CD8+ T Cell-mediated Selection Enriches for HIV Integration Site Features and Expanded Clones In Vivo

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ABSTRACT

In rare individuals who exhibit CD8-mediated control of HIV replication and people on very 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 and people on long-term antiretroviral therapy (ART), 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:

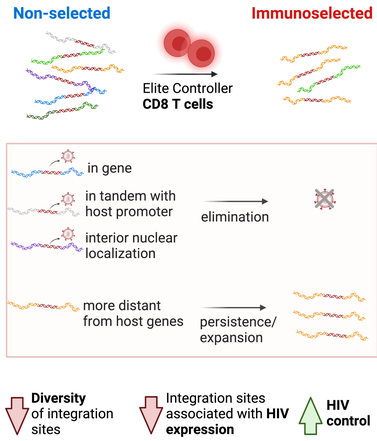
- HLA*B27-restricted HIV-KK10 epitope specific cells expanded to >20% of CD8 T cells, driving sustained >3 log reductions in viral load
- Marked reduction in the number and diversity of detected integration sites in +CD8 mice (-38.91 ±4.356*pp*, p=0.0001)

CD8 T cells shape the proviral landscape 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)

CONCLUSION

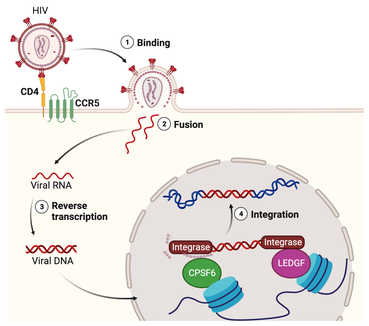
Our findings validate the idea that CD8 T cells can shape the integration site landscape by selecting for latent proviruses and describe a precise signature of this footprint. This mirrors features seen in HIV controllers and provides guidance for interpreting the impacts of clinical interventions.



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

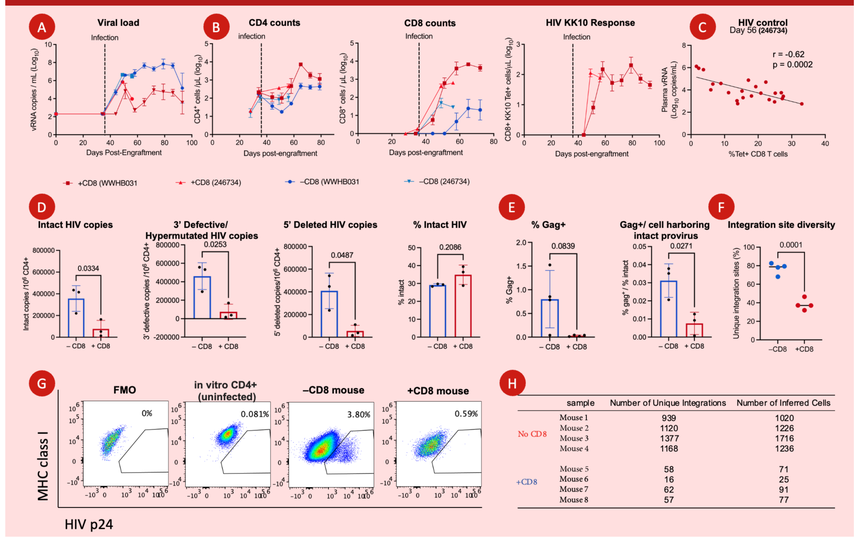
HIV preferentially integrates into transcriptionally active loci of the human genome. HIV-reactive Elite controller CD8 T cells eliminate the vast majority of infected cells with transcriptionally active provirus, thus skewing the proviral landscape in favor of integration sites associated with viral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

BACKGROUND

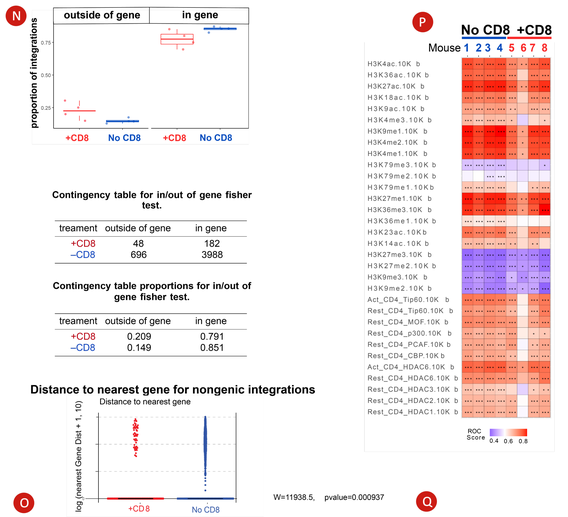


Mechanism of HIV genomic insertion:
Host proteins including LEDGF and CPSF6 recruit HIV proviral DNA to actively transcribed genes.

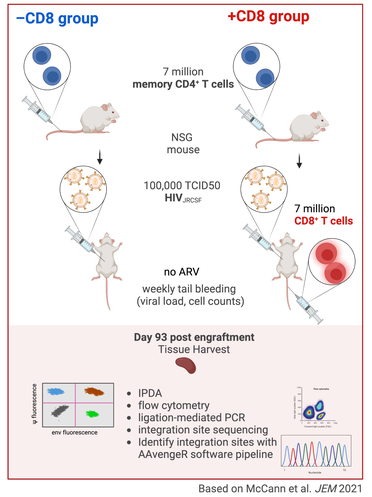
SUSTAINED CD8 T CELL PRESSURE ELIMINATES THE VAST MAJORITY OF INFECTED CELLS



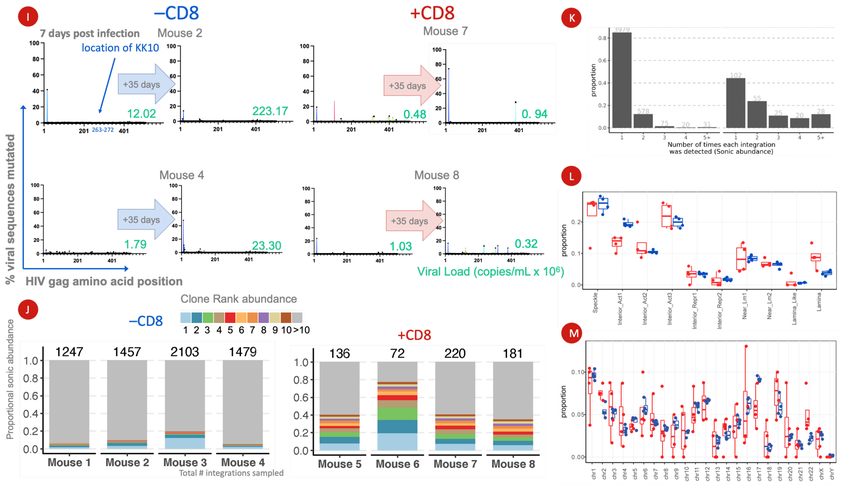
CD8 T CELLS SELECT FOR HIV INTEGRATION SITES IN LOCI ASSOCIATED WITH TRANSCRIPTIONAL SILENCE



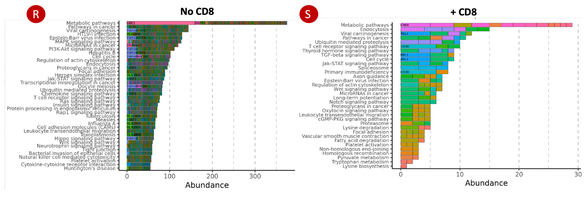
METHODS



CD8 T CELLS SELECT FOR CLONAL CD4 T CELLS

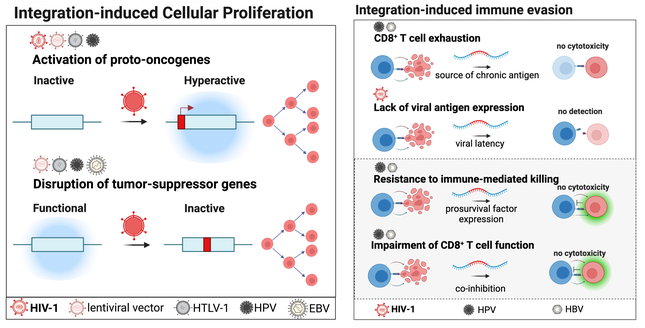


ENRICHMENT IN HIV INTEGRATIONS IN HOTSPOT GENES/ PATHWAYS?



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.
- Bioinformatic analysis to compare integration hotspots (IPA, gene ontology, and gene families) harboring integration sites in the +CD8 with those in -CD8 mice
- Generate autologous ATAC-seq and RNA-seq reference datasets from mouse-derived human cells



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