MODELING HIV RESERVOIR DECLINE AFTER ART INITIATION AS A FUNCTION OF NK CELL FEATURES

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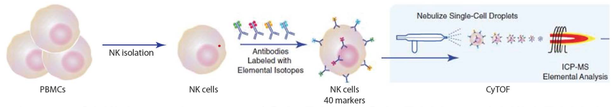
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BACKGROUND

- The persistence of HIV latent reservoir is a major challenge for the development of cure strategies
- Understanding mechanisms that determine HIV reservoir size may inform development of effective cure approaches.
- **QUESTION**: Do changes in the natural killer (NK) cell repertoire correlate with the HIV reservoir size?

METHODS

- 50 participants from the ACTG A5321 cohort. The A5321 cohort consists of people with HIV who initiated antiretroviral therapy (ART) while participating in ACTG treatment naïve trials and who have had sustained HIV suppression for 4-15 years.
- CyTOF was used to assess NK cell receptor/ligand repertoire at 3 different timepoints: timepoint 1, a median of 7.1 years after ART initiation; timepoint 2, 24 weeks after timepoint 1; timepoint 3, 48 weeks after timepoint 1.



- Markers of HIV persistence (CA-DNA, CA-RNA and HIV RNA by single copy assay) were assessed pre-ART, 1 year on ART and at timepoint 1.
- Inflammatory markers (IL-6, hsCRP, sCD14, sCD163, IP-10) were measured pre-ART, 1 year on ART and timepoint 1
- T cell responses to HIV peptides were measured at timepoint 1.

Natural killer cell receptors/ligands and T cell responses are associated with the drop in HIV reservoir levels following treatment initiation.

CONCLUSIONS

- Expression of specific NK cell markers and ligands, T cell responses and inflammatory markers can be used as explanatory variables in the regression analysis of the decline in HIV DNA levels following ART initiation.
- Some of the markers identified are associated with NK cell cytotoxicity: LFA-3 and ICAM-1 stimulate NK cell cytotoxicity and perforin mediates cytotoxicity.
- This suggests that NK cell receptor/ligand interactions may drive an enhanced cytotoxic response to infected cells in the context of treatment initiation.
- If these results are independently validated, harnessing this potential may inform to the development of novel therapeutic strategies for HIV infection.

CONTACT INFORMATION

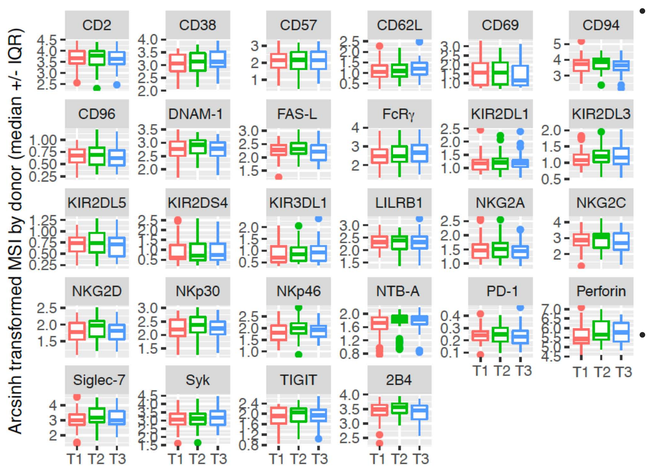
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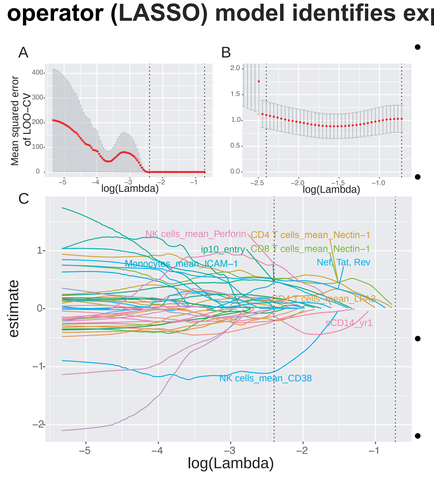
RESULTS

Fig 1. NK cell receptor expression was assessed on A5321 participants



- Expression of NK cell receptors was not significantly different between timepoints: timepoint 1, median of 7.1 years after ART initiation (T1), week 24 after T1 (T2), and week 48 after T1 (T3).
- NK receptor ligand expression on monocytes/T cells was also stable over time (not shown).

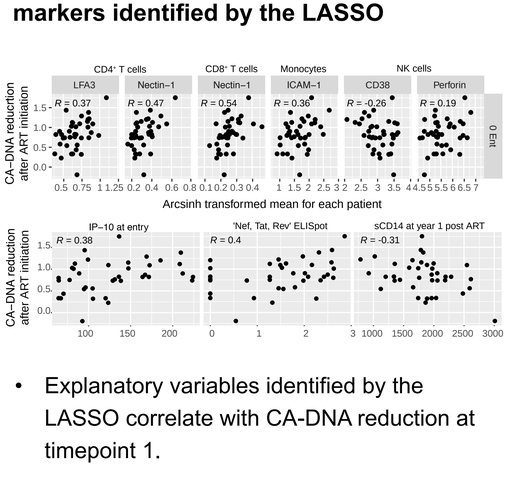
Fig. 2. A supervised multivariate regression using the least absolute shrinkage and selection operator (LASSO) model identifies explanatory variables for CA-DNA reduction at timepoint 1



- Reduction in CA-DNA from pre-ART to timepoint 1 was used as outcome for the LASSO.
- (A&B) Mean square error plots for the LASSO. A log (Lambda) between -2.4 and -0.72 was used to identify explanatory variables.
- (C) Coefficient plots of the explanatory variables of CA-DNA reduction.
- (Table) Lasso Coefficients for explanatory variables.

Explanatory Variables	LASSO Coefficients	
	minimum MSE	log (Lambda) of -2.4
sCD14 at yr1 post-ART	-0.385	-0.117
IP-10 at entry	0.114	0.469
Nef,Tat,Rev	0.343	0.503
CD4+ T cells - Nectin-1	0.459	0.516
CD8+ Tcells - Nectin-2	0.453	0.523
Monocytes - ICAM-1	0.0838	0.455
CD4+ T cells - LFA3	0.337	0.132
NK cell - CD38	-0.0357	-1.08
NK cell - Perforin	0	0.776

Fig. 3. Spearman correlations of the markers identified by the LASSO



- Explanatory variables identified by the LASSO correlate with CA-DNA reduction at timepoint 1.