Elevated Expression of Anti-HIV-1 Restriction Factors in Effector Memory CD4+ T cells in vivo

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BACKGROUND
- Recent observations suggest that there may be less viral outgrowth from effector memory than central memory CD4+ T cells from ART-suppressed individuals, despite similar levels of HIV-1 DNA in these cellular subsets.
- This may be driven by cell-intrinsic factors suppressing viral production, and/or the disproportionate presence of replication-incompetent HIV-1 variants in effector memory cells.

METHODS
- Fresh blood was collected from 20 individuals enrolled in the SCOPE cohort: 10 HIV-negative, 5 HIV-1-infected untreated, and 5 HIV-1-infected ART-suppressed individuals.

RESULTS
- Most anti-HIV-1 restriction factors are significantly elevated in effector memory CD4+ T cells in comparison to central memory CD4+ T cells in HIV-negative individuals, elite controllers, and viremic non-controllers (Table 1, Figure 1).
- Within the ART-suppressed group, Four restriction factors were significantly elevated in effector memory cells: APOBEC3F, APOBEC3H, TRIM11, and PML / CuRe.

FUTURE DIRECTIONS
- Gene expression patterns will be characterized in additional subjects to increase sample size and validate observations.
- Protein-level analyses will be implemented to complement mRNA expression data.
- Ultra-deep sequencing of HIV-1 DNA from CD4+ T cell subsets will be performed to examine viral genetic features associated with each cell type, focusing on evidence of APOBEC3-mediated hypermutation.
- Expression profiling of cellular subsets from lymphoid tissues will be performed.

CONCLUSIONS
- The majority of anti-HIV-1 restriction factors are expressed at higher levels in the effector memory CD4+ T cells of ART-suppressed subjects, as compared to central memory CD4+ T cells.
- Restriction factors that are elevated in effector memory CD4+ T cells of ART-suppressed individuals include particular TRIM family members that attack HIV-1 at the post-integration phase of the viral life cycle, and APOBEC3 cytidine deaminases that hypermutate HIV-1 genomes.
- Expression data from our exploratory analyses of sorted T cell subsets indicate that enhanced host restriction factor expression may contribute to the reduced viral outgrowth observed in effector memory CD4+ T cells.
- Variation in selection pressure from cell-intrinsic immune mechanisms may drive viral genetic compartmentalization between tissues and cell types.

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