Submitter Name: Fengchun Ye
PI Name: Jonathan Karn

Submitted Email: fxy63@case.edu
PI Email: jxk153@case.edu

Nurr-est neighbors: RXR induces epigenetic silencing of HIV-1 in microglial cells

Fengchun Ye, Kien Nguyen, Yoelvis Garcia-Mesa, Sheetal Sreeram, David Alvarez-Carbonell, Konstantin Leskov, and Jonathan Karn

Department of Microbiology & Molecular Biology, School of Medicine, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, Ohio 44106

Methamphetamine (METH) selectively injures dopaminergic neurons. We have demonstrated that healthy neurons silence HIV while damaged neurons induce reactivation of latent HIV and microglial activation, suggesting a role of METH in exacerbating the development of HIV-associated neurocognitive disorder (HAND) by inducing HIV expression. Indeed, HIV infected METH abusers often display a more severe cognitive impairment and possess a smaller hippocampal volume. We therefore attempt to explore cellular mechanisms that antagonize and/or reverse the effects of METH on HIV expression and microglial activation as potential therapeutic targets for treatment of HAND. Previously, we identified the glucocorticoid receptor (GR) and the orphan nuclear receptor Nurr1 as key components of HIV silencing machinery in microglial cells. Here report that the ligand-dependent nuclear receptors RXRs are additional factors that contribute to HIV silencing in microglial cells. Activation of RXRs with bexarotene, a specific RXR agonist, substantially reduced HIV-1 expression in both immortalized human microglial cell model (HC69) and induced pluripotent stem cells (iPSC)-derived microglial cells (iMG). We also found strong interactions between RXRs, GR, and Nurr1 and observed additive effects on HIV silencing when all three types of nuclear receptors are activated with specific agonists. Like GR and Nurr1, activation of RXRs also results in recruitment of the CoREST repressor complex, which contains multiple epigenetic silencing factors, to the 5'LTR of HIV-1 proviruses, leading to rapid epigenetic changes for transcriptional shutdown. Our data highlight great therapeutic potentials of pharmaceutical targeting these nuclear receptors for reversing the effects of METH and treatment of HAND.