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Methamphetamine-Induced Upregulation of Deubiquitinating Enzymes (DUBs) Promote HIV Proviral Transcription by Enhancing SWI/SNF Chromatin Remodeling Complex

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Methamphetamine (METH) is a potent and addictive psychostimulant that causes the pathogenesis of the end-organs, including central nervous system (CNS) and liver. METH abuse also increases the risk of human immunodeficiency virus 1 (HIV-1) infection and HIV-1-associated neurocognitive disorder (HAND). The molecular mechanisms by which METH contributes to HIV persistent infection, however, remain poorly understood. In this study, we investigated the impact of METH on microglial cells, which are the key mediators of neuroinflammation in the context of HIV infection. Using RNA sequencing (RNA-seq) approach, we identified a series of differentially expressed genes in METH-treated microglia. Our findings show that METH treatment leads to the significant upregulation of the pro-inflammatory chemokines of CXCL family. Furthermore, we observed the increase of deubiquitinating enzyme (DUB) expression in METH-treated microglia, suggesting the disruption of protein turnover pathways. Notably, DUBs have been implicated in regulating protein ubiquitination and stability of SWI/SNF chromatin remodeling complexes that are required for HIV transcriptional activation. We propose that upregulation of DUBs in response to METH would promote HIV persistent infection in microglia by elevating protein level of chromatin remodelers that participate in HIV proviral transcription. Our findings provide the novel insights how METH-mediated changes of gene expression, including CXCLs and DUBs, would regulate HIV infection at the CNS. Further exploration of these pathways will improve our understanding of HIV and substance use disorder (SUD) comorbidities of neuroHIV and HIV-associated neurological complications. It will also provide the new therapeutic strategies to curtail HIV infection at the CNS in the context of SUDs for people living with HIV (PLWH).