Promoting Resident Memory CD8⁺ T-Cell Phenotypes to Enhance HIV Reservoir Elimination

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BACKGROUND

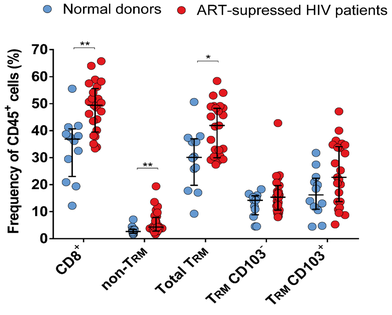
In tissues, where most of the HIV burden persists, antiviral resident memory CD8⁺T cells (T_{RM}) may be critical to eliminate latent cellular reservoirs and transcriptionally-active infected cells. Here we aimed to address the functional capacity of CD8⁺ T_{RM} phenotypes and the control they exert on the viral reservoir.

METHODS

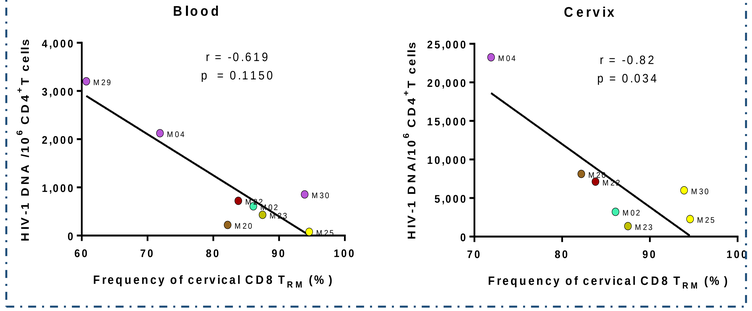
Based on CD69 CD103 to define T_{RM} subsets, CD8⁺T cells from cervical tissues were phenotyped and compared between healthy (n=12) and ART-suppressed HIV⁺ women (n=23). In a subset of these patients, we determined total vDNA in blood and cervix (n=7-8). A functional assay was established to assess suppression of reactivated CD4⁺T cells by cervical CD8⁺T_{RM} from an ART-suppressed HIV⁺ woman undergoing hysterectomy. To expand T_{RM}-like phenotypes from circulating CD8⁺T cells, PBMC obtained from ART-suppressed HIV⁺ patients were treated with cytokines. In these expanded CD8⁺ T_{RM}-like cells degranulation and IFNγ secretion against Gag was measured by flow cytometry (n=7), together with their capacity to eliminate the HIV reservoir (n=6).

RESULTS

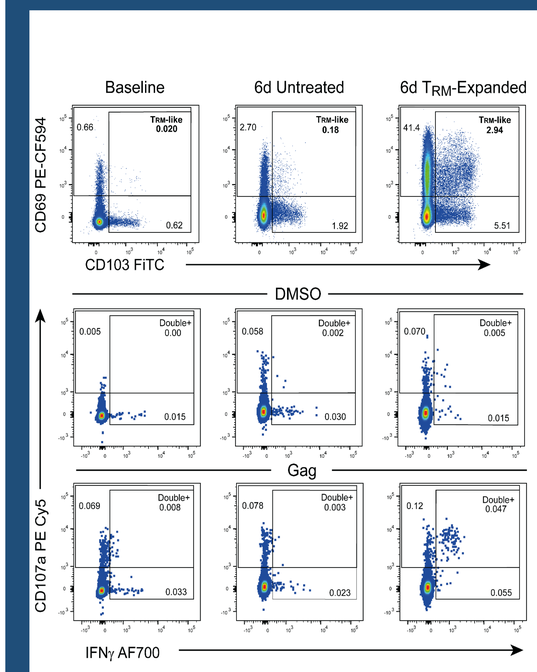
Higher frequencies of CD8⁺ T_{RM} and non-T_{RM}

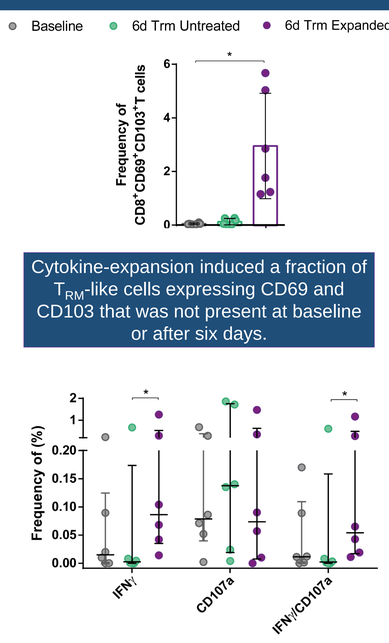


Frequency of CD8⁺ T_{RM} correlates with proviral DNA



Expanded-T_{RM} like cells from PBMC induce polyfunctional HIV-specific CD8⁺ T cells

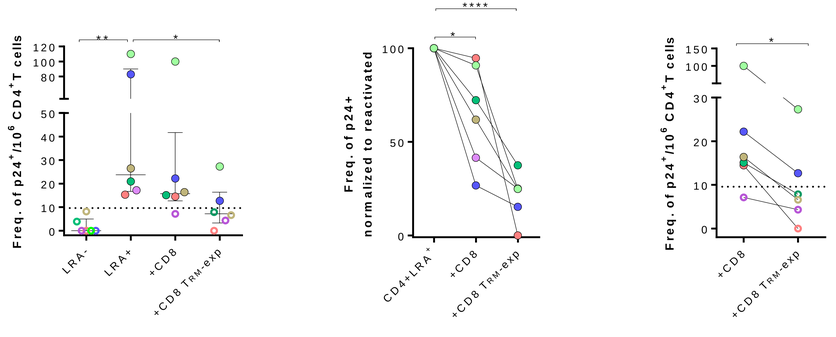




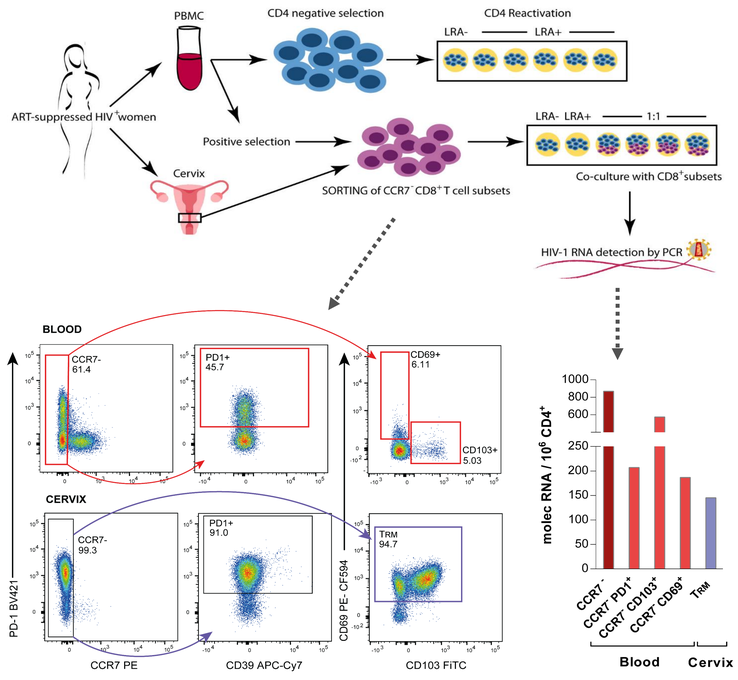
Cytokine-expansion induced a fraction of T_{RM}-like cells expressing CD69 and CD103 that was not present at baseline or after six days.

This expansion was accompanied by a polyfunctional IFNγ/CD107a Gag-specific CD8⁺ T cell response

Cytokine-expanded CD8⁺ T cells display enhanced elimination of the viral reservoir



CD8⁺T_{RM} from an ART-treated HIV⁺ patient control the viral reservoir



CONCLUSIONS

- Alterations of the CD8⁺ T cell compartment within the cervical mucosa remain in HIV⁺ women even after several years of effective ART-suppression.
- The association between higher proportion of CD8⁺ T_{RM} in cervix and less proviral HIV-1 DNA, together with data showing higher control of virally-reactivated infected cells by CD8⁺ T_{RM}, indicates that these cells may be critical to control persisting virus in tissues.
- CD8⁺ T_{RM} -like phenotypes should be potentiated to enhance control of viral persistence: we identify a promising immunotherapeutic strategy to achieve control of reactivated viruses.

ADDITIONAL KEY INFORMATION

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