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Drug self-administration in a rodent model of HIV: from RNA-Seq to druggable targets.

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Substance use disorder (SUD) exacerbates the deleterious effects of HIV infection. A major challenge in the AIDS therapeutic development field is to identify targetable mechanisms to avert persistent neuronal dysfunction in HIV-infected individuals undergoing otherwise successful antiretroviral therapy (ART). Our interdisciplinary approach integrates transcriptomics, behavior methods, and computational strategies to formulate novel testable mechanistic hypotheses that can lead to transformative new therapeutic concepts for SUD in the HIV setting. We use gene expression profiling by RNA-Seq at the bulk and single nucleus levels in intravenous self-administration paradigms in HIV transgenic and wild type rats under conditions of either short access (ShA), which is characterized by a non-dependent, “recreational” pattern of drug use, or long access (LgA) conditions, which leads to escalated (dependent) drug intake. Parallel studies with stimulants and opioids self-administration are designed to highlight both common and diverse transcriptional dysregulations and candidate therapeutic targets. We employ network-based algorithms based on approaches that proved exceptionally effective in deconvolving molecular interactions in cancer. Our systems biology analyses are aimed at identifying key master regulator genes governing the gene signatures associated with escalated drug self-administration and HIV, their co-regulators and targets that can serve as candidate therapeutic targets to improve neuropsychological functioning in people with HIV and SUD comorbidity. We leverage the capabilities of the Scripps Molecular Screening Center to carry out high-throughput screenings to identify small molecule inducers of a candidate target for the neurodegenerative changes that characterize SUD and neuroHIV inferred using the present experimental-computational strategy.