Distinct signatures of trained immunity reveal Heterogeneity Among Elite HIV Controllers

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BACKGROUND

Pathogen stimuli can induce distinct mechanisms that can lead to long-term functional training of both the innate and adaptive immune responses. This shapes the immune responses to bacterial and viral infections. These mechanisms provide long-term functional epigenetic reprogramming of immune cells, playing a crucial role in shaping immune responses and influencing disease outcomes. Recent evidence suggests that trained immunity contributes to long term viral control in a subset of individuals: Elite Controllers (ECs), that spontaneously control viremia without antiretroviral therapy. This study applied multi-omics approaches to identify the mechanisms that define the control of HIV viral load in PLWH.

METHODS

The study analyzed samples from 13 ECs, 27 VCs, 10 VNCs, and 20 HDs to evaluate cytokines, metabolites, and gene expression. Enrichment mapping, K-means clustering with bootstrapping, and gradient boosting identified heterogeneity and predictors among groups.

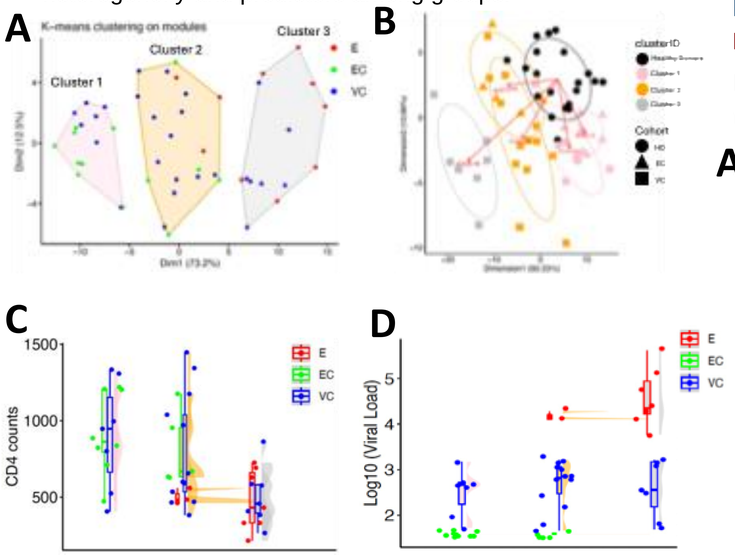
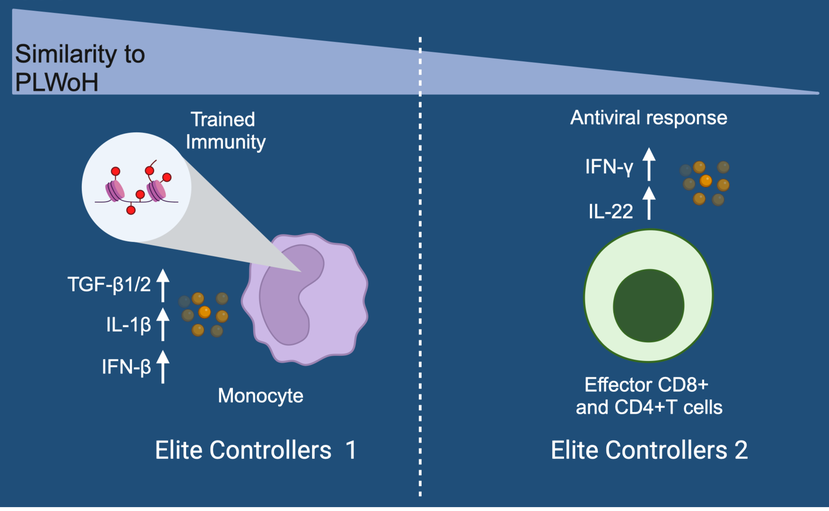


Figure 1: Transcriptomic analysis associated with CD4 counts and clustering revealed three clusters. Within the clusters, it is possible to identify two different Elite Controllers populations and three different Viremic Controllers populations (A). Cluster 1 appears to be the closest to Healthy Donors, while Cluster 2 is an intermediate between Cluster 1 and 3, the one that differs the most from healthy individuals (B). CD4 count and VL were not confounding factors (C-D).

HIV Elite Controllers exhibit two different phenotypes. The first one driven by **innate trained immunity** and more similar to People Living Without HIV (PLWoH), while the second one is based on higher IFN-**γ** levels that lead to heightened **innate antiviral immunity** and protection from viral dissemination.



RESULTS

Elite Controllers 1 display an enrichment in genes associated with Innate Immune response, trained immunity and inflammasome

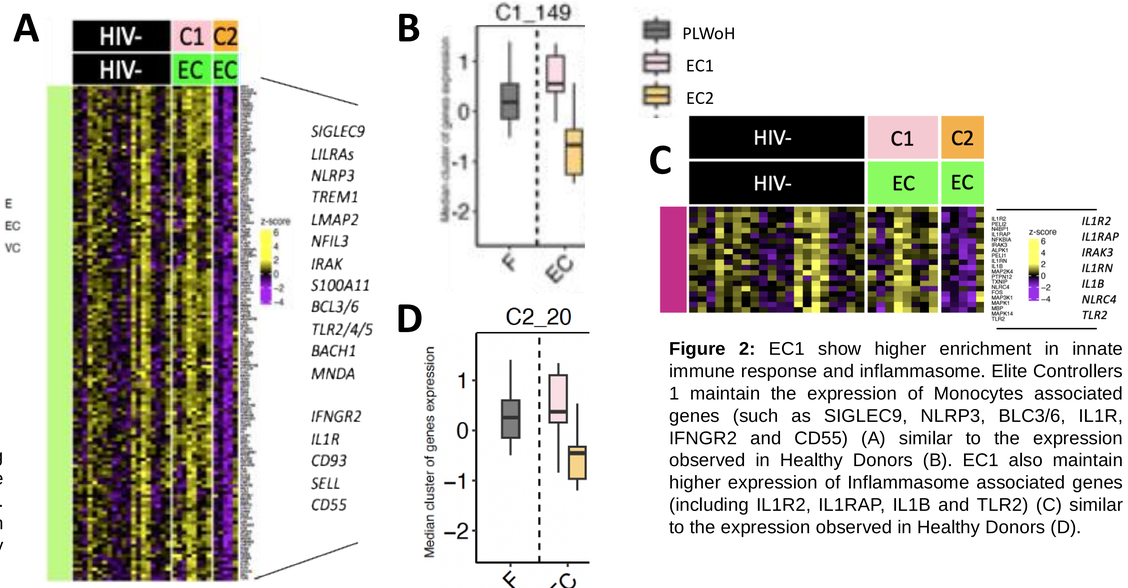


Figure 2: EC1 show higher enrichment in innate immune response and inflammasome. Elite Controllers 1 maintain the expression of Monocytes associated genes (such as SIGLEC9, NLRP3, BLC3/6, IL1R, IFNGR2 and CD55) (A) similar to the expression observed in Healthy Donors (B). EC1 also maintain higher expression of Inflammasome associated genes (including IL1R2, IL1RAP, IL1B and TLR2) (C) similar to the expression observed in Healthy Donors (D).

Elite Controllers 2 show higher antiviral capacity in T cells, that can difficult HIV attachment and replication

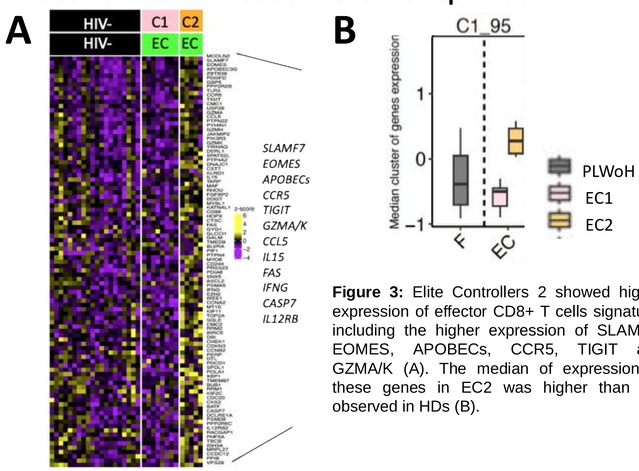


Figure 3: Elite Controllers 2 showed higher expression of effector CD8+ T cells signature, including the higher expression of SLAMF7, EOMES, APOBECs, CCR5, TIGIT and GZMA/K (A). The median of expression of these genes in EC2 was higher than the observed in HDs (B).

Elite Controllers 1 and 2 display different cytokine profiles, specially in IFN levels

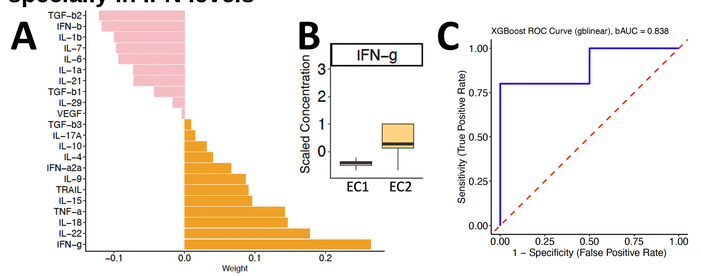


Figure 4: Cytokine profile was also different between the 2 EC populations. EC1 PLWH display higher levels of cytokines associated with trained immunity and stemness (IL-1B and TGF-B), while EC2 PLWH display a profile of innate/adaptive antiviral responses, characterized by IFN-g (A). IFN-g represented the major difference between the groups (B), being able to differentiate the two EC groups with 83% accuracy (C)

CONCLUSIONS

EC1 displays a better innate immune response, with enrichment to trained immunity and stemness, in the transcriptome and on the cytokine profiles. On the other hand, EC2 displays an enrichment in the adaptive compartment, with enrichment in potent antiviral profile that is capable of inhibiting the viral attachment and proliferation, with higher levels of IFN-**γ** and higher expression of ISGs, such as APOBECs

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