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Epigenetic signature of N-terminal acetyltransferases role in HIV-Neuropathogenesis

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HIV infection is often accompanied by activated macrophages/microglia in the central nervous system (CNS), which is the primary reservoir and driver of disease progression. HIV-associated neurocognitive disorder (HAND) is characterized by depression, behavioral, and motor dysfunctions. HIV infection affects epigenetic signatures such as post-translational gene changes, protein modifications and subcellular localization. However, the exact mechanism of the N-terminal acetylation (N-acetylation) role needs to be elucidated. We hypothesize that the epigenetic changes caused by HIV infection induces through the activation of N-terminal acetyltransferase in the HIV-positive (HIV+) brain and HIV-Tat-exposed CNS cells. The present study uses integrated quantitative proteome analysis to comprehensively uncover the changes in protein profiles in human brain samples of HIV+ brain tissues compared to normal brain tissues. Label-free LC/MS-MS analysis of HIV+ brain tissue samples revealed alteration in the mitochondrial proteins with N-terminal acetylated protein as indicated by proteomic and bioinformatics approach using the data-independent acquisition method. Validation analysis of expression of N-terminal acetyltransferase proteins (NAT) in the CNS primary human astrocytes, microglia, and neuroblastoma cell expression was conducted by western blot. The integrative bioinformatics analysis showed that 3294 proteins were altered and 426 protein expressions were differentially expressed in the HIV+ brain compared with normal. Specifically, the HIV+ frontal and temporal lobes differentially expressed 132 and 119 proteins, respectively. The HIV+ frontal lobe region showed significant alterations in GOLPH3, IMPDH2, DYNLL1, RPL11, and GPNMB proteins compared to normal brain tissues. The specific role of NAT proteins in the brain was further analyzed and validated in CNS cell culture after exposure to HIV-Tat protein. N-terminal acetylation expression was observed predominantly in brain tissues and primary microglial cells compared with either astrocytes or neurons. Our results suggest that HIV infection and HIV-Tat protein exposure affect the epigenome signature, especially in N-terminal acetylation in microglia, suggesting a crucial role of microglia in HAND pathogenesis in HIV-positive individuals.

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