Open Access
www.openaccessjournals.com

Journal of Experimental Stroke & Translational Medicine

Dysregulation of macrophage-secreted cathepsin B contirbutes to HIV-linked neuronal apoptosis

Loyda M Melendez

University of Puerto Rico Medical Sciences, USA

Abstract

Chronic human immunodeficiency virus type one (HIV-1) infection leads to a spectrum of neurological and cognitive abnormalities, termed HIV-associated neurocognitive disorders (HAND). HAND remains prevalent, particularly in its milder forms, despite effective combination antiretroviral therapy (cART). The pathogenesis of HAND is caused by HIV-infected perivascular macrophages and microglia, whose activation leads to the release of pro-inflammatory cytokines and other soluble factors toxic to neurons. One factor that may be involved in macrophage-mediated HIV neurotoxicity is cathepsin B (CATB), a cysteine protease. We recently demonstrated that monocyte-derived macrophages (MDM) secreted, CATB has increased neurotoxic activity in vitro. Our studies demonstrate that cathepsin B interacts with MMP-9 in uninfected cells but this interaction disappears in HIV infection and develops a new interaction with serum amyloid P component (SAPC), related to amyloid deposition in Alzheimer's disease (AD). Studies in the literature also suggest that CATB might be involved in amyloid-beta (Aβ)- related inflammatory response, which results in neuronal death. Our hypothesis is that increased secretion of monocyte-derived cathepsin B and SAPC after HIV infection causes neuronal dysfunction and death, and contributes to the pathogenesis of HAND. SK-N-SH neuronal cells were exposed to active recombinant histidine-tagged cathepsin B (His-CATB). His-CATB entry was tracked by intracellular flow cytometry, and neuronal dysfunction was verified by western blot. Neurons internalized His-CATB, an effect that was partially decreased by pre-treatment with anti-CATB antibody. Pre-treatment with CATB and SAPC antibodies decreased cleavage of caspase-3 and restored synaptophysin in neurons. CATB secreted both free and in EVs, is internalized by neurons. HIV-replication levels modulate the amount of CATB neuronal uptake, and neuronal dysfunction can be decreased with CATB antibodies or with CATB inhibitor CA074. In conclusion, the CATB/SAPC complex represents a novel target against HAND and current studies will test this approach in a small animal model.

Publications

1. HIV Infection Induces Extracellular Cathepsin B Uptake and Damage to Neurons
2. Sigma-1 Receptor Antagonist (BD1047) Decreases Cathepsin B Secretion in HIV-Infected Macrophages Exposed to Cocaine
3. Dimethyl Fumarate Prevents HIV-Induced Lysosomal Dysfunction and Cathepsin B Release from Macrophages
4. Microwave & magnetic proteomics of macrophages from patients with HIV-associated cognitive impairment
5. Cystatin B and HIV regulate the STAT-1 signaling circuit in HIV-infected and INF-β-treated human macrophages
6. HIV gp120 sequence variability associated with HAND in Hispanic Women
7. Macrophage secretome from women with HIV-associated neurocognitive disorders
8. Interacting partners of macrophage-secreted cathepsin B contribute to HIV-induced neuronal apoptosis
9. Cathepsin B and serum amyloid p component contribute to HIV-induced neuronal apoptosis
10. Cocaine Potentiates Cathepsin B Secretion and Neuronal Apoptosis from HIV-Infected Macrophages

Biography

Loyda M Meléndez completed a Bachelor in Science from University of Puerto Rico (UPR), a MS in Microbiology from University of Georgia, USA, and a Ph.D. in Experimental Pathology-Immunology at Emory University, Atlanta USA. She is currently a Professor of Virology at UPR School of Medicine Department of Microbiology and has mentored 42 Hispanic students and 4 post-doctoral fellows in Puerto Rico. Her research involves studies on HIV-infected macrophages and the proteins associated with restriction of HIV replication in placental macrophages, and HIV neuropathology. She is director of the Translational Proteomics Center and has published about 50 articles, two book chapters. She has one patent, is reviewer for NIH, for the Journals of Leukocyte Biology, PlosONE, and Proteomics and Clinical Applications. She has participated as member to International Society for Neurovirology women in science committee and in the Society for Neuroimmune Pharmacology Diversity and Inclusion committee and has been Council member.

Citation: Loyda M Melendez, *Dysregulation of macrophage-secreted cathepsin B contirbutes to HIV-linked neuronal apoptosis*, Vascular Dementia 2020, 13th International Conference on Vascular Dementia and Dementia, Paris, France, February 19-20, 2020