NFκB SIGNALING IN NATURAL KILLER CELLS PREDICTS POST-TREATMENT HIV CONTROL

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BACKGROUND

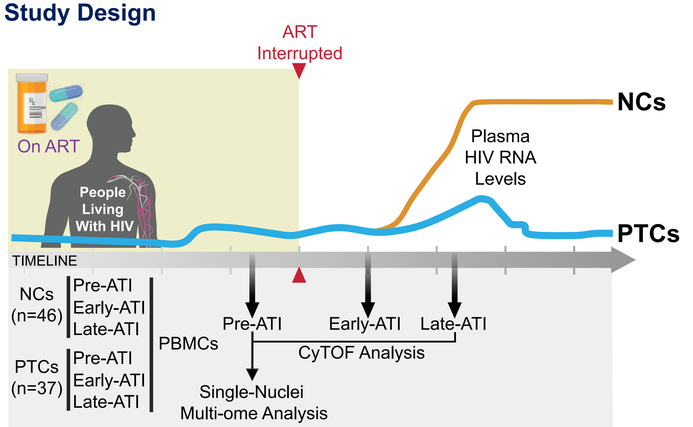
- For most people living with HIV (PLWH) on antiretroviral therapy (ART), cessation of ART results in rapid rebound of viremia.
- However, in rare individuals, called post-treatment controllers (PTCs), HIV is controlled through poorly understood mechanisms.

OBJECTIVE

- Our objective was to leverage multiomics approaches to assess the extent to which the transcriptomic and epigenetic features of immune cells in PTCs differ between those of non-controllers (NCs).

METHODS

(1) Study Design



CHAMP Study (PI: Jon Li)

- Longitudinal ATI study of 14 cohorts of PLWH
- Identified PTCs and NCs
- PBMCs collected before and during ATI

Biomark Study (PIs: Nadia Roan / Warner Greene)

- Longitudinal (pre- and post-ATI) PBMCs from PTCs and NCs:
  - CHAMP cohort
  - UCSF OPTIONS cohort
- PBMCs from all timepoints were analyzed by CyTOF, RNAseq, and other "omics" assays

Single-Nuclei "Multi-ome" Analysis

- Sub-study of Biomark
  - Pre-ATI timepoint
  - N = 7 PTCs (N = 6 PTCs after QC) and N = 7 NCs
  - UCSF OPTIONS cohort
- Paired single-nuclei assay for transposase-accessible chromatin (snATAC) and single-nuclei RNA (snRNA) sequencing (10X Genomics)

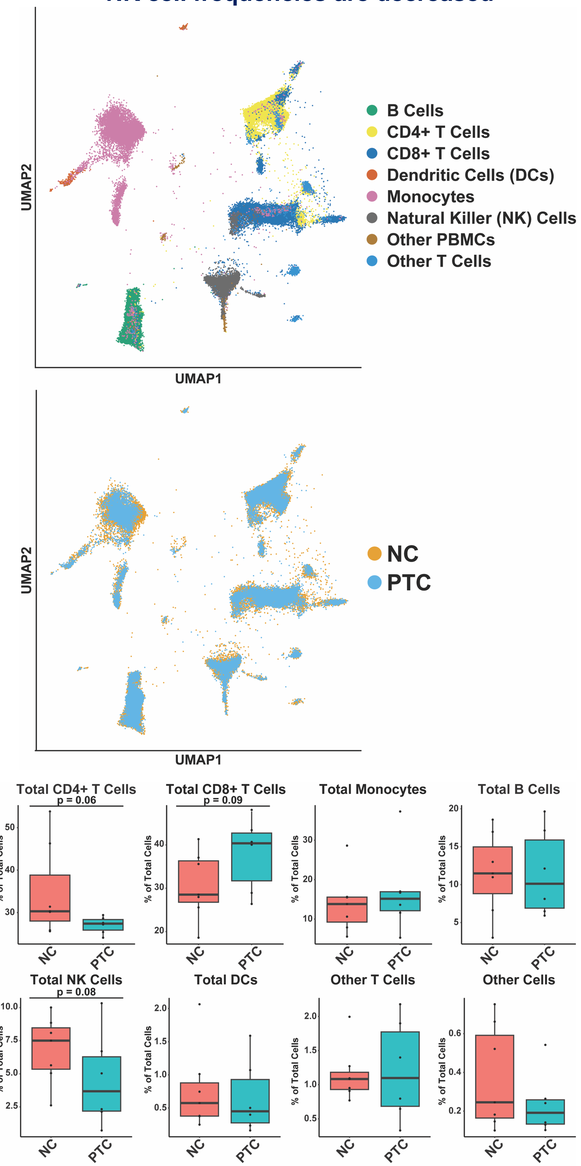
A special thanks to all of the participants!

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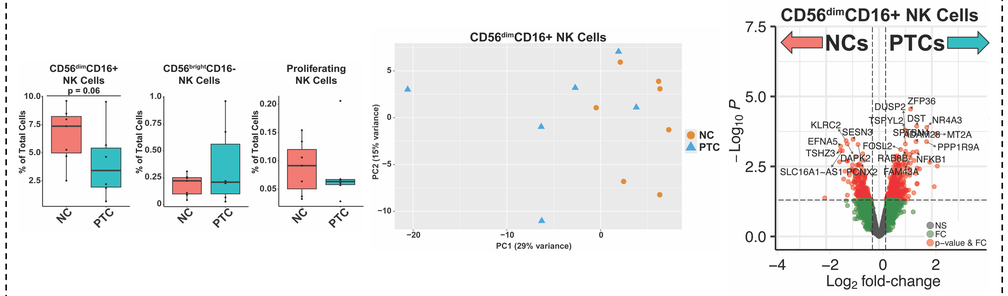
- NIH K99 HD110319 and Gilead HIV Cure Mentored Scientist Award (AFG)
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RESULTS

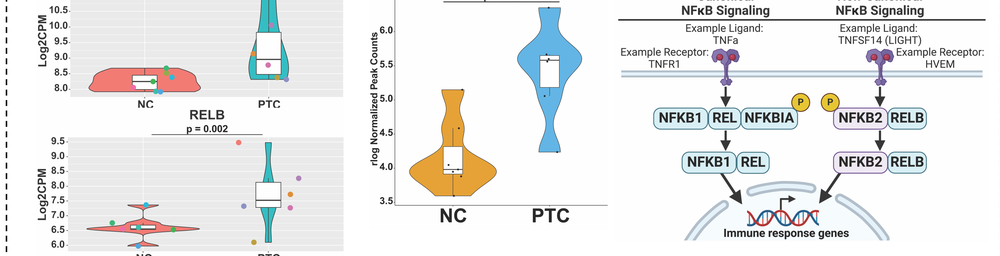
(1) In PTCs relative to NCs, CD8+ T cell frequencies are increased, while CD4+ T cell and NK cell frequencies are decreased



(2) CD56^{dim}CD16+ NK cells are enriched in NCs and are phenotypically distinct from their PTC counterparts

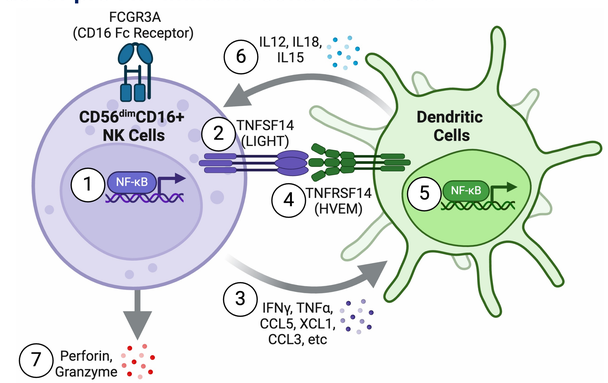


(3) Canonical and non-canonical NFκB signaling pathways are upregulated in CD56^{dim}CD16+ NK cells from PTCs



(4) Proposed model of pre-ATI immune control in PTCs

1. Activation of NFκB signaling in NK cells
2. Upregulation of TNFSF14
3. Cytokine production by NK cells, leading to recruitment of DCs
4. TNFSF14 engages with TNFRS14 receptor on DCs
5. NFkB activation and maturation of DCs
6. Increased production of cytokines by DCs
7. Enhanced cytotoxicity in NK cells



CONCLUSIONS / PERSPECTIVES

- Upregulation of genes within the NFκB signaling pathway among PTCs suggests that highly functional NK cells could play a critical role in mediating ART-free control of HIV, possibly by enhancing DC activation and maturation.
- Further investigation of how NFκB influences NK cell function, DC priming, and recognition of HIV-infected cells may inform the development of therapeutic strategies aimed at enhancing immune-mediated control of HIV.