HIV Integration Site Features Associated with Persistence of Infected Cells Under CD8 Pressure

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ABSTRACT

In rare individuals who exhibit CD8-mediated control of HIV replication and people on long-term antiretroviral therapy (ART), the integration sites of intact HIV proviruses become skewed towards transcriptionally inactive genomic loci but the underlying mechanisms remain to be elucidated. Here we determine the role of elite controller CD8+ T cell pressure in shaping the HIV integration site landscape.

INTRODUCTION

- During HIV infection**, proviral DNA integrates into human chromosomes** – preferentially into transcriptionally active genes
- In HIV elite controllers, proviral integration sites in **transcriptionally silent genomic loci are overrepresented**.
- Understanding the **processes that drive the selection** for cells with such integration characteristics will support the interpretation of clinical studies.
- We hypothesize that **elite controller CD8 T cells** are sufficient in selecting for cells that expand into large clones and harbor provirus preferentially in genomic regions associated with HIV control.

KEY FINDINGS

EC CD8 T cells control HIV infection:

- HLA*B27-restricted HIV-KK10 epitope specific cells expanded to >20% of CD8 T cells, driving sustained >3 log reductions in viral load
- Marked reduction in the number and diversity of detected integration sites in +CD8 mice (-38.91 ±4.356*pp*, p=0.0001)

CD8 T cells shape the proviral l andscape in favor of provirus:

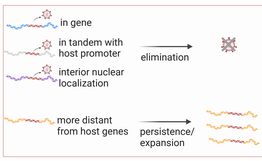
- Outside of genes (p=0.018)
- Further away from genes (p<0.001)
- Closer to the nuclear periphery (p=0.01)
- In opposite orientation relative to host gene transcription (p=0.002)
- in genes involved in chromatin organization, mRNA transport, and SUMOylation (p.adj<1e-9).

CONCLUSION

Our findings validate the idea that CD8 T cells can shape the integration site landscape by selecting for latent proviruses and describe a precise signature of this footprint. This mirrors features seen in HIV controllers and provides guidance for interpreting the impacts of clinical interventions.

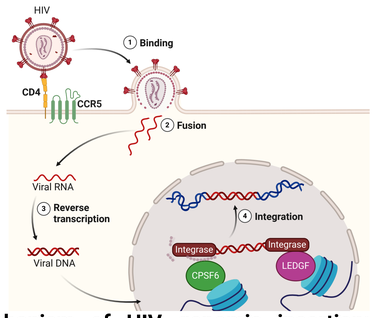
Current working model: CD8 T cells eliminate integration sites associated with HIV transcription





HIV preferentially integrates into transcriptionally active loci of the human genome. HIV-reactive Elite controller CD8 T cells eliminate the vast majority of infected cells with transcriptionally active provirus, thus skewing the proviral landscape in favor of viral latency and HIV control.

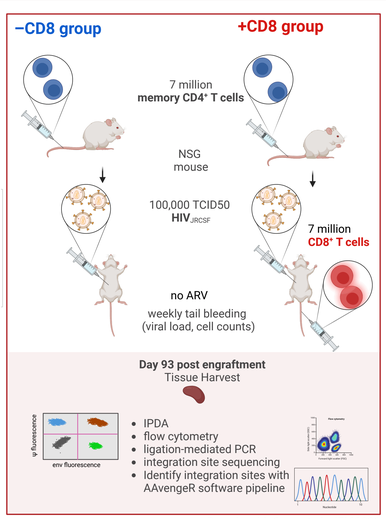
BACKGROUND



Mechanism of HIV genomic insertion: Host proteins including LEDGF and CPSF6 recruit HIV proviral DNA to actively transcribed genes.

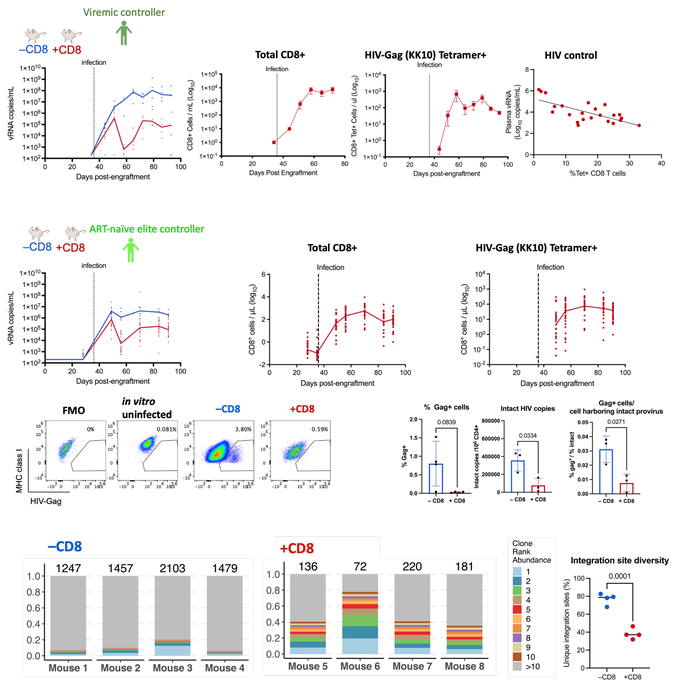


METHODS

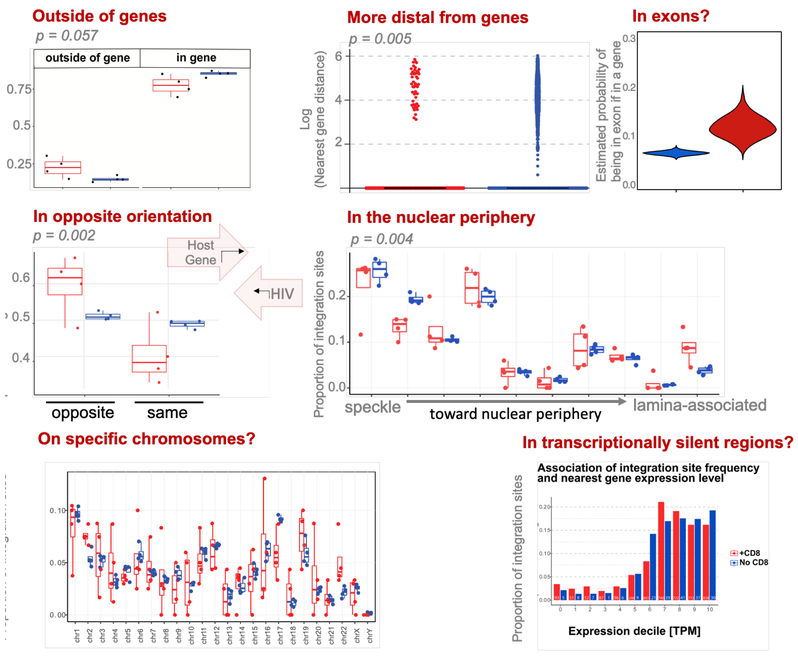


Based on McCann et al. *JEM* 2021

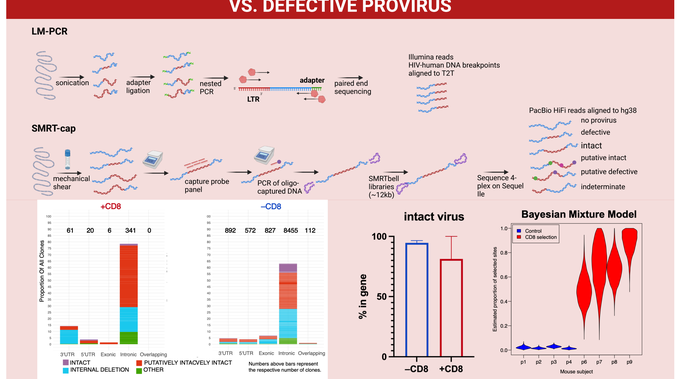
SUSTAINED CD8 T CELL PRESSURE ELIMINATES THE VAST MAJORITY OF INFECTED CELLS, BUT FAILS TO ELIMINATE INFECTED CLONES



CD8 T CELLS SELECT FOR HIV INTEGRATION SITES IN LOCI ASSOCIATED WITH TRANSCRIPTIONAL SILENCE



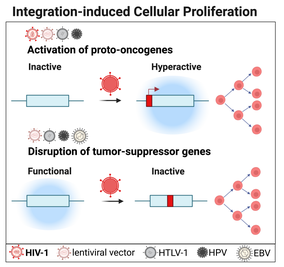
ANALYSIS OF TOTAL INTEGRATION SITES AND DIFFERENTIATION OF INTACT VS. DEFECTIVE PROVIRUS

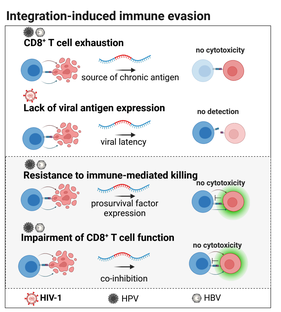


ENRICHMENT IN HIV INTEGRATIONS IN HOTSPOT GENES/ PATHWAYS



FUTURE DIRECTIONS





- Identify integration sites of intact provirus
- Distinguish clonal integration site features from unique integration events
- Killing assays to test relative immune resistance of PDX mouse-derived human cells.
- Sort HIV protein expressing cells and determine integration site pool
- Generate autologous ATAC-seq and RNA-seq reference dataset donors.

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