Chromosomal integration site profile of HTLV-1 infected cells is distinct from HIV-1 infected cells

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Alexander Hochroth[1], Nicolas Ducasa[2], Maxime Bellefroid[1], Ce Gao[1], Chloe Naasz[1], Xu Yu[1], Mirna Biglione[2], Mathias Lichterfeld[1]

[1]Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA, USA [2] Instituto de Investigaciones Biomédicas en Retrovirus y SIDA (INBIRS), CONICET – Universidad de Buenos Aires, Buenos Aires, Argentina

BACKGROUND

- Both HTLV-1 and HIV-1 cause lifelong, incurable infections.
- In HIV-1, intact proviruses progressively accumulate in areas of heterochromatin, likely due to immune mediated selection (1)
- Whether and how proviral integration site locations influence persistence of HTLV-1-infected cells remains less clear.
- By analyzing individual proviral sequences and integration sites from people living with HTLV-1 (PLWHT) we hope to investigate differences in integration site profiles between HIV-1 and HTLV-1 cells

COHORT

Sample ID	Clinical Characteristics	Cells Assayed (thousands of cells)	Presumed Intact Sequences	Defective Sequences
HTLV01	Asymptomatic	0.85	19	9
HTLV02	Asymptomatic	3.67	21	14
HTLV03	Asymptomatic	14.9	16	5
HTLV04	Asymptomatic	1.90	20	10
HTLV05	Smoldering T-cell Leukemia Lymphoma	0.71	38	15
HTLV06	Acute T-cell Leukemia Lymphoma	1.00	33	6

METHODS

- Individual proviruses were identified in PBMCs collected from PLWHT using previously published full-length individual proviral sequencing (2,3)
- Integration sites of proviruses were determined using Integration Site Loop Analysis (ISLA) (3) and Ligation-Mediated PCR (LM-PCR) (4)
- Proviruses in HTLV05 and HTLV06 were identified by sorting single cells into a 96-well plate using Fluorescence Active Cell Sorting (FACS) and screening with HTLV-1 specific primers
- We compared HTLV-1 reservoir profiles to previously published HIV-1 reservoir profiles from Elite Controllers (EC) (1) and long-term ART treated individuals (LTART) (5)

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HTLV-1 proviruses appear more frequently than HIV-1 proviruses in centromeric regions and are more distant from transcriptional start sites

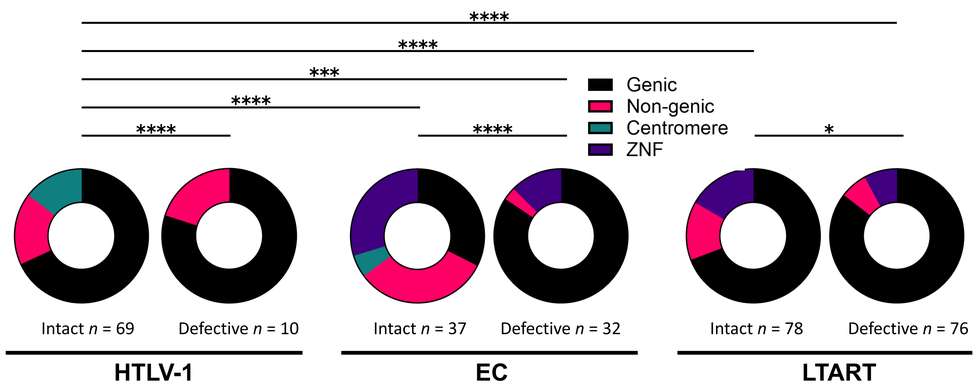


Figure 1. Proportionate representation of chromosomal locations of integrations sites in HTLV-1, EC, and LTART.

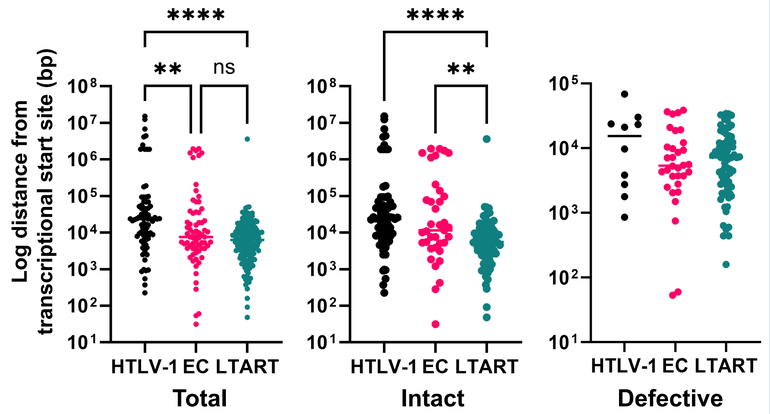


Figure 2. Distance of integration sites from Transcriptional Start Sites (TSS) for total, intact, and defective proviruses.

HTLV-1 proviral reservoirs exhibit low genetic diversity but diverse integration site profiles

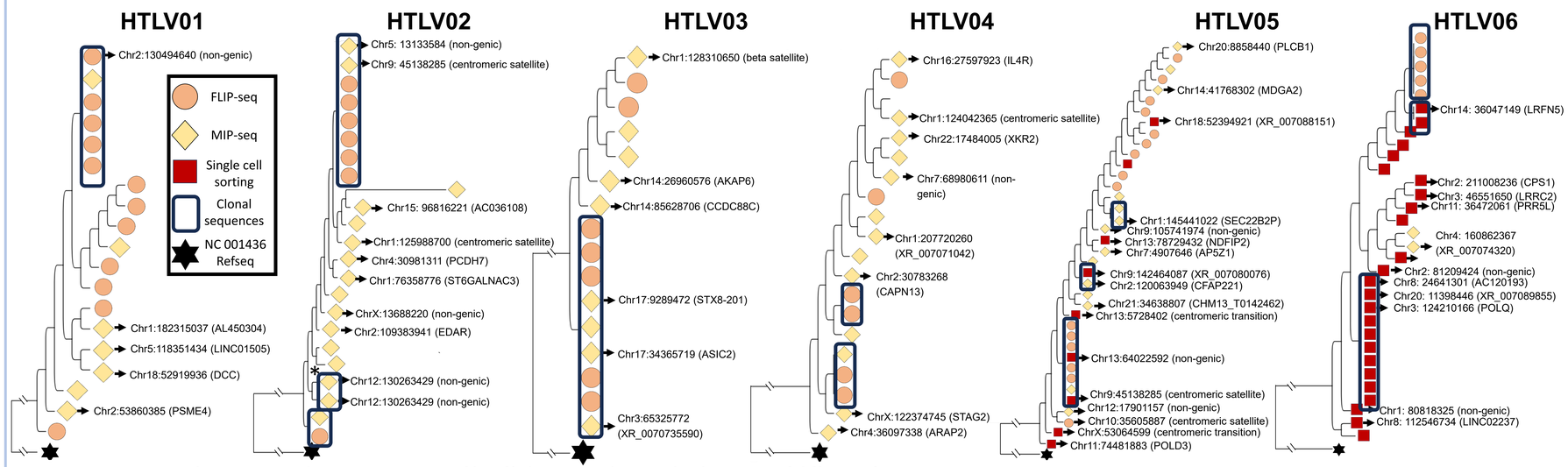


Figure 3. HTLV-1 proviral sequence and integration site profiles. (* denotes a clone with 1 base pair of difference)

CONCLUSIONS

Integration sites of HTLV-1 proviruses were distinct from those of HIV-1 proviruses in EC or long-term ART treated individuals, with higher proportions of proviruses in centromeric locations and a greater distance from transcriptional start sites. No HTLV-1 proviruses were found in ZNF genes. of HTLV-1 proviruses in these locations may indicate that they are less dependent on the chromatin microenvironment for long-term survival.

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