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## **Virus on the brain: Inflammation and cross-talk between microglia and neurons regulate HIV latency**

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HIV latency in microglia was modeled using cells derived from adult human brain cortex transformed with SV40 large T antigen and hTERT. Proviral silencing is primarily through recruitment of CoREST epigenetic repressive complexes and inhibition of the histone methyltransferases G9a/EHMT2 or GLP/EHMT1 promotes HIV emergence from latency. HIV is reactivated in response to a wide range of TLR agonists, but especially in response to poly(I:C), a TLR 3 agonist, where the virus is induced by a previously unreported mechanism mediated by IRF3. Addition of dexamethasone (DEXA), a glucocorticoid receptor (GR) agonist and mediator of anti-inflammation, or shRNA to GR, silenced the HIV provirus. Remarkably, in a clonal activated microglia/HIV population (HC69), healthy neurons induced HIV latency in a neuron/microglia ratio-dependent manner. By contrast, damaged neurons, including primary mouse neurons exposed to METH, reactivated HIV expression in latently infected cells. Thus, our results demonstrate that the cross-talk between neurons and microglia regulates HIV expression and that HIV expression can exacerbate METH-induced neuronal damage. To extend these in vitro studies, we developed a humanized mouse model. When radiation or busulfan conditioned, immune-deficient NSG mice are transplanted with human hematopoietic stem cells, human cells from the bone marrow enter the brain and differentiate to express microglia-specific markers, reaching levels of up to 10% engraftment. After infection with replication competent HIV, virus was detected in these bone-marrow derived human microglia. HIV latency can be demonstrated in this model using compounds identified in our studies of microglial HIV latency reactivate the provirus, such as poly(I:C).