HIV-induced Lung Inflammation in Humanized Mice

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BACKGROUND

HIV infection-related lung diseases continue to be one of the leading causes of morbidity and mortality for people living with HIV. The cross-sectional design of population studies has made it impossible to elucidate a causal relationship between immune biomarkers and lung diseases. Therefore, established an animal model to longitudinally monitor HIV infection and the lung immune activation as well as immune perturbation.

METHODS

We established HIV-1 infection in humanized mice engrafted with human cord blood hematopoietic stem and progenitor (CD34⁺) cells (HSPCs). Blood, lung, and spleen of infected (n=4) and control (n=4) mice were collected three weeks post infection. Human CD45⁺ cells from each tissue were sorted for single cell RNA-sequencing. HIV⁺ cells were identified by screening for cells expressing at least 2 reads of any HIV transcripts.

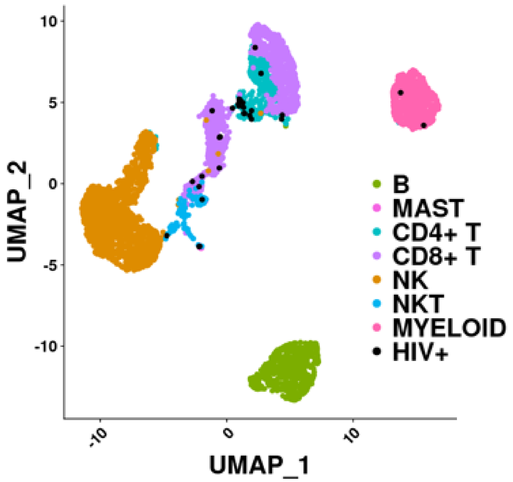


Figure 2. **Human immune cells in HIV-infected lung tissues. Black cells represent cells containing HIV transcripts.**

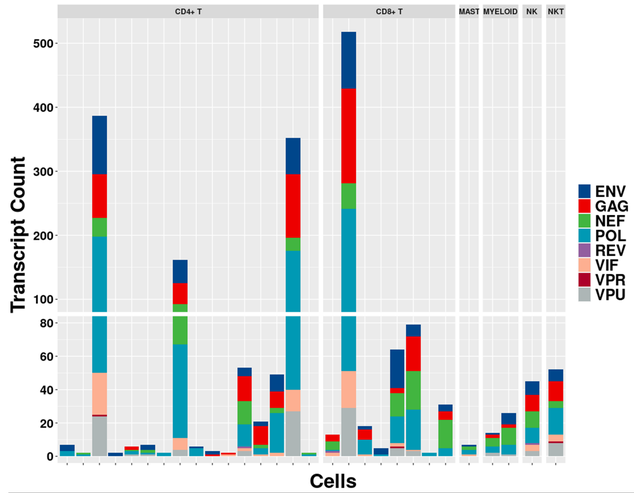


Figure 3. **Number of transcript counts aligning to HIV genes for each of the 29 HIV⁺ cells in lung tissues. Each bar represents a singular cell, and bars are categorized into their respective cell-type.**

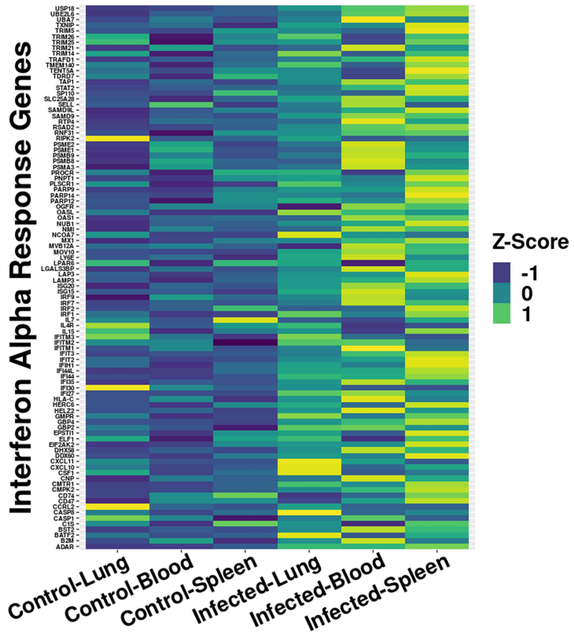


Figure 1. **Heatmap of interferon alpha related genes in each tissue between control and HIV infected mice.**

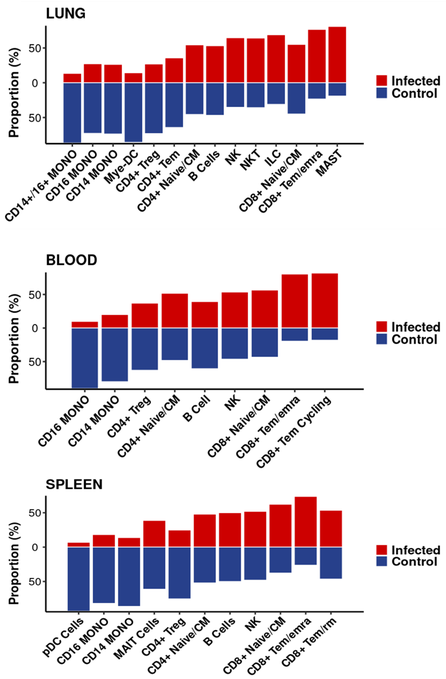


Figure 4. **Bar charts revealing the proportion of infected and control cells for each sub-type of cells for blood, lung, and spleen tissues.**

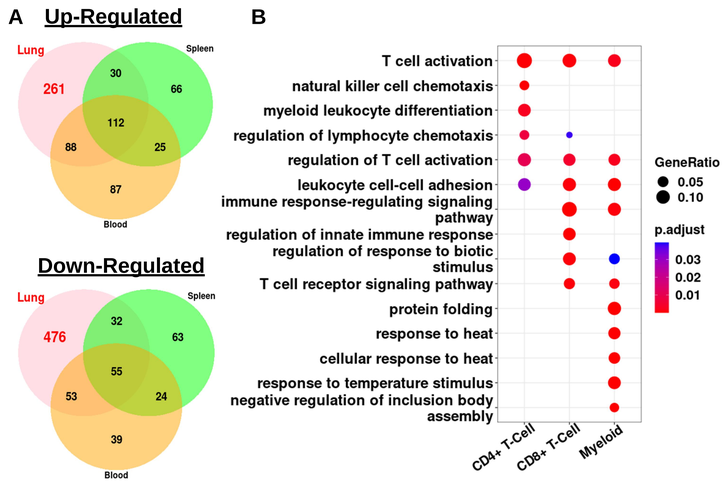


Figure 5. **(A) Venn Diagrams showing the number of significant differential expressed genes found to be up-regulated or down-regulated in infected samples in comparison to controls for lung, blood and spleen. (B) Dot plot displaying the enriched gene-ontology biological process gene sets for significant up-regulated genes that were found only in the lung for CD4⁺ T cells, CD8⁺ T cells, and myeloid cells, respectively. The top 5 enriched gene-sets are shown on the y axis for all three cell-types. Gene ratio is the number of genes in the gene set divided by the total number of genes supplied to the analysis.**

RESULTS

The HIV-infected humanized mice had a systematic augment of interferon alpha responses in the blood, spleen, and lung tissues.

We found significant depletions of lung effector and tissue-resident CD4⁺ T cells and CD4⁺ regulatory T cells, as well as many subsets of antigen presenting cells (APCs). By contrast, CD8⁺ T cells, NK cells, and ILCs expanded and produced inflammatory cytokines in the infected lungs, which was in line with human studies.

Genes associated with cell proliferation and interferon responses were significantly upregulated in the lungs of HIV-infected mice.

Compared to the blood and spleen, the lungs had a larger amount of differentially expressed genes between the infected and control mice, which is majorly driven by differentially expressed genes in CD4⁺ and CD8⁺ T cells, and myeloid cells in the lung.

Our humanized mouse model allows us to perform mechanical studies to understand HIV-driven pathogenesis and lung complications. There are unique features of HIV-induced immune perturbation in the lung.

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