

Submitter Name: Samikkannu Thangavel  
Submitted email: thangavel@tamu.edu

## **Epigenetic Modification of Mitochondrial DNA in the Development of NeuroAIDS**

Kalaiselvi Sivalingam<sup>1</sup>, Venkatesh Jeganathan<sup>1</sup> and Samikkannu Thangavel<sup>1</sup>

<sup>1</sup>Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M University

HIV infections and cocaine use have been identified as risk factors for neurodegeneration. Astrocytes are the primary regulators of energy metabolism in the central nervous system (CNS), in which mitochondria maintains this cellular energy homeostasis. Impaired astrocytic energy metabolism may trigger neurodegeneration. Cocaine abuse and HIV infections are known to interfere with this energy homeostasis and could possibly affect mitochondrial DNA (mtDNA) in which DNA methylation, an important epigenetic modification has not been elucidated yet. We hypothesize that HIV-1 Tat and cocaine exposure could impair DNA methylation by suppressing the function of mtDNA methyltransferase, thereby mediating the mitochondrial genome elicited disease progression. To study our hypothesis, we treated human astrocytes with HIV-Tat and cocaine, individually or in combination. We then examined the mtDNA methylation as well as the targeted genome region D-loop and NADH dehydrogenase subunit 1–6 [ND1-ND6]. Methylation of mtDNA was analyzed by targeted next-gen bisulfite sequencing, whereas the mRNAs levels of mtDNA encoded genes were quantified by QPCR. We observed a significant decrease in DNMTs in mtDNA extracts. The detected regions in mtDNA include D-loop, ND1-ND6, and CYTB. Bisulfite pyrosequencing analysis of mtDNA D-loop (+121 to +62) and encoded gene ND1-ND6 regions revealed that the overall decrease in mtDNA methylation from HIV-Tat/cocaine exposure was predominantly in RNR1, ND1, ND5, and CYB regions compared with controls. Our data support the evidence that cocaine and HIV-Tat affect astrocyte energy metabolism by impairing mtDNMTs activity, which might be a contributing factor to neurodegeneration, as observed in HIV-positive cocaine users.