Submitter Name: Kaycie Lawson
Submitted email: klawson1@bidmc.harvard.edu
PI Name: Jerome E. Groopman
PI email: jgroopma@bidmc.harvard.edu

Methamphetamine alters innate immune signaling by inducing an IL-1β-miR-146a negative feedback loop and contributes to anti-retroviral drug resistance in CD4$^+$ T-cells

Kaycie Lawson[1], Anil Prasad[1], Shuxian Jiang[1], and Jerome E. Groopman[1]

[1]Division of Experimental Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School

Methamphetamine (Meth) abuse is a prevalent public health concern worldwide, and has been shown to contribute to increased HIV-1 pathobiology and poor adherence to anti-retroviral therapies. Specifically, Meth has been shown to alter molecular mechanisms to provide a more conducive environment for HIV-1 replication and maintenance. Recently, microRNAs (miRNAs) have been show to play an integral role in fine-tuning the innate immune response, but the exact mechanisms governing these processes are poorly understood. In addition, the effects of Meth abuse on miRNA expression are largely unknown. By gaining a clearer understanding of the interactions between Meth and miRNAs, we can elucidate the mechanisms through which Meth affects innate immunity at the post transcriptional level, and promotes HIV-1 pathobiology. We investigated miR-146a, a well-characterized member of the innate immune signaling network, for its role in Meth-mediated effects on HIV-1 in primary CD4$^+$ T-cells. We hypothesized that miR-146a would play a key role in altering host innate immune pathways in the presence of Meth to promote HIV-1 replication. Moreover, we explored the role of miR-146a in Meth-induced anti-retroviral drug resistance. Our results showed that Meth induces an Interleukin-1β (IL-1β)-miR-146a axis to disrupt innate immune signaling. In addition, we observed decreased efficacy of the integrase inhibitor Raltegravir in the presence of Meth, which correlated with altered expression of IL-1β and miR-146a. Our findings indicate that Meth activates a negative feedback loop involving IL-1β and miR-146a to alter innate immune pathways and provide a more favorable environment for HIV-1 replication and anti-retroviral evasion.