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

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 an 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

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