Transcriptional signatures of CD4 T cell Subsets and Control of HIV Reservoirs in Elite Controllers

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Introduction. Understanding the molecular mechanisms associated with the exceptional quasi-equilibrium between HIV reservoirs and host cells in the model of functional cure represented by Elite Long-Term Nonprogressors (E-LTNPs) should provide clues for developing strategies to purge the HIV reservoirs.

Methods. We compared the whole-genome transcriptional profiling of the 4 major resting (CD25−CD69−DR−) CD4 T cell subsets (naïve [TN], central-memory [TCM], transitional-memory [TM], effector-memory [TEM]) sorted from PBMCs of 14 HIV-1-infected individuals including 7 E-LTNPs. The HIV-1 cellular DNA and mRNA levels were quantified in parallel in each sorted subset.

Results. Host gene transcriptomes followed subset differentiation and viremia except in E-LTNPs where T_CM, the main CD4 compartment, showed the highest activity with 3 specific signatures involving: (i) overexpression of TCR and co-stimulation signaling pathways, (ii) overexpression of the PRDM-1/Blimp-1 transcriptional repressor and (iii) down-modulation of type-1 IFN-related genes. Among subsets, the PRDM1/Blimp-1 upregulation was associated with lower levels of both cellular HIV-DNA and HIV mRNA levels.

Conclusions. This unique Blimp-1 transcriptional repressor signature and the contrast between host and virus transcriptional activities in T_CM from ECs suggest Blimp-1 might be involved in controlling the HIV reservoirs in the key T_CM subset.

Fig 1. Characteristics of the main CD4 T-cell subsets in HIV infected LTNPs and uninfected individuals (a) Distribution of the HIV reservoirs in the patient study groups. Total cell HIV DNA was quantified in sorted resting CD25−CD69−HLA-DR−CD4 T cell subsets (naïve [Tn], CD45RA+CCR7+ and memory subsets: [Tcm], CD45RA−CCR7+; [Ttm], CD45RA+CCR7−; [Tem], CD45RA−CCR7−) by ultrasensitive real-time PCR. LTNPs, elite long-term non-progressors; V-related LTNPs, viremic long-term non-progressors (b) Relative frequency of each resting CD4 T-cell subset in percentages of the global resting CD4 T-cell pool in each group as determined by flow cytometry. (c) Number of differentially expressed genes between Tn, Tem and Tcm resting CD4 T cells from UI and LTNPs. UI-LTNPs compared to Tn, Tcm, Tem, and Tcm resting CD4 T cells from UI-LTNPs and UI-Tn, Tem, and Tcm resting CD4 T cells from UI-LTNPs and UI-TN.

Fig 2. Transcriptional signatures of memory CD4 T cells in elite controllers (a) Venn diagrams of common differentially expressed genes across all groups of subjects in each memory CD4 T cell subset as compared to UI-Tn. Numbers represent the number of differentially expressed genes in each CD4 T cell subset compared to UI-Tn, with a threshold of FDR<0.05. (b) Transcriptional signatures of central memory CD4 T cells from elite controllers. Histograms represent the fold changes related to the comparison of the mean expression values of the corresponding genes in central memory CD4 T cells from elite controllers (E-LTNP TCM) versus naïve CD4 T cells from uninfected individuals (UI-Tn). FDR<0.05 (c) Venn diagram of common differentially expressed genes in the following comparisons: E-LTNP TCM versus UI-Tn, E-LTNP TCM versus UI-Tm, E-LTNP TCM versus UI-Tm, E-LTNP TCM versus UI-Tm.

Fig 3. PRDM1 overexpression is associated with lower cellular HIV-DNA and HIV RNA transcription in memory CD4 T cells from elite controllers (E-LTNPs) and viremic long-term non-progressors (v-LTNPs). (a) Inverse association between PRDM1 expression intensity as determined by microarray and cellular HIV DNA level in T_CM of HIV-infected patients. HIV patients were separated into 2 groups according to the HIV DNA level in T_CM and PRDM1 expression, below and at or above the median HIV DNA level and the median PRDM1 expression in T_CM. A Fisher’s exact test was applied (p<0.02). (b) RT-PCR quantification of PRDM1 mRNA transcript and HIV RNA transcripts in pooled sorted CD4 T-cell subsets from E-LTNPs and v-LTNPs.

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