BRAIN AND HIV

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AGING IN HIV
BARCELONA – BUENOS AIRES
8TH EDITION

HAND: HIV-1 associated neurocognitive disorder

- 15-60% HIV-1+ individuals present neurocognitive impairment (NCI).

- In the brain: HIV-1 infects and replicates in microglia (and astrocytes)

- mechanisms underlying HIV-associated NCI still not clear:

    a) systemic inflammation

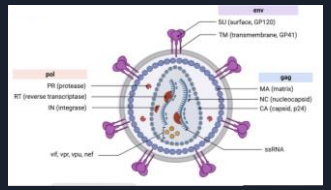
    b) neuroinflammation

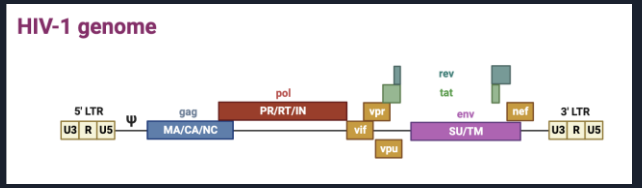
    c) a combination of two

-Antiretroviral therapies (ART): extend lifespan and postively impact on cognitive performance but does not abolish systemic or CNS inflammation

Reviewed in Sreeram S., et al., Trends in Immunology (2022)

Neuropathogenesis of HAND:





HOST IMMUNE RESPONSE

INNATE IMMUNE RESPONSE:
- Interferons
- Myeloid cell activation

Mitochondrial dysfunction: ROS/ Energy failure Fe2+ and Ca2+ dysregulation

Impaired autofagic flux

INFLAMMATION

INFLAMMASOME ACTIVATION
IL-1b/IL-8/TNF

NEUROINFLAMMATION

NEURODEGENERATION:
- ↑NfL, Tau
- ↓MAP2

COGNITIVE IMPAIRMENT

ADAPTATIVE IMMUNE RESPONSE:
- T cells activated by HIV proteins
  - -Tat,
  - Nef
  - gp120

Figure adapted from Ellis R.J et al., Nature Reviews Neurology (2023) and Biorender.com

Neuropathogenesis of HAND:

HOST IMMUNE RESPONSE
INFLAMMATION

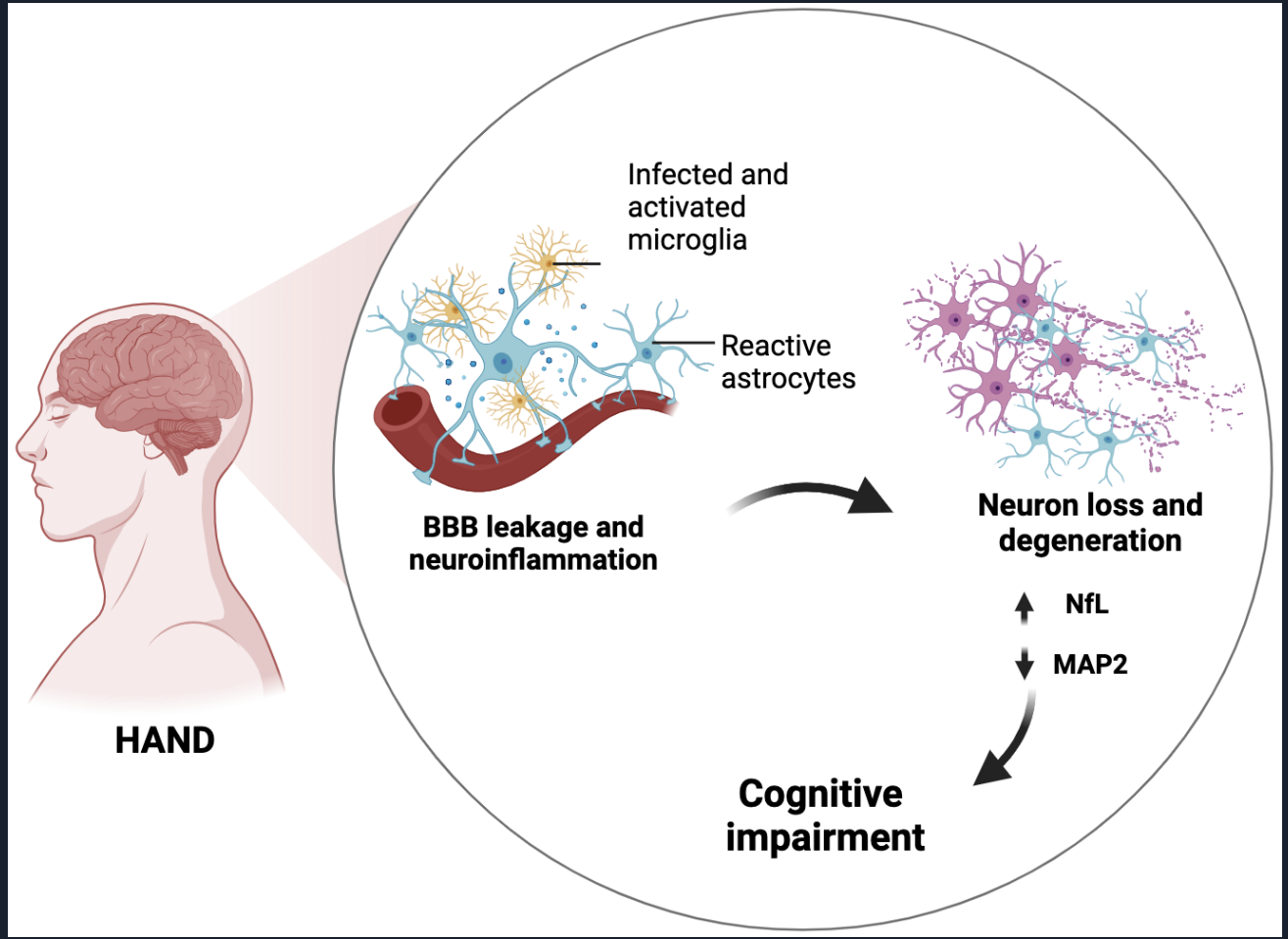


Figure adapted from Ellis R.J et al., Nature Reviews Neurology (2023) and Biorender.com

Neuropathogenesis of HIV-associated neurocognitive impairment:

a) Infected microglia/astroglia in less extend→ GLIOSIS
b) Cytokines and chemokines released from reactive and infected cells
c) Glutamate and Ca2+ dysregulation
d) Damaged neurons actively can contribute to the neuroinflammatory loop.
e) Extracellular vesicles with pro-inflammatory cargo: viral particles/viral proteins

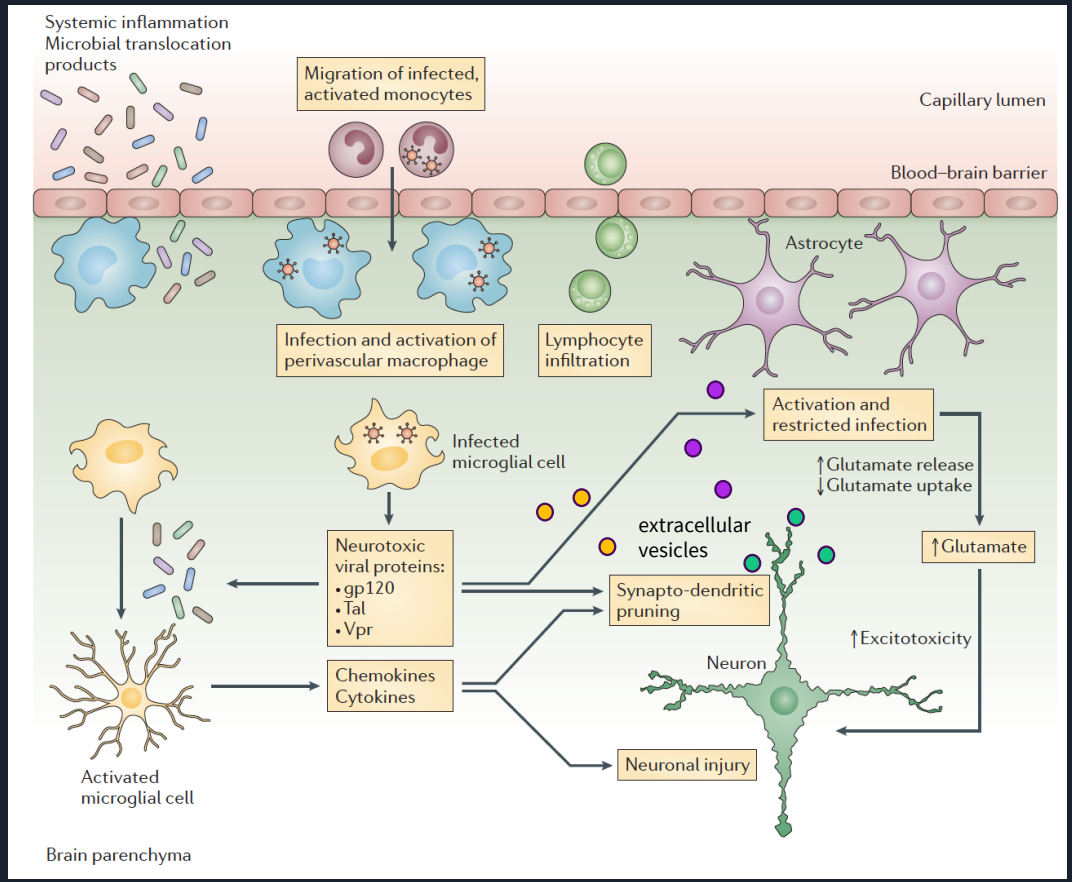


Figure adapted from Saylor D. et al., Nature Reviews Neurology (2016)

Why are we interested in
HIV-1 associated neurocognitive disorder?

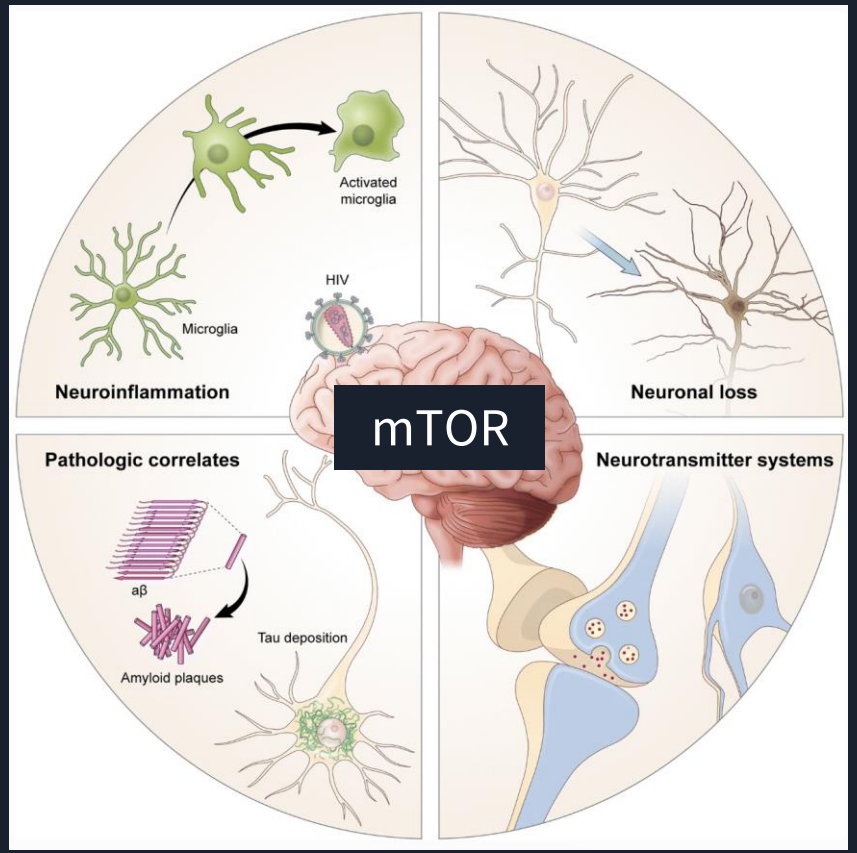
Because there are common traits between HIV neuroinfection and Alzheimer's disease

NEUROINFLAMMATION

OXIDATIVE STRESS

APP MISSPROCESSING AND Aβ SYNTHESIS

ABNORMAL TAU PHOSPHORYLATION



NEURODEGENERATION

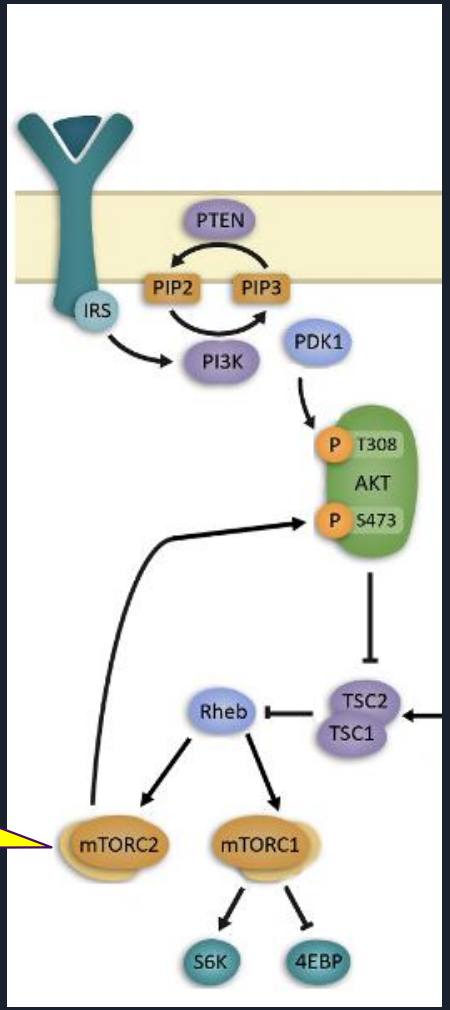
ACTIVATION OF CELL DEATH PATHWAYS

COGNITIVE DEFICITS

EXCITOTOXICITY

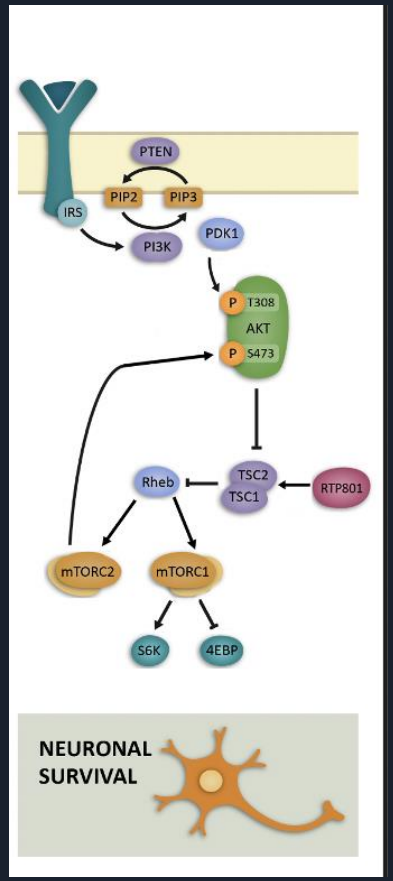
Adapted from Sanhita Sinharay & Dima A. Hammoud ,Current HIV/AIDS Reports (2019)

mTOR pathway and NCI in HIV:



Adapted from Canal et al., Front. Cell Neurosci. 2014

RTP801/REDD1 protein as a regulator of mTOR signaling



Canal et al., Front. Cell Neurosci. 2014

RTP801 in neurodegeneration, so far:

- UPREGULATED IN HUMAN POSTMORTEM BRAINS FROM PATIENTS WITH :

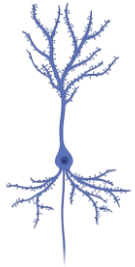
- ✓ PD[1]
- ✓ HD[2]
- ✓ AD[3]

- UPREGULATED IN MURINE MODELS
  - ✓ PD: MPTP[4]
  - ✓ HD: R6/1[5]
  - ✓ AD: 5XFAD, rTG4510[3]

1. Malagelada et al., J Neurosci 2006
2. Martín Flores et al., Molecular Neurobiol 2016
3. Pérez-Sisqués et al., Cell Death and Dis 2021
4. Malagelada et al., J Neurosci 2010
5. Martín Flores et al., Cell Death and Dis 2020

Silencing RTP801 in the 5xFAD mouse model of AD:

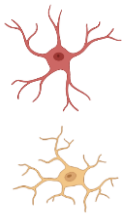
→ IN HIPPOCAMPAL NEURONS



✓ PREVENTED COGNITIVE IMPAIRMENT

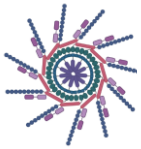
✓ PREVENTED INFLAMMATION

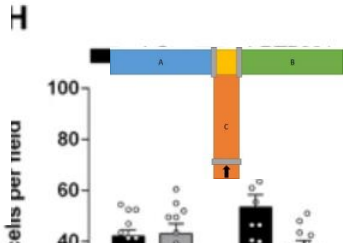
- ⇊ GFAP
- ⇊ IBA1

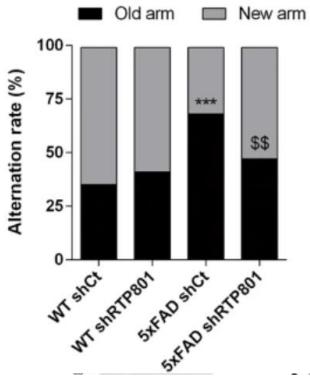


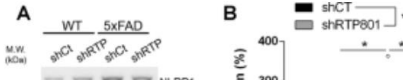
✓ PREVENTED INFLAMMASOME ACTIVATION

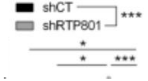
- ⇊ NLRP1
- ⇊ NLRP3
- ⇊ PROCASP1

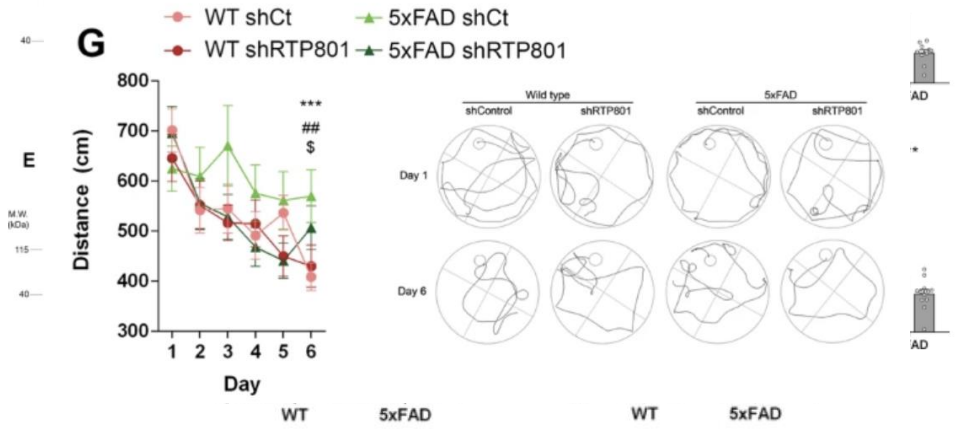






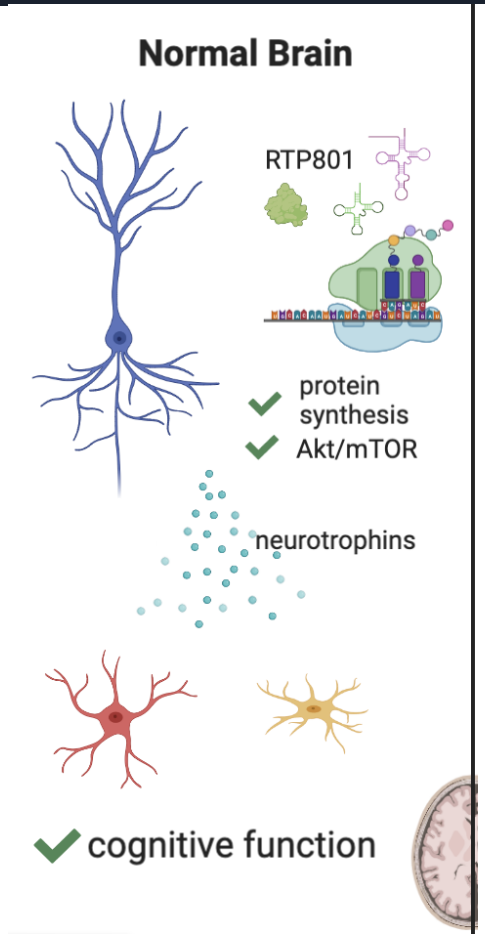






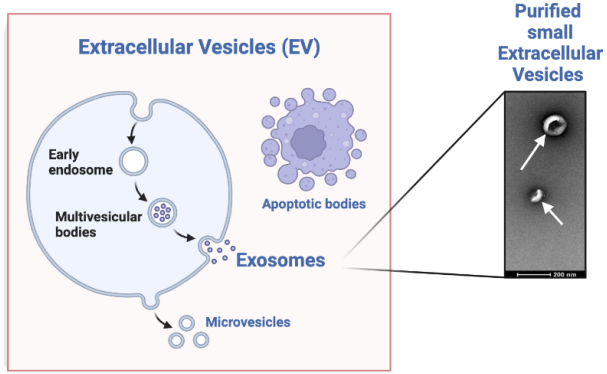
Pérez-Sisqués et al., Cell Death and Dis, 2021

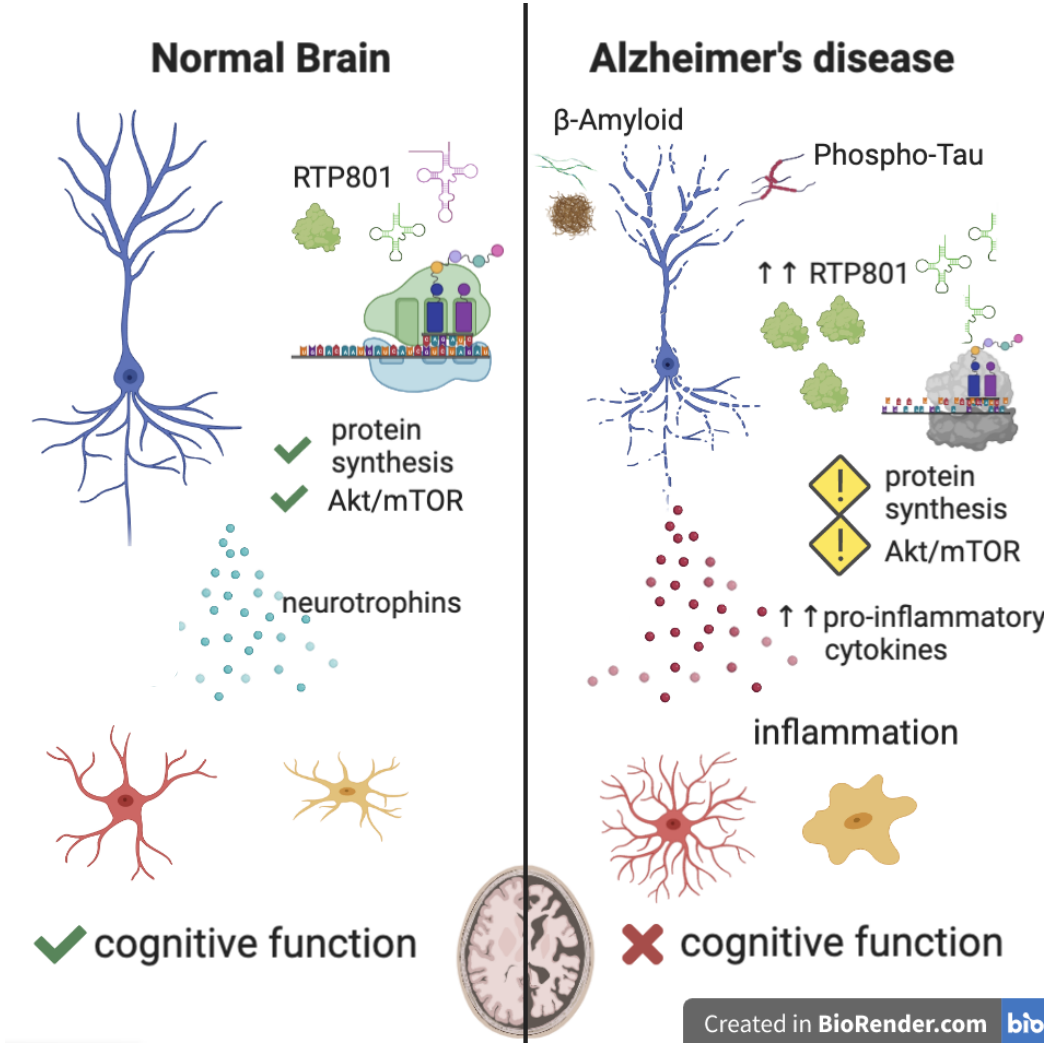
RTP801 mediates cognitive impairment and inflammation



RTP801 mediates cognitive impairment and inflammation, but…

HOW DOES IT DO IT?





RTP801 transfers its toxicity transneuronally via extracellular vesicles *(Solana-Balaguer et al., JEV 2023)*

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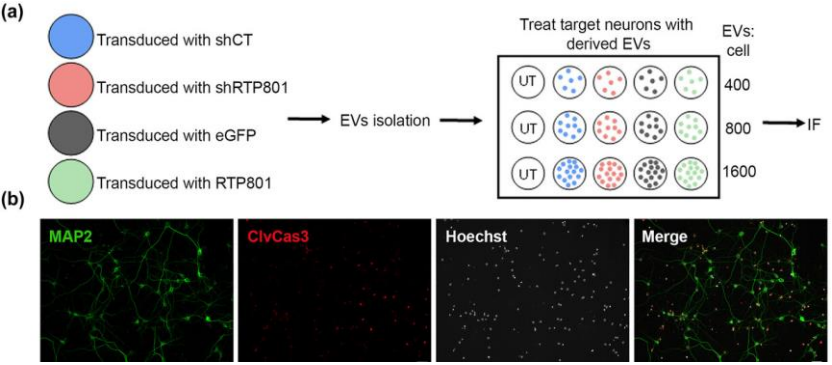
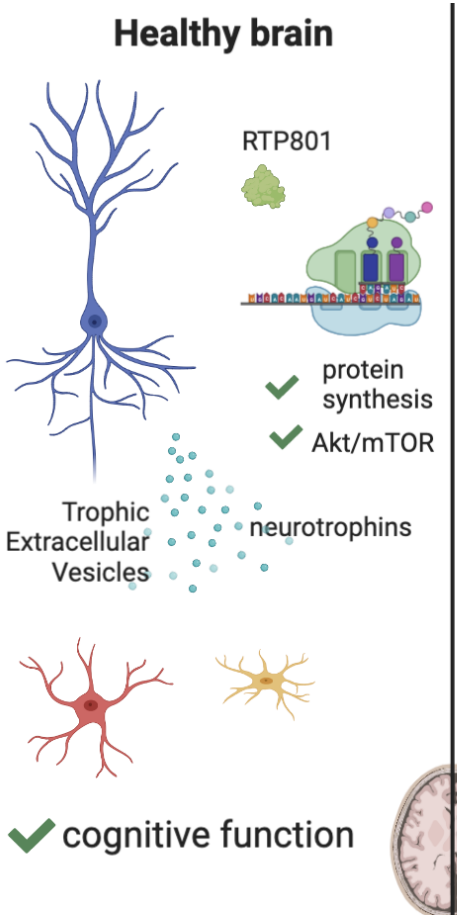


Hypothesis in NCI-HIV:



We would like to study this plausible connection...

we started an intramural collaboration with :

Dr. Esteban Martínez
Infectious Diseases Unit
Hospital Clínic

Dr. Jordi Blanch
Dept Psychiatry
Hospital Clínic

Malagelada's Lab

UNIT OF BIOCHEMISTRY
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ALMUDENA CHICOTE-GONZÁLEZ
GENÍS CAMPOY CAMPOS
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COLLABORATORS :

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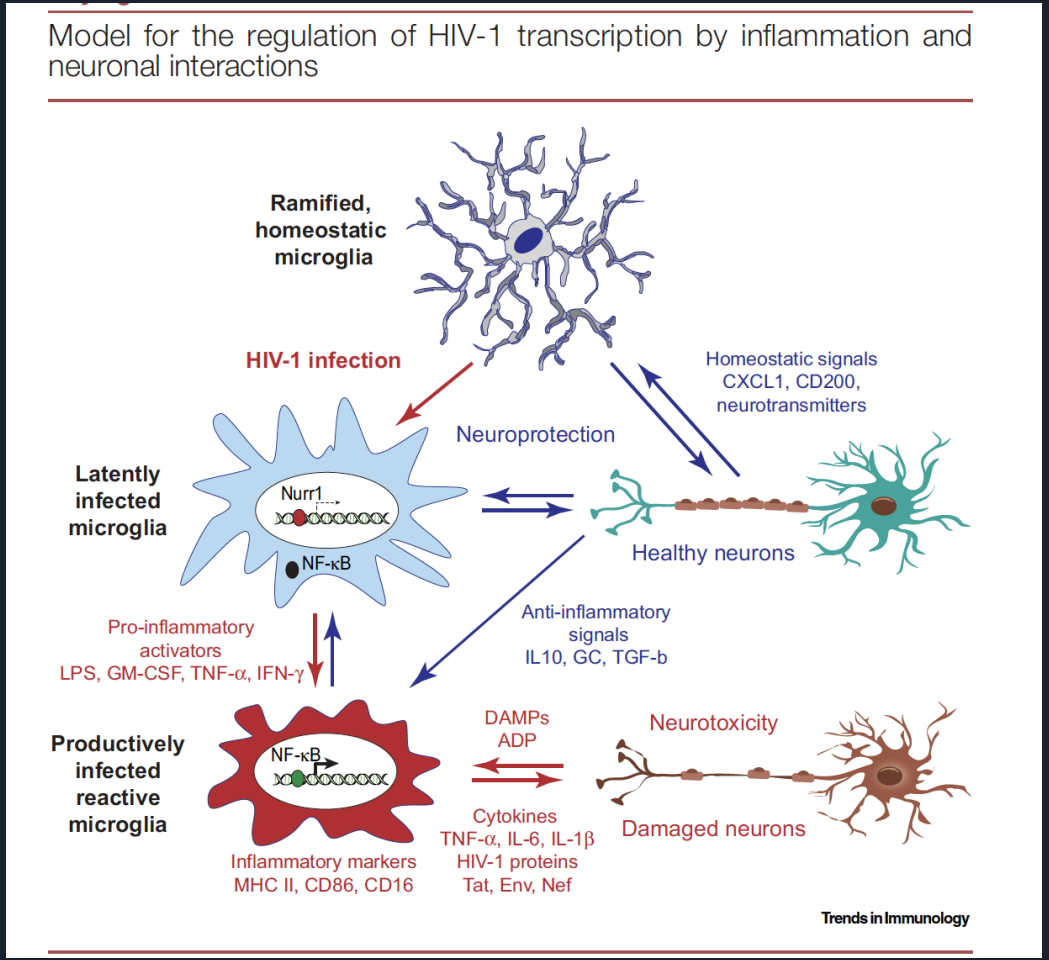
Jordi Alberch, MD/PhD.
Guadalupe Soria, PhD.
Mercè Massana.,PhD.
Esther Pérez-Navarro, PhD.
Eulàlia Martí, PhD.
Ana Gámez, PhD.
Enrique Santamaría (Navarra Biomed)
Joaquín Fernández (Navarra Biomed)

Laura Molina, Banc de
Teixits Neurològics UB
IDIBAPS Clínic

Microglia serves as a latent reservoir for HIV



Sreeram S., et al., Trends in Immunology 2022

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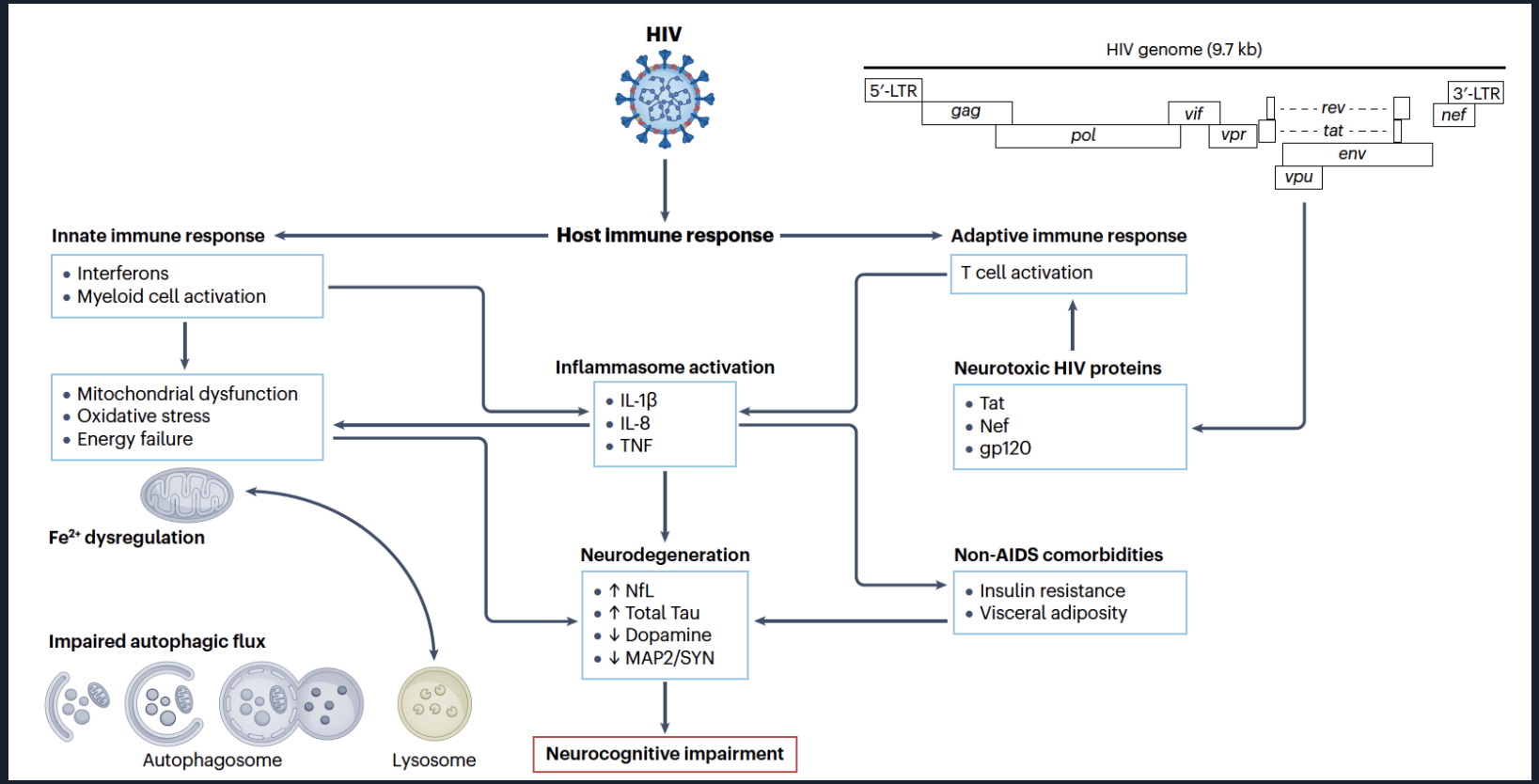

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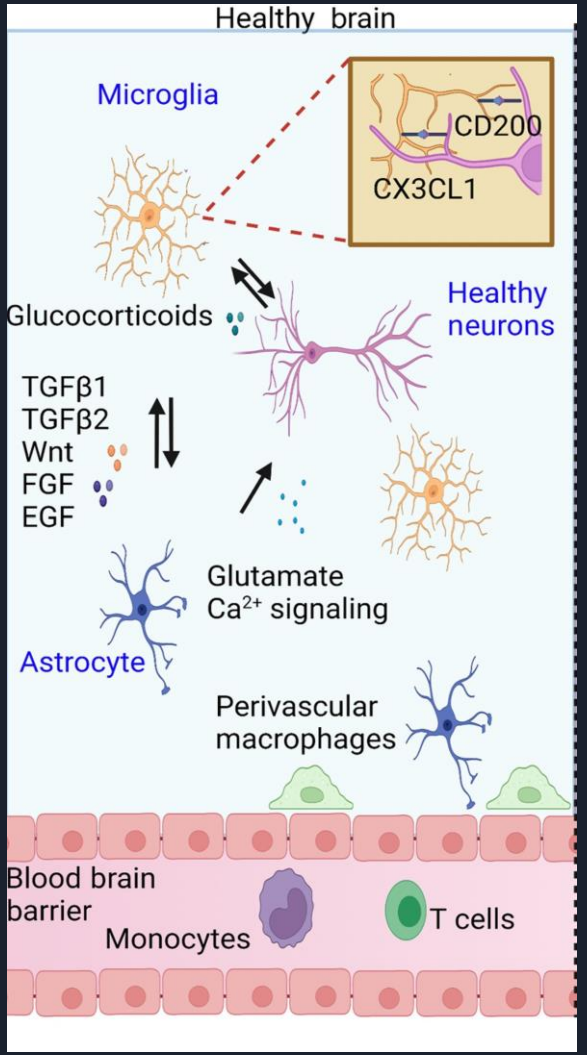

→ *Trends in Immunology* 2022 43630-639DOI: (10.1016/j.it.2022.06.003)

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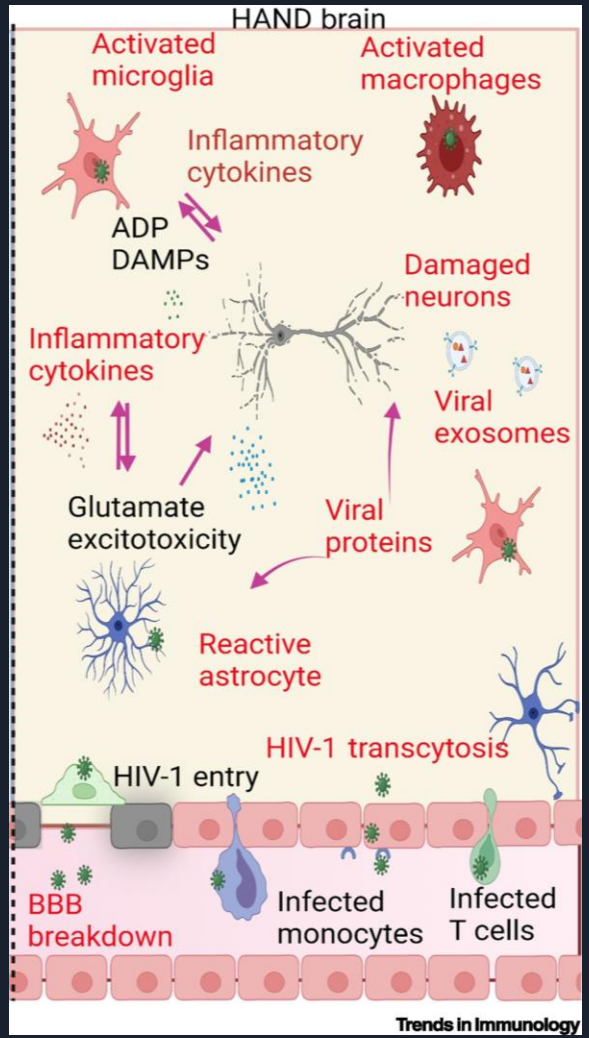

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