

Name: Samikkannu Thangavel

Email: thangavel@tamu.edu

HIV-1 Tat and Cocaine Impact the LIN01133-hsa-miR-4726-5p - NDUFA9 axis to Modulate Astrocyte Energy Metabolism

Mayur Doke ¹, Jay P. McLaughlin ² and Thangavel Samikkannu¹

¹Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M University Health Science Center, Kingsville, Texas-78363; ² Department of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, Florida-32611, USA

HIV infections and cocaine use are known to impact neuronal function. Clinical research has also proved that HIV positive patients (HIV+) using cocaine show deterioration of brain metabolic functions associated with behavioral and neurocognitive disorders. In the central nervous system (CNS), astrocytes are the primary regulators of energy metabolism, and impairment of astrocyte energy resources may trigger neurodegeneration. HIV and cocaine use interfere with energy homeostasis and alter epigenetic modification, including lncRNAs, which can target gene expression post-transcriptionally. Previous reports have shown that non-coding RNAs such as lncRNAs and miRNAs regulate the gene expression in HIV infection and drug abuse studies. However, no specific lncRNA and miRNAs biomarkers are associated with HIV infection and cocaine-induced neuropathogenesis. Moreover, previous research showed that genes could be regulated through an independent mechanism of lncRNA-miRNA interactions. The integrative bioinformatic analysis of our study showed significant expression alterations in 10 lncRNA, 10 miRNA, and 4 mRNA found in human primary astrocytes exposed to HIV-1/cocaine, and in the brains of mice *in vivo* after exposure to cocaine and/or HIV-Tat protein. We further characterized the alteration in expression of two miRNAs (hsa-miR-2355 and hsa-miR-4726-5p), four lncRNAs (LINC01133, H19, HHIP-AS1, and NOP14-AS1), and four genes (NDUFA9, KYNU, HKDC1, and LIPG). In addition, application of an siRNA targeting LINC01133 uncovered interactions between LIN01133- hsa-miR-4726-5p - NDUFA9. Our data support the evidence that cocaine and HIV-Tat modulate astrocyte energy metabolism by impairing the LIN01133- hsa-miR-4726-5p - NDUFA9 axis, thereby contributing to the neurodegeneration observed in HIV+ cocaine users.

National Institute on Drug Abuse Grant DA044872 supported this work.