Extracellular vesicle-mediated amyloid transfer to neural progenitor cells: implications for RAGE and HIV infection

CURRENT STATUS: ACCEPTED

Molecular Brain BMC

Ibolya E. András
University of Miami School of Medicine

Marta Garcia-Contreras
University of Miami School of Medicine

Christopher Yanick
University of Miami School of Medicine

Paola Perez
University of Miami School of Medicine

Brice Sewell
University of Miami School of Medicine

Leonardo Durand
University of Miami School of Medicine

Michal Toborek
University of Miami School of Medicine

mtoborek@med.miami.edu*Corresponding Author*
ORCiD: https://orcid.org/0000-0003-4475-2119

DOI:
10.21203/rs.2.17417/v1

SUBJECT AREAS
Cellular & Molecular Neuroscience

KEYWORDS
Extracellular vesicles, blood-brain barrier, amyloid beta, neural progenitor cells, RAGE

Abstract

Amyloid beta (Aβ) deposition was demonstrated to be elevated in the brains of HIV-infected patients and associated with neurocognitive decline; however, the mechanisms of these processes are poorly understood. The goal of the current study was to address the hypothesis that Aβ can be transferred via extracellular vesicles (ECVs) from brain endothelial cells to neural progenitor cells (NPCs) and that this process can contribute to abnormal NPC differentiation. Mechanistically, we focused on the role of the receptor for advanced glycation endproducts (RAGE) and activation of the inflammasome in these events. ECVs loaded with Aβ (Aβ-ECVs) were readily taken up by NPCs and Aβ partly colocalized with the inflammasome markers ASC and NLRP3 in the nuclei of the recipient NPCs. This colocalization was affected by HIV and RAGE inhibition by a high-affinity specific inhibitor FPS-ZM1. Blocking RAGE resulted also in an increase in ECV number produced by brain endothelial cells, decreased Aβ content in ECVs, and diminished Aβ-ECVs transfer to NPC nuclei. Interestingly, both Aβ-ECVs and RAGE inhibition altered NPC differentiation. Overall, these data indicate that RAGE inhibition affects brain endothelial ECV release and Aβ-ECVs transfer to NPCs. These events may modulate ECV-mediated amyloid pathology in the HIV-infected brain and contribute to the development of HIV-associated neurocognitive disorders.

Full-text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.