Submitter Name: Ke Xu
Submitter email: Ke.Xu@yale.edu
PI Names: Eric O Johnson
PI emails: ejohnson@rti.org
Bradley E Aouizerat
bea4@nyu.edu

Epigenome-wide characterization reveals aberrant DNA methylation of host genes regulating CD4+ T cell HIV-1 latent reservoir size in women living with HIV

Ke Xu, MD, PhD [1,2], Xinyu Zhang, Ph.D. [1, 2], Josephine N. Garcia, BS [3,4], Carlos V. Domingues, BS [3,4], Bryan C. Quach, PhD [5], Grier P. Page, PhD,[5,6] Dana B. Hancock, PhD[5], Eric Otto Johnson, PhD[5,6], Bradley E. Aouizerat, PhD[3,4]

[1]Department of Psychiatry, School of Medicine, Yale University; [2]VA Connecticut Health Care eteran's Affairs Connecticut Healthcare System; [3]Department of Oral and Maxillofacial Surgery, New York University; [4]Translational Research Center, New York University; [5]GenOmics, Bioinformatics, and Translational Research Center, Biostatistics and Epidemiology Division, RTI International; [6]Fellow Program, RTI International

Abstract

The HIV-1 latent reservoir (HLR) is a major barrier to HIV cure, but the underlying mechanism of HIV-1 latency is largely unknown. Immune defense and HIV-1 DNA integration perturbs the host epigenetic landscape that may silence HIV-1 replication. Applying bisulfite capture DNA methylation sequencing, we profiled approximately 3.2 million CpG sites (CpGs) in $CD4^+$ T cells isolated from 427 virally suppressed women with HIV. The average total HLR_{CD4} size was 1,409 copies/10^6 cells. Most of the provirus were defective with a small proportion of the HLR being intact provirus. We identified 245 differentially methylated CpGs and 85 differentially methylated regions associated with the HLR_{CD4} size. Fifty-two percent of significant CpGs were in intronic regions. HLR_{CD4}-associated genes are involved in viral replication (e.g. *ISG15*), HIV-1 latency (e.g. *MBD2*), and cell growth and apoptosis (e.g. *IRF9*). A subset of the identified genes that harbored aberrant CpGs are established targets of HIV-1 integration (e.g. *NFIA, SPPL3, DLEU2, ELMSAN1*). Overall, HLR_{CD4} size was inversely associated with CpG methylation of the interferon signaling gene family while being positively associated with methylation of regions that are established HIV-1 integration sites. HLR-associated genes were enriched in pathways including immune defense against virus (i.e. interferon-α and -γ response), DNA binding transcription repression, and host-virus interaction such as Tau protein binding. Together, our results demonstrate that significant epigenomic alteration in $CD4^+$ T cells contribute to HIV-1 latency, which adds new knowledge of the understanding of HIV-1 latency and may provide molecular targets for HIV-1 eradication in the future.