Submitter Name: Fengchun Ye
Submitted email: fxy63@case.edu
PI Name: Jonathan Karn
PI email: jonathan.karn@case.edu

Modulation of HIV-1 replication in microglial cells by the competing orphan nuclear receptors Nurr1 and Nor1

Fengchun Ye[1], David Alvarez-Carbonell[1], Curtis Dobrowolski[1], and Jonathan Karn[1]

[1]Department of Molecular Biology and Microbiology, Case Western Reserve University

To study the molecular events controlling HIV expression in the microglia, we have used SV40 T and hTERT antigens to develop immortalized microglial cells from primary glial sources. The immortalized cells have microglia-like morphology, express key microglial surface markers including CD11b, TGFβR, and P2RY12, and the RNA expression profiles are characteristic of microglial cells. While HIV latency is achieved in most cells, a subset of cells constantly undergo spontaneous HIV reactivation, due to autocrine stimulation by TNF-α. In contrast to T-cells, where HIV latency arises due to quiescence of the host cell and epigenetic silencing, microglial cells have evolved gene attenuation mechanisms mediated by the nuclear orphan receptors Nurr1 and Nor1. Nurr1/Nor1 agonists substantially inhibit Tat expression in microglial cells and help recruit the CoREST (EHMT2) suppressive histone methyltransferase complex. However, the two receptors act at distinct stages to suppress both HIV transcription and the expression of inflammatory cytokines. Overexpression of FLAG-tagged Nor1 blocks HIV expression when cells were exposed to low dose TNF-□or methamphetamine (METH), suggesting that Nor1 prevents reactivation of latent HIV-1. In contrast, over expression of FLAG-tagged Nurr1 did not inhibit HIV induction, but effectively suppressed cells fully activated by TNF-□or METH. Thus, Nurr1 and Nor1 promote HIV-1 latency in microglial cells at two different stages, most likely by interacting with NF-□B to recruit the CoREST complexes. These results suggest the potential use of Nurr1/Nor1 agonists for silencing HIV in the brain.