

Submitter Name: Palsamy Periyasamy
Submitted email: palsamy.periyasamy@unmc.edu
PI Name (if different): Shilpa Buch
PI email (if different): sbuch@unmc.edu

HIV Tat and morphine-mediated activation of astrocytes: Epigenetic involvement of NLRP6 inflammasome in HAND

Palsamy Periyasamy¹, and Shilpa Buch¹

¹Department of Pharmacology and Experimental Neuroscience, 985880 Nebraska Medical Center, University of Nebraska Medical Center

Background: CDC describes HIV infection and drug abuse as intertwined epidemics, leading to compromised cART adherence and exacerbation of HIV-associated neurocognitive disorders (HAND) pathogenesis. Opiate use/abuse is highly prevalent in HIV-infected individuals. The interplay of HIV and opiates thus raises concerns regarding the effects of both on HAND pathogenesis. **Rationale/significance:** Chronic low-level inflammation (mediated by viral proteins, antiretrovirals, and abused drugs) has been implicated as a significant underlying factor in the HAND pathogenesis. Inflammation has been identified as an essential correlate of HAND. **Hypothesis:** Herein, we hypothesized that exposure of astrocytes to HIV Tat and morphine exacerbates astrocyte activation involving a) activation of the NLRP6 inflammasome via promoter DNA hypomethylation and, b) downregulation of miR-152, which in turn, targets NLRP6, leading to cleavage and release of IL1 β and IL18. Ultimately, this culminates into increased neuroinflammation. **Results:** Whole-genome bisulfite sequencing in the frontal cortices of SIV- infected macaques demonstrated increased DNA hypomethylation of NLRP6 promoter with a concomitant upregulation of NLRP6 inflammasome. miRNA array analysis of HIV Tat and morphine exposed primary astrocytes showed decreased levels of miR-152 with a concomitant upregulation of NLRP6 inflammasome signaling and astrocyte activation. Pharmacological inhibition/gene silencing approaches further validated HIV Tat and morphine-mediated activation of NLRP6, cleavage of caspase1 and IL1 β , and IL18 in primary astrocytes. Cell culture findings were also validated in the brains of Tat transgenic mice administered morphine. **Discussion:** These findings underpin the epigenetic involvement of NLRP6 inflammasome signaling in the activation of astrocytes in the context of HIV Tat and morphine.