Regulation of HIV Silencing by Nuclear Receptors

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Although HIV-infected individuals develop HIV-associated neurocognitive disorder (HAND), the correlation between cognitive impairment and CSF viral load is not particularly robust, and the development of HAND is strongly associated with the presence of inflammatory cytokines in the CNS. A likely resolution of this paradox is that HIV persists in the CNS due to latent infection of microglial cells, which then become reactivated in response to inflammatory signals. We recently reported that damaged neurons and inflammatory cytokines can induce HIV transcription in latently infected microglia whereas healthy neurons silence reactivated HIV. shRNA-based gene knock-down (KD) in microglial cells identified glucocorticoid (GR/NR3C1), Nurr1 (NR4A), and retinoid X (RXR) receptors as key mediators of HIV silencing. Following stimulation with TNF-α, shRNA KD or Cas-9/CRISPR-based knock-out (KO) of each of these nuclear receptors strongly inhibited HIV silencing during a “chase” in the absence of inflammatory cytokines. Similarly, specific agonists of the nuclear receptors enhanced HIV silencing and the simultaneous activation of all three nuclear receptors resulted in a more robust silencing of HIV. Mechanistically, we found that these nuclear receptors interact with and recruit the CoREST/HDAC/G9a/EZH2 repressor complex to the HIV promoter, inducing histone deacetylation and di or tri-methylations that inactivate HIV transcription. We conclude that these nuclear receptors work in concert to silence HIV in microglial cells by recruiting epigenetic silencing complexes, and that their agonists can potentially be exploited pharmaceutically to limit neuronal damage due to HIV infections in the CNS.