Mechanism of HIV Infection in Human Astrocytes

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Turnover rate of astrocytes may be very low: 0.4% astrocytes/day in corpus callosum of mice.


Ranki et al. AIDS 1995
AIMS

- To determine if a persistent HIV infection can be established in astrocytes;

- To determine the mechanism of HIV entry into astrocytes.
Persistent HIV replication in astrocytes following introduction of proviral DNA

NL4-3/VSV-G = HIV pseudotyped virus
pNLENG1 = NL4-3_based reporter plasmid
Persistent HIV replication in astrocytes post-treatment with chloroquine

A  Infection with T-tropic

B  

C  Infection with M-tropic

D  

\[ \text{ChQ} = \text{chloroquine} \]

\[ \text{NLENG1} = \text{NL4-3-based reporter virus} \]

\[ \text{SF162R3} = \text{SF163-based reporter virus} \]
Which receptor mediates the infection of astrocytes?

A. CD4-independent virus

B. CD4-dependent virus

C. Blocking with Anti-CD4 Ab
Low level of CD4 expression detected in astrocytes

Expression of CD4 mRNA in Different Cells (Semi-qPCR)

PDA = progenitor derived astrocytes
HFA = human fetal astrocytes
Transmission of HIV from the infected lymphocytes to astrocytes by cell-to-cell contact
The transmission from lymphocytes to astrocytes can be blocked by anti-CXCR4 or anti-CD4

**Graphs:**
- **x-axis:** Days post-infection
- **y-axis:** Total Number of Positive Cells
- Line graph showing the effect of Anti-CXCR4 + NLENG1-JK-Tat compared to NLENG1_JK-Tat alone.
- Bar graph comparing different treatments:
  - NLENG1_JK-Tat Ctrl
  - Anti-CD4 Ab
  - Anti-CXCR4 Ab
  - Anti-4f47 Integrin Ab
  - T20
  - AMD

**Legend:**
- Red line: Anti-CXCR4 + NLENG1-JK-Tat
- Blue line: NLENG1_JK-Tat alone

**Key:**
- **T20** = fusion inhibitor
- **AMD** = CXCR4 antagonist
HIV is released from T cells at sites of contact and travels along filopodia
1. HIV infection of astrocytes leads to persistent viral replication and thus is an important reservoir for the virus.

2. Cell-free HIV poorly infects astrocytes because of entrapping in endosomes/lysosomes post-entry.

3. Cell-to-cell contact with HIV-infected lymphocytes leads to more efficient infection of astrocytes.

4. Low level of CD4 in astrocytes plays an important role in HIV infection by both cell-free viruses and cell-cell contact.
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Transmission of HIV from Astrocytes to T cells

NLENG1-infected HFA (50 days) + Jurkat-Tat

1st day

5 days

22 days

122-day infected HFA

+ Jurkat-Tat 6 days

145-day infected HFA

+ Jurkat-Tat 18 days

93-day infected HFA

+ Jurkat E6-1 14 days
Evidences of CD4+ T Cells in the Brain of HIV+ Individuals

- **Peng H et al.** HIV-1-infected and/or immune activated macrophages regulate astrocyte SDF-1 production through IL-1β. *Glia* 2006; 54(6): 619-29.

  ![Diagram](image.png)


  Lymphocyte infiltration of the leptomeninges and of perivascular spaces occurred at all stages, but the frequency was significantly higher in asymptomatic carriers.


  The main component of mononuclear aggregates in group A (clinically unaffected) were lymphocytes, in contrast to group B (animals with AIDS), in which macrophages dominated.


  The most significant lesions following both routes (intraperitoneal and intravenous) of infection were lymphocyte-rich perivascular infiltrates. Infiltrates were composed of CD79+ B cells and CD3+ T cells. The latter population contained a mixture of CD4+ and CD8+ cells.

CNS-Immune reconstitution inflammatory syndrome (IRIS)

Riedel et al., Nature Cl Neurol 2006

Chronic T cell activation in CSF

Sinclair et al., JAIDS; 2008