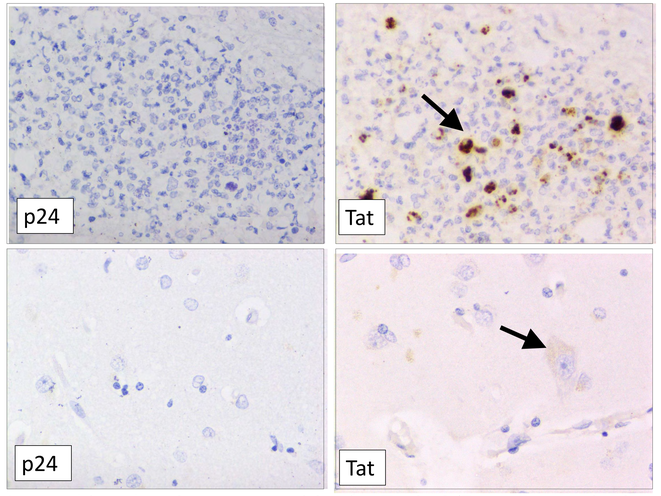
Results

Detection of Tat in brain tissue of patients with CNS-IRIS



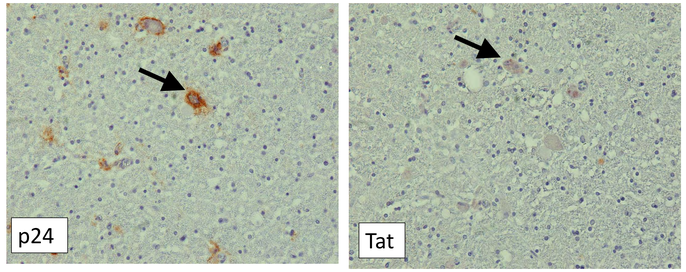
Biopsy of two HIV-infected patients with CNS-IRIS
but no opportunistic infection was positive for Tat but not for p24.

Detection of Tat in brain tissue of HIV-infected individuals on ART



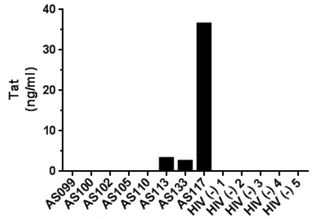
Immunhistochemistry was positive for Tat in 2/7 autopsy brain tissue of HIV-infected individuals on ART without evidence of p24.

In HIV encephalitis both p24 and Tat are detected

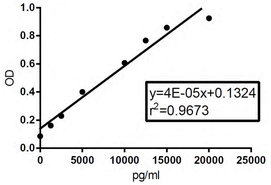


HIVE brain tissue shows Tat and p24 expressing macrophages.

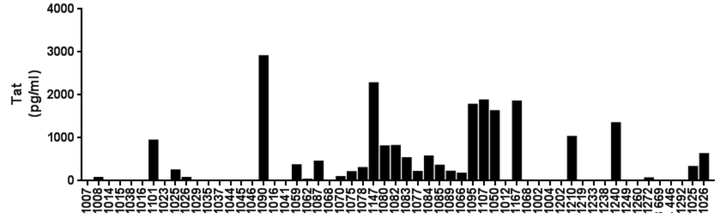
Detection of Tat in CSF of 49% of HIV-infected individuals on ART



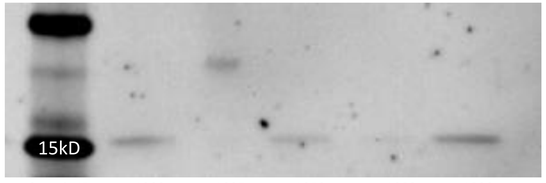
Cohort A: Tat detected in CSF of 3/8 HIV-infected, no Tat detected in 5 HIV negative donors



CSF Tat ELISA standard curve



Cohort B: 29/57 HIV-infected individuals with detectable levels of Tat in CSF



Presence of Tat in CSF was confirmed by Western blot in a subset of samples.

Conclusion

- While ART controls HIV replication it fails to impact Tat production.
- HIV-Tat protein may drive inflammation in the form of acute CNS-IRIS or chronic inflammation in the CSF of individuals controlled on ART.
- Tat may therefore be an important therapeutic target.

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