IL-10 and IFN Signaling Define Epigenetic States Linked to HIV Persistence or Resistance in Memory CD4⁺ T Cells

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INTRODUCTION

HIV persistence during antiretroviral therapy (ART) is sustained by immunoregulatory pathways that suppress antiviral responses. IL-10 has been linked to reservoir size and shown to inhibit interferon stimulated genes (ISG). In SIV-infected rhesus macaques (RMs), dual IL-10/PD-1 blockade enabled durable control after treatment interruption, while anti-IL-10 alone (aIL10) achieved partial control, highlighting IL-10 as a central regulator of reservoir persistence. We therefore investigated whether IL-10 reinforces viral persistence through Polycomb-mediated epigenetic silencing (PRC1/PRC2), which deposit repressive histone marks that constrain antiviral gene expression.

METHODS

In ART-suppressed SIV-infected rhesus macaques treated with anti–IL-10 or control, plasma vRNA, cell-associated vDNA, and lymph node multiome profiles (scRNA-seq and scATAC-seq) were analyzed (**Fig. 1A**). In humans, memory CD4⁺ T cells from ART-suppressed individuals were profiled by DOGMA-seq to map HIV vDNA within transcriptionally and epigenetically defined cell clusters (**Fig. 1B**)..

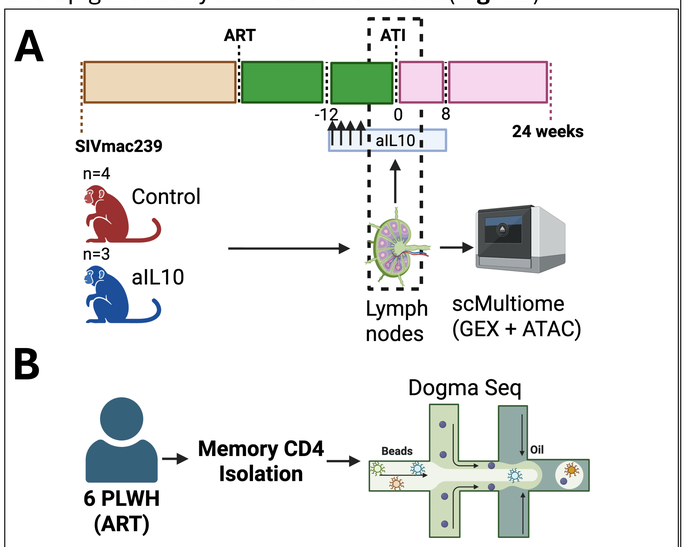


Figure 1. Study design and multiomic profiling strategy.

RESULTS

Differential Plasma Viral Suppression After aIL-10 Treatment

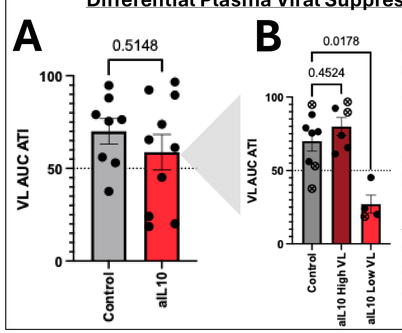


Figure 2. aIL-10 treatment identifies a responder subgroup with improved plasma viral control. (A) Plasma viral load measurements show that a **(B)** subset of treated NHPs exhibits enhanced viral suppression compared to controls, indicating heterogeneity in response to IL-10 blockade.
Animals indicated by crossed circle show comparable viral reservoir levels, indicating that reservoir size was not a confounding factor in this analysis.

IL-10 Blockade Reprograms T Cell States

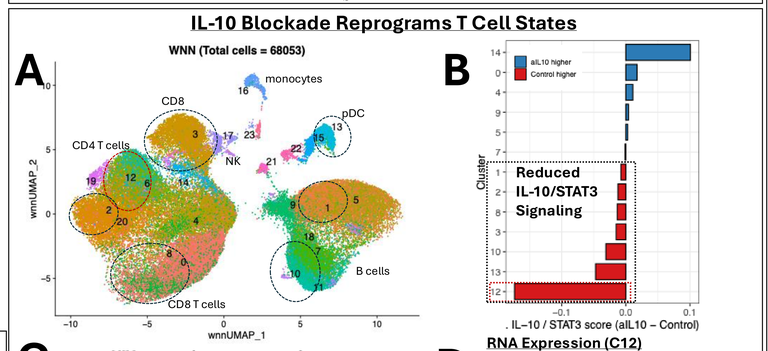


Figure 3. IL-10 blockade reshapes T cell states. (A) WNN integration of multi-omic lymph node data (68,053 cells) resolves major immune populations. **(B)** Cluster 12 shows reduced IL-10/STAT3 signaling (aIL-10 – Control). **(C)** Cluster 12 cells enriched for HIV reservoir-associated genes exhibit a heightened activation profile. **(D)** Increased TCR and activation markers are confirmed in aIL10 group animals.

Chromatin Accessibility Remodeling After IL-10 Blockade

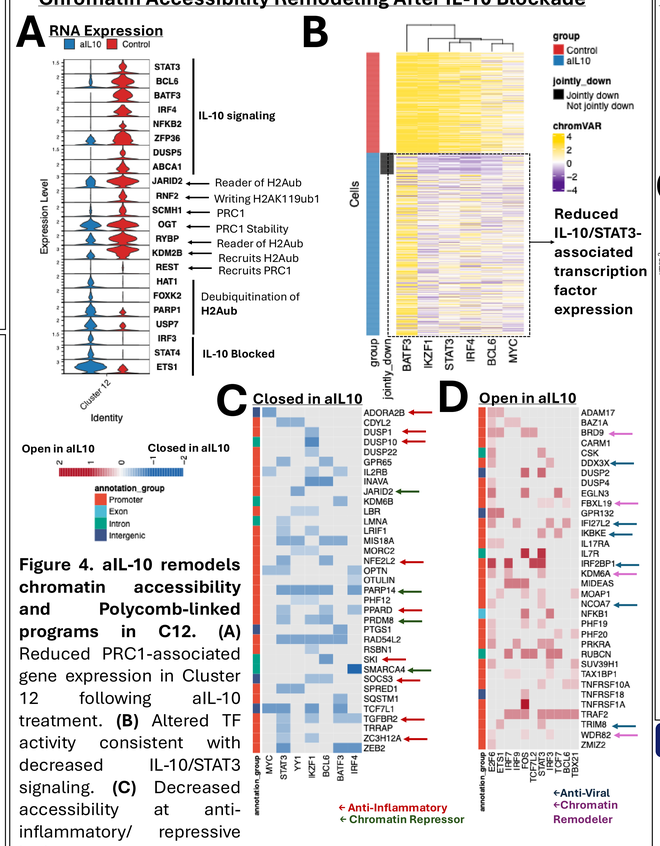


Figure 4. aIL-10 remodels chromatin accessibility and Polycomb-linked programs in C12. (A) Reduced PRC1-associated gene expression in Cluster 12 following aIL-10 treatment. **(B)** Altered TF activity consistent with decreased IL-10/STAT3 signaling. **(C)** Decreased accessibility at anti-inflammatory/ repressive loci. **(D)** Increased accessibility at ISG and chromatin remodeling genes, suggesting an enhanced antiviral state.

HIV Reservoir Localizes to STAT3–Polycomb States

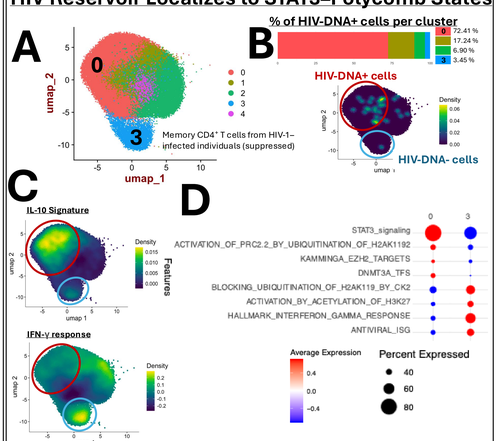


Figure 5. HIV vDNA localizes to distinct transcriptional and chromatin states in memory CD4⁺ T cells. (A) UMAP of memory CD4⁺ T cells from ART-suppressed individuals identifies five transcriptionally defined clusters. **(B)** HIV-DNA⁺ cells are unevenly distributed across clusters, with enrichment in Cluster 0 and lower representation in Cluster 3. **(C)** Density plots show Cluster 0 enriched for IL-10 signaling, whereas Cluster 3 exhibits stronger IFN-γ responses. **(D)** Pathway analysis reveals Cluster 0 is associated with STAT3/Polycomb-linked programs, while Cluster 3 displays enhanced interferon and antiviral signatures.

WORKING MODEL

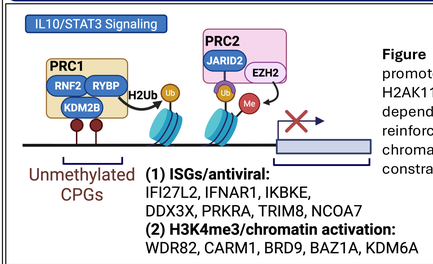


Figure 6. IL-10/STAT3 signaling promotes variant PRC1–mediated H2AK119ub deposition and JARID2-dependent recruitment of PRC2.2, reinforcing H3K27me3 at antiviral and chromatin activation loci and constraining ISG expression.

CONCLUSION

Our findings identify an IL-10/STAT3-dependent niche that sustains HIV reservoir persistence by reinforcing PRC1-mediated chromatin repression while maintaining a poised epigenetic state. Targeting IL-10 signaling relieves this constraint, enabling antiviral activation and potential reservoir clearance.

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