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Spinal Cord Disease in HIV Infection

Zoe Keese
University of Nebraska Medical Center

Amanda Fernandes
University of Nebraska Medical Center

Lili Guo
University of Nebraska Medical Center

Edward Makarov
University of Nebraska Medical Center

Saumi Mathews
University of Nebraska Medical Center

See next page for additional authors

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Zoe Keese[1], Amanda Fernandes[1], Lili Guo[1], Ed Makarov[1], Saumi Mathews[1], Santhi Gorantla[1]

Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha

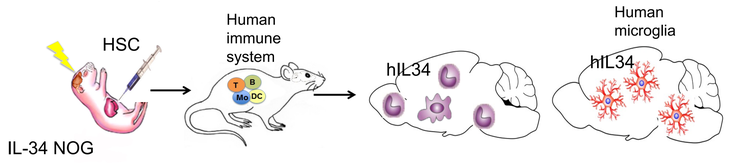
Introduction

HIV infection is associated with numerous spinal cord diseases, such as vacuolar myelopathy, primary HIV-associated acute transverse myelitis, and primary CNS lymphoma, amongst others. These diseases had a much higher prevalence in the pre-cART era, however, some individuals are still affected despite cART treatment. Moreover, a previous study has shown that HIV-1 gp120 induces synaptic degeneration in the spinal pain neural circuit, which is likely a critical step in neuropathogenesis of the spinal cord in HIV. Further study is needed to better understand how HIV patients are affected by spinal cord disease, and to develop therapeutic strategies.

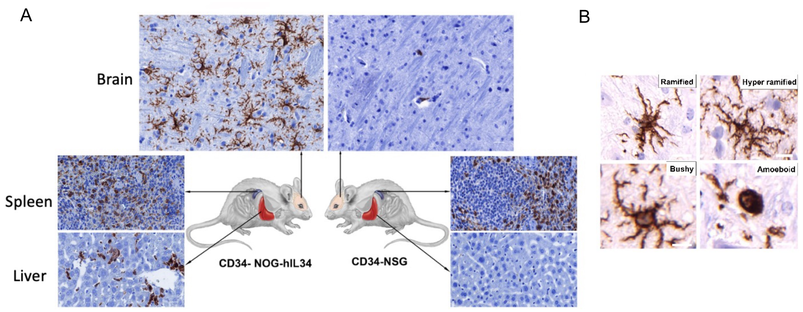
To study HIV in its relation to spinal cord disease, we used a recently developed humanized mouse model that has human microglial cell reconstitution. This model allows for the HIV infection in central nervous system and the observation of resulting pathology.

Humanized mouse model

Immune deficient NOD/*Scid* IL2Rg-/- (NOG) mice when transplanted with human CD34+ hematopoietic stem cells (HSC) at birth develop complete human immune system that can be studied for the life of the mouse.
When the cytokine human Interleukin-34 (IL-34) was introduced transgenically into NOG mice, human microglia were spontaneously developed in the mouse brain of HSC transplanted humanized mice.



Human microglia in mouse brain



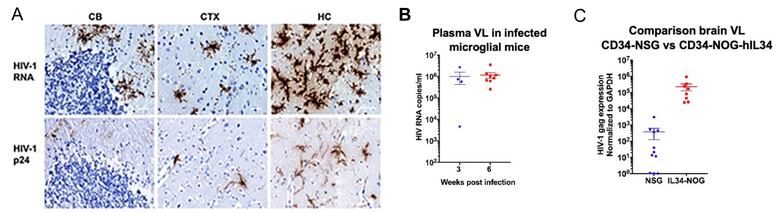
Mathews et al. Molecular Neurodegeneration, 2019

A. Immunohistology staining of brain and different tissues for human microglia and macrophages (HLA-DR, brown) in humanized NSG. And IL-34-NOG mice. Human microglia are present only in humanized IL34-NOG mice. ***B.*** Human cells in mouse brain had typical microglial morphology.

Hypothesis

Human microglial mice can be used to study peripheral neuropathy and spinal cord myelopathy in HIV infection

HIV infection in the brain

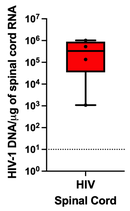


A. Immunohistology staining for HIV-1 infected microglial cells (top HIV RNA, bottom HIV-1p24, brown) in different brain regions (Cerebellum, CB; Cortex, CTX; Hippocampus, HC). ***B.*** Plasma viral RNA levels at 3 and 6 weeks post infection, ***C.*** Brain viral RNA levels measured by real-time PCR in IL34-NOG microglial mice.

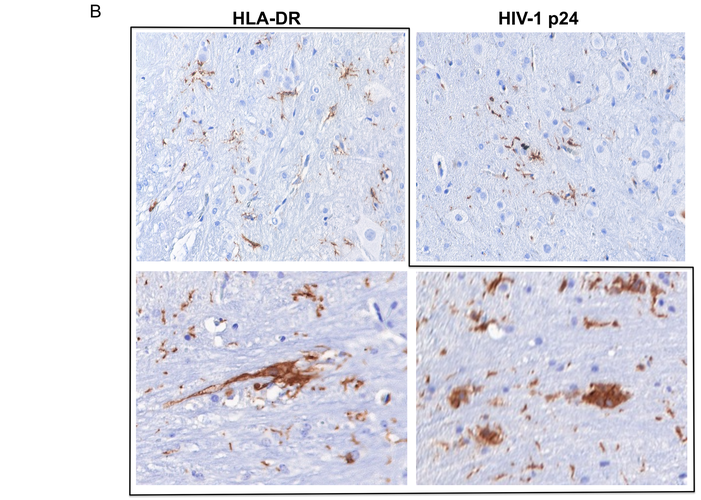
HIV infection in the spinal cord

A

Mouse ID	Spinal cord HIV RNA/µg of tissue
B802	1080
B739	1020000
B709	531000
B696	135500

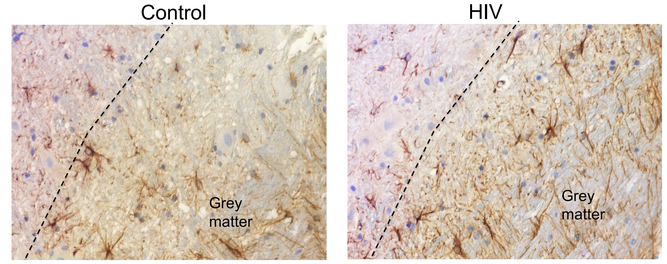


B



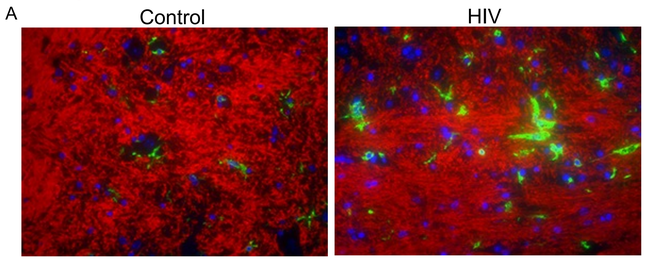
A. Spinal cord HIV RNA levels measured by droplet digital PCR (DDPCR***). B.*** Immunohistology staining for human microglia (HLA-DR, brown). Bottom panels show multi-nucleated giant cells that are typical pathological feature I. HIV infection. HIV-1 infected microglial cells (HIV-1p24, brown) are also present at significant levels.

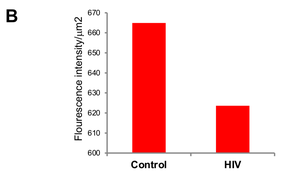
Glial activation in the HIV-infected SC



Immunohistology staining for glial fibrillary acidic protein (GFAP, brown) to assess astrogliosis.

Myelin loss in the HIV infected SC





A. Immunofluorescence staining for Myelin associated glycoprotein (MAG, Red) and human microglia (HLA-DR, green) from control and HIV mice. ***B.*** Quantification of MAG fluorescence intensity captured by multispectral imaging.

Conclusion and Future Directions

- This is the first demonstration of human microglial reconstitution and productive HIV infected in a mouse spinal cord.
- HIV infection resulted in myelin loss in the anterior column white matter.
- Further analysis of glial activation in the grey matter and demyelination in different regions of SC and the resulting consequences in behavioral phenotype needs to be evaluated.
- Studying SC disease in the human microglial mice during combination antiretrovirally (cART) suppressed HIV infection will provide a means to understand the disease in people living with HIV (PLWH).
- The new mouse model can be used to study the mechanisms underlying the pathology, discover therapeutic targets and for therapeutic testing.

Funding

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