HIV-1 Infection Triggers Hematopoietic Suppression and Multilineage cytopenia through IFN-γ Signaling

0377

Shuai Gao[1], Sara K. Nicholson[1], Hongbo Gao[1], Liang Shan[1]
[1]Department of Medicine, Washington University in St Louis, St Louis, MO, USA

Acute HIV-1 infection severely depletes hematopoietic progenitors, particularly myeloid progenitors, accompanied by reducing their stemness and differentiation potential. Genetic ablation of IFNγ receptor rescues HIV-1-induced hematopoietic suppression. Moreover, activated CD8⁺ T cells are identified as the primary source of IFNγ. IFNγ promotes rapid HSPC proliferation, ultimately leading to HSPC pool exhaustion.

BACKGROUND

Various hematological abnormalities, including anemia, thrombocytopenia, neutropenia, and leukopenia, are common in people with HIV-1, indicating interference with multipotent hematopoietic progenitor cells. The hematopoietic dysfunction triggered during HIV-1 infection remains unclear because this process is difficult to model in vitro due to the complexity of the bone marrow niche.

METHODS

In this study, we utilized humanized mouse models to dissect the molecular and cellular mechanisms driving multilineage cytopenia during HIV-1 infection. Newborn mice were transplanted with human cord blood CD34⁺ cells. Mice were infected with HIV-1 9-10 weeks post-transplantation when sufficient levels of human CD45⁺ (huCD45⁺) cells were confirmed. The changes in hematopoietic stem and progenitor cells (HSPCs) in the bone marrow were analyzed using flow cytometry, RNA-seq, and scRNA-seq etc.

RESULTS

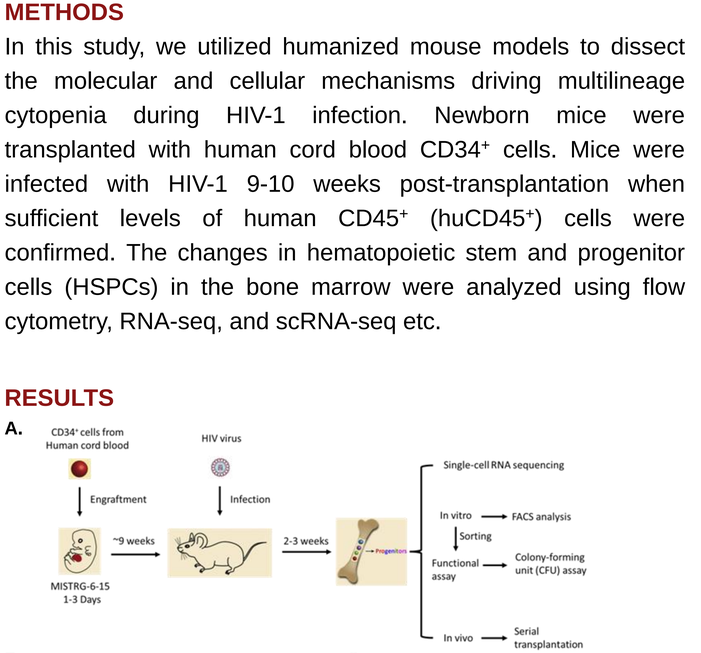


Figure 1. HIV-1 Infection Reduces HSPC Pool. (**A**)Schematic diagram illustrating the generation of humanized mice and the procedure for HIV-1 infection. (**B**) Cell percentage changes of hCD45⁺ and CD4⁺ in blood. (**C**) Cell count changes of hCD45⁺, Lin⁻CD34⁺, CD34⁺ and (**D**) HSPC progenitors (HSC, MPP, CLP, CMP, MEP, and GMP) in bone marrow post HIV-1 infection.

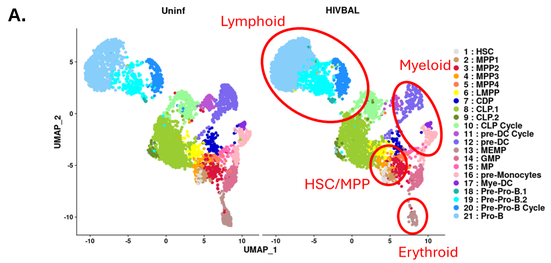


Figure 2. Single-Cell Transcriptome Analysis of Human Hematopoiesis. (**A**) Cell distribution of single-cell RNA-seq data UMAP visualization comparing the uninfected and HIV_{BaL} groups, colored by cell type. (**B**) Comparison of cell proportion changes between myeloid and lymphoid lineages.

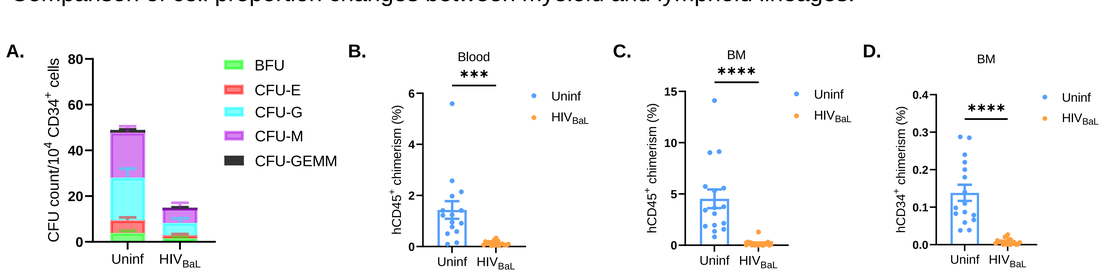


Figure 3. HIV-1 Infection Impairs HSPC Function. BM CD34⁺ cells were purified from primary donors (uninfected and HIV_{BaL} groups) for CFU assay and secondary transplantation. (**A**) CFU assay. Different colonies (GEMM, G, M, E, BFU) were calculated. (**B-D**) Secondary transplantation: (**B**) Percentage of hCD45⁺ cells in blood. (**C-D**) Percentage of hCD45⁺ and CD34⁺ cells in bone marrow.

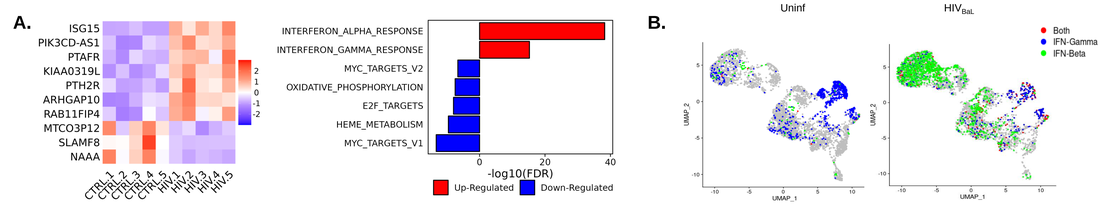


Figure 4. IFNγ Signaling Plays a Dominant Role in Regulating HSC Depletion. (**A**) Heatmap and GSEA analysis of RNA-seq showing IFNα and IFNγ signaling changes between uninfected and HIV_{BaL} HSC/MPPs, indicating up-regulated of IFNγ signaling in HIV_{BaL} group (FDR p < 0.05%). (**B**) Classification of BM HSPCs from uninfected and HIV_{BaL}-infected mice based on responsiveness to IFNγ, type I IFN, both, or neither.

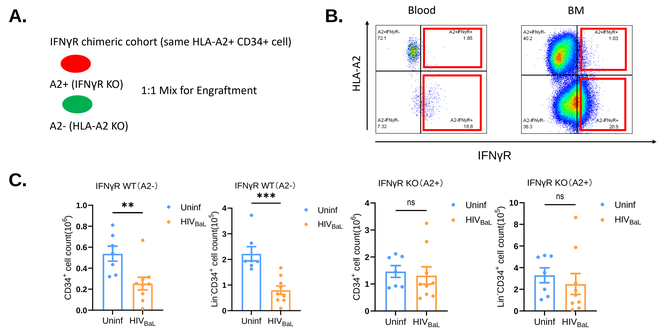


Figure 5. IFNγR Knockout Rescues the BM HSPC Defect. (**A**) Strategy for generating IFNγR-edited chimeric humanized mice. (**B**) FACS plot results show the depletion of IFNγR in both blood and bone marrow. (**C**) Comparison of HSPC cell count changes post-infection in the IFNγR chimeric cohort (same donor). The Lin⁻CD34⁺ and CD34⁺ were checked.

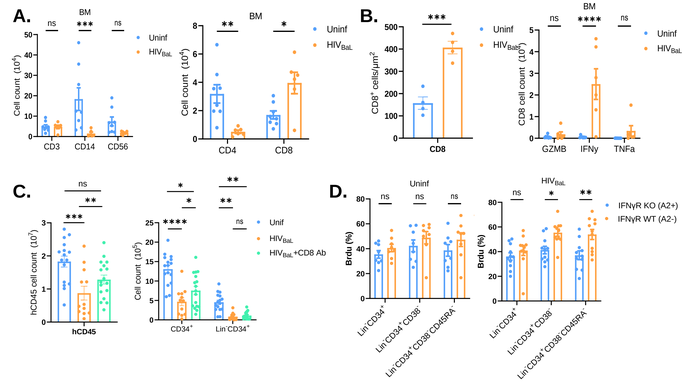


Figure 6. IFNγ Signaling is Derived from BM-Infiltrated CD8⁺ T Cells. (**A**) Changes in mature cell count post-infection (CD3, CD14, CD56, CD4, CD8 in BM) (**B**) Changes in counts of activated CD8⁺ T cells (GZMB, IFNγ, TNFα-positive). (**C**) Analysis of BM cells post-CD8 antibody blockage in vivo. The BM cells were collected for analysis. The hCD45⁺, Lin⁻CD34⁺ and CD34⁺ counts were shown. (**D**) BrdU assay results using the IFNγR chimeric cohort (same donor).

CONCLUSIONS

Using humanized models, we identified IFNγ signaling as a key factor in driving bone marrow failure post HIV infection. Importantly, blocking IFNγ signaling rescued HSPC defects, thereby protecting the hematopoietic system during HIV-1 infection. These findings offer valuable insights into the clinical treatment of PLWH.