CD103 EXPRESSION ON CD8 T CELLS PREDICTS LONGER TIME REBOUND OF HIV AFTER ATI 380

Tongcui Ma[1,2], Ashley F. George[1,2], Min-Gyoung Shin[3], Mauricio Montano[1], Satish Pillai[4], Katherine S. Pollard[3], Jonathan Z. Li[5], David Smith[6], Steven Deeks[7], Reuben Thomas[3], Warner C. Greene [1], Nadia R. Roan[1,2]

[1]Gladstone Institute of Virology, San Francisco, CA 94158, USA, [2]Department of Urology, University of California, San Francisco, CA 94143, USA, [3]Gladstone Institute of Data Science and Biotechnology, San Francisco, CA 94158, USA, [4]Vitalant Research Institute, San Francisco, CA 94105, USA, [5]Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA, [6]School of Medicine, University of California, San Diego, La Jolla, CA 92093, USA, [7]School of Medicine, University of California, San Francisco, CA 94110, USA

Background

Antiretroviral therapy (ART) suppresses HIV replication in people living with HIV (PLWH), but is not curative. Upon interruption of ART, viral typically rebounds within a period of several weeks, although prolonged time-to-rebound occurs in some individuals through unclear mechanisms. In this study, we used CyTOF to identify phenotypic features of T cells associated with time-to-rebound in the ACTG A5345 analytical treatment interruption (ATI) cohort, which included both individuals who initiated treatment during the acute and chronic phases of HIV infection.

Methods

We designed a 39-parameter CyTOF T cell phenotyping panel, which included markers of T cell differentiation, activation, exhaustion, and homing. We applied the panel on pre-ATI blood specimens from 33 chronic-treated and 11 acute-treated individuals from the ACTG A5345 cohort. We then performed clustering analysis to identify associations with time-to-rebound upon ATI.

Results

11 clusters were identified using a leave-one-out cross-validation model with a resolution of 0.2. Within the 11 clusters, 2 clusters were significantly ($p<0.01$) and positively associated with longer time-to-rebound. One of these, Cluster 8, consisted of memory CD8+ T cells, and the other cluster, Cluster 10, were memory CD4+ T cells. Cells in both clusters exclusively express high levels of CD103, the resident memory T cell marker. To explore other phenotypic features of the 2 clusters, we examined the expression levels of other markers within our panel. We found that memory CD8+ T cells in Cluster 8 expressed high levels of CD49d, the integrin alpha subunit that makes up half of the α4β1 homing receptor associated with mucosal tissue homing, and that has been used as a marker of T resident memory (Trm) cells. Cluster 8 cells also expressed CD73, a hypoxia-regulated ectonucleotidase recently identified as a host determinant of HIV latency. The second associated cluster, Cluster 10, expressed high levels of the co-stimulatory molecule CD28, CD29 (the beta integrin chain of α4β1), and gut-homing chemokine receptor CCR6. However, low levels of Birc5 (Survivin) were expressed on Cluster 10 cells.

Main findings

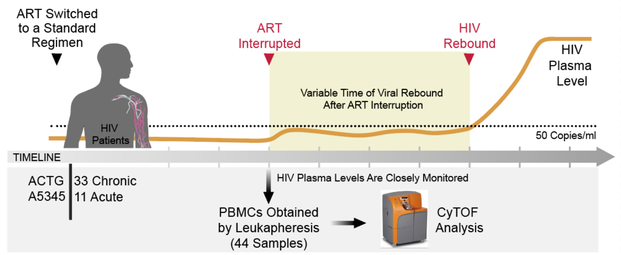
- CyTOF and clustering analysis identified 11 subsets of T cells from blood of ART-suppressed individuals
- Two clusters (one CD4, one CD8) were significantly and positively associated with longer time-to-rebound upon ART interruption
- Cells in both clusters uniquely express high levels of Trm marker CD103
  - CD103 may serve as a useful biomarker of HIV time-to-rebound upon ART interruption
- Cells in both clusters exhibit unique homing receptor expression, and may be poised to migrate into tissues where HIV persist

Future Directions

- To assess for differences in CD103 expression on T cells in individuals treated during acute vs. chronic infection
- To determine whether CD4+ and CD8+ Trm play a direct role in limiting viral replication upon ART interruption
- To determine whether CD103 expression on Trm can predict time-to-rebound upon ART interruption in other cohorts, including those receiving cure-based interventions

Study Design and Results

Schematic of the ACTG cohort undergoing analytical treatment interruption (ATI)



CyTOF panel for T cell phenotyping

Lineage Markers

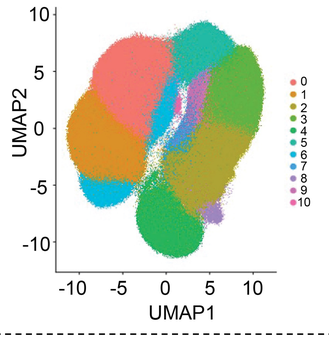
T Cells: CD3, CD4, CD8

B Cells: CD19

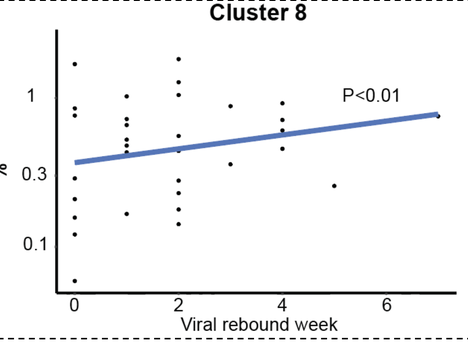
Phenotyping Markers

Differentiation State:	Activation State:	Homing Receptors:	Checkpoint Moleculars:	Adhesion and integrins:
CD45RO	CD69	CCR5	PD1	CD49d(α4)
CD45RA	CD25	CCR6	TIGIT	CD103
CD62L	CD28	CCR7	CTLA4	CD29(β1)
CD57	CD30	CXCR4		α4β7
CD127	HLADR	CXCR5		
CD27	CD38			
RORγt	ICOS			
Tbet	OX40			
CRTH2				
CD73				
Blimp1				
CD7				

11 clusters of T cells were identified from 39-parameter CyTOF panel phenotyping of ACTG PBMCs

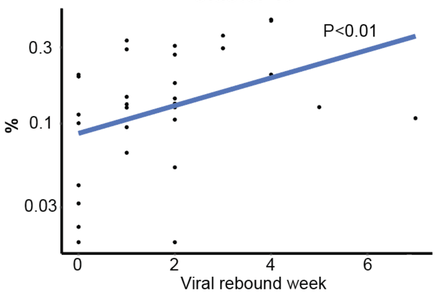


Cluster 8 is associated with longer time-to-rebound

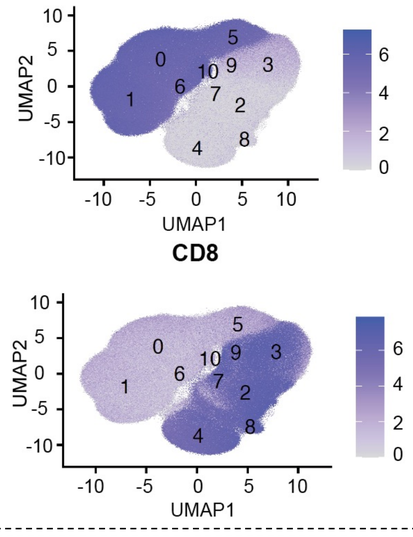


Results

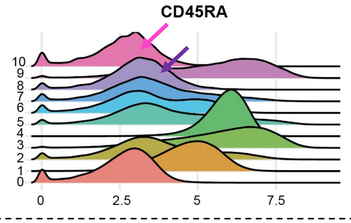
Cluster 10 is associated with longer time-to-rebound



Cells in Cluster 10 are CD4+ T cells and cells in Cluster 8 are CD8+ T cells

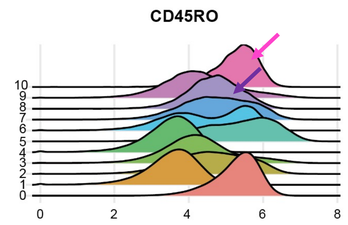


Cells in Clusters 8 and 10 express low levels of naïve T cell marker CD45RA

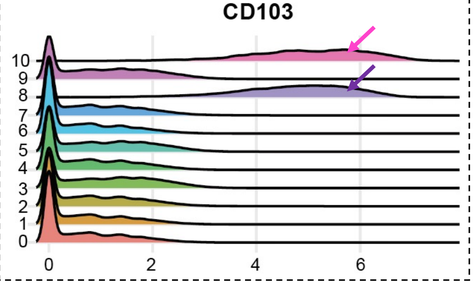


Results

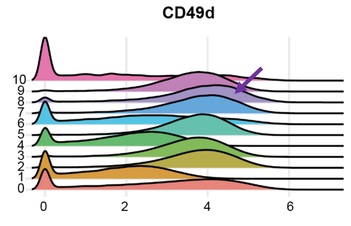
Cells in Clusters 8 and 10 express high levels of memory T cell marker CD45RO



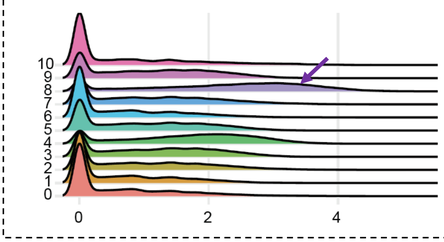
Cells in both Clusters 8 and 10 uniquely express high levels of CD103



CD8+ T cells in Cluster 8 express high levels of CD49d

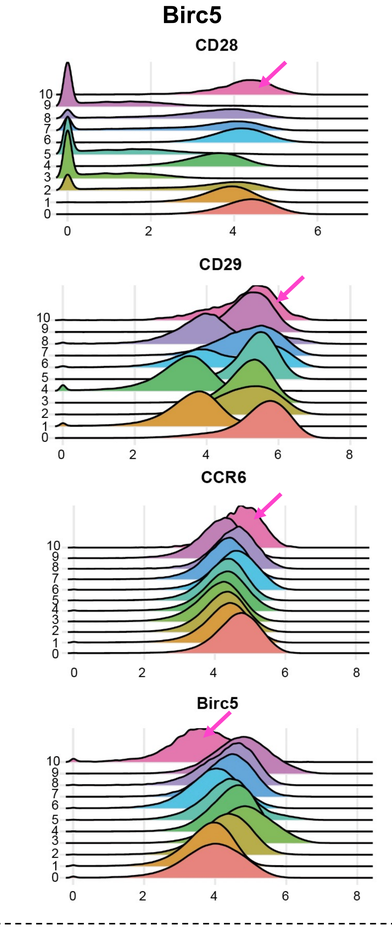


Memory CD8+ T cells in Cluster 8 uniquely express high levels of CD73



Results

CD4+ T cells in Cluster 10 express high levels of CD28, CD29 and CCR6, but low levels of Birc5



Conclusions

These data demonstrate that the expression of CD103 on T cells may serve as a marker predicting longer time-to-rebound. More broadly, the findings suggest that different subsets of CD4+ and CD8+ Trm with distinct features are associated with temporary ART-free HIV control. To what extent these cells play an active role in this control remains to be deciphered.

Acknowledgements

Funding Support: R01 AI127219, R01 AI147777, and P01 AI131374; and the generous researchers and participants of ACTG A5345