Host environment triggers two distinct trained immunity profiles in Elite Controllers' HSCs

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BACKGROUND

Growing evidence suggests that long-term immune function can be shaped at the level of hematopoietic stem cells (HSCs) through sustained cytokine and metabolic cues that bias lineage differentiation. Whether such stem cell–imprinted programs contribute to distinct immune trajectories enabling durable HIV control has not been systematically investigated.

We hypothesize that the host immune environment shapes HSC differentiation trajectories into two distinct programs, giving rise to divergent immune architectures in Elite Controllers (EC): a myeloid-biased, trained immunity–driven profile (ECM) and a lymphoid-biased, adaptive antiviral–oriented profile (ECL). These alternative stem cell–imprinted pathways represent distinct but convergent mechanisms leading to durable HIV control.

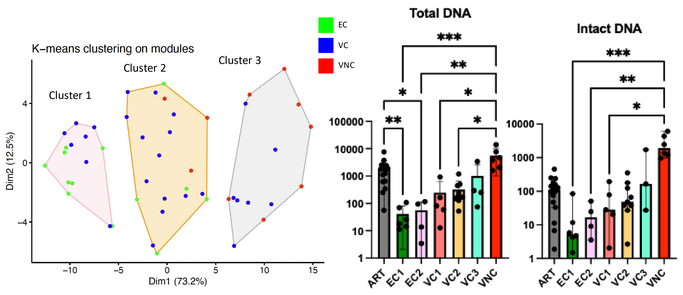


Figure 1: a) Based on bulk RNAseq, Elite Controllers (EC) were clustered in two different clusters. b-c) The two EC groups do not show any differences regarding reservoir size, including Total and Intact HIV DNA.

METHODS

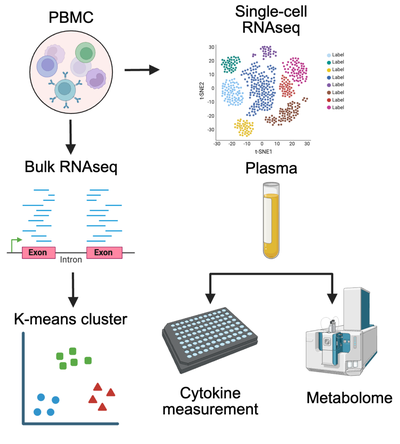
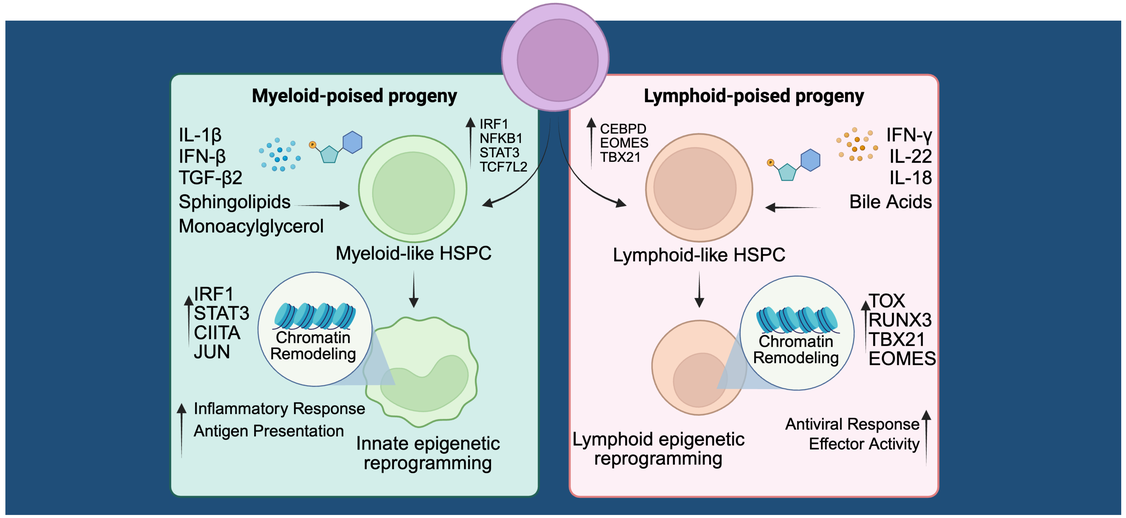


Figure 2: PBMCs were used for bulk and single-cell RNAseq and plasma samples were used to assess metabolome and cytokines.

Unbiased analysis of single cell multi-omics, cytokine and metabolome quantitative monitoring was performed in plasma and PBMCs from two cohorts of untreated ECs (n = 13), 10 viremic non-controllers (VNCs), and 20 people without HIV (PWoH). Transcriptional signatures were mapped onto hematopoietic stem cells (HSC) using in-silico deconvolution.

Pseudotime analysis reconstructed HSPC differentiation trajectories. Cytokine profiles were validated in an independent cohort (n = 14).



RESULTS

Transcriptionally, CD34+ HSCs from ECM and ECL display distinct programs

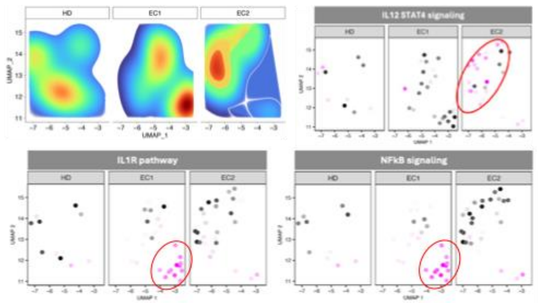


Figure 3: scRNAseq analysis of HSCs from ECM and ECL revealed distinct programs, with ECM enriched for TNF and IL-1β pathways and ECL enriched for IL-7, IL-12, and interferon signaling, suggesting divergence at the progenitor level.

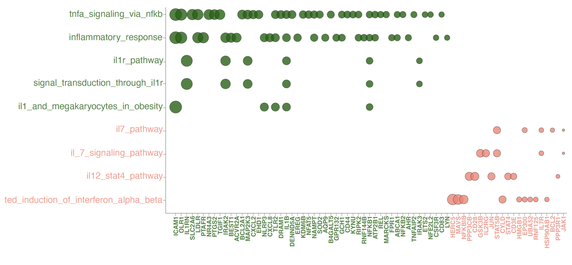


Figure 4: CD34⁺ HSCs from ECM (green) are enriched for TNF-α and IL-1β signaling, promoting myeloid-biased priming, whereas ECL HSCs show enrichment of IL-7, IL-12, and IFN signaling, favoring lymphoid antiviral differentiation

The host environments of ECM and ECL are distinct in their cytokine and metabolic profiles

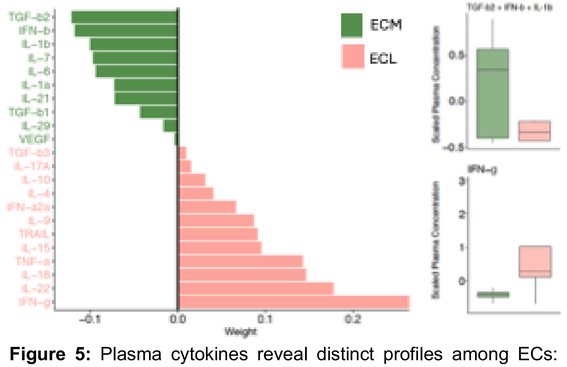


Figure 5: Plasma cytokines reveal distinct profiles among ECs: ECM is linked to myeloid and inflammasome pathways (TGF-β2 and IL-1β), whereas ECL shows higher IFN-γ levels, consistent with an antiviral lymphocyte response.

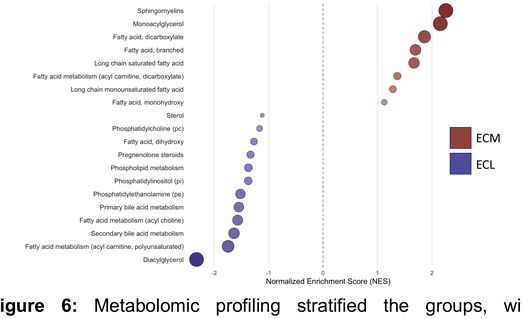


Figure 6: Metabolomic profiling stratified the groups, with sphingolipids and monoacylglycerols enriched in ECM, and ceramides and secondary bile acids enriched in ECL, reflecting distinct inflammatory and T cell–associated metabolic programs.

The host environments of ECM and ECL are distinct in their cytokine and metabolic profiles

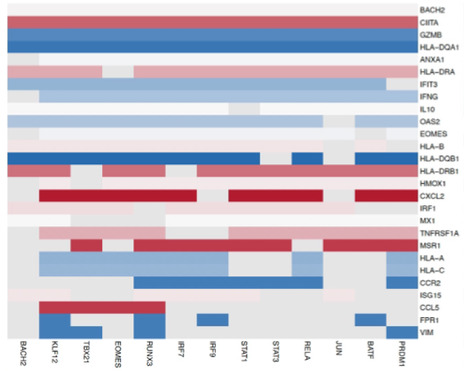


Figure 7: Epigenetic analysis showed that ECM have increased chromatin accessibility at TNF-response genes, whereas ECL shows enhanced accessibility at IFNG and GZMB loci, supporting distinct inflammatory and cytotoxic programs

CONCLUSIONS

- HIV Elite Control is associated to reprogramming at the epigenetic level of Hematopoietic Stem Cells (HSCs).
- This reprogramming is triggered by host environment characteristics, involving both Metabolites and Cytokines.
- HSCs from Elite Controllers can be poised to respond in two different ways, one involving myeloid training, the other driven by lymphoid adaptive antiviral immunity.

ADDITIONAL KEY INFORMATION

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PLAIN LANGUAGE SUMMARY

Some people can control HIV without treatment. We found that this may be determined by how their immune stem cells are programmed early on, creating two different immune strategies that both allow the virus to remain suppressed.