Integrated Analysis of Multicellular Immune Dynamics During Hyperacute HIV-1 Infection

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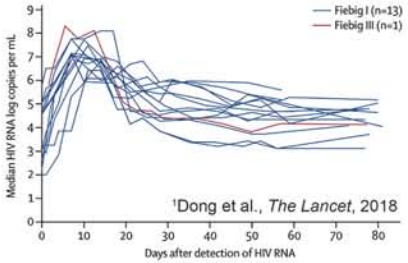
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258

Motivation & Background

There were 1.7 million new HIV Infections in 2018.

New vaccines require a detailed understanding of the earliest host responses to HIV during **hyperacute infection** (timepoints prior to and at peak viremia).

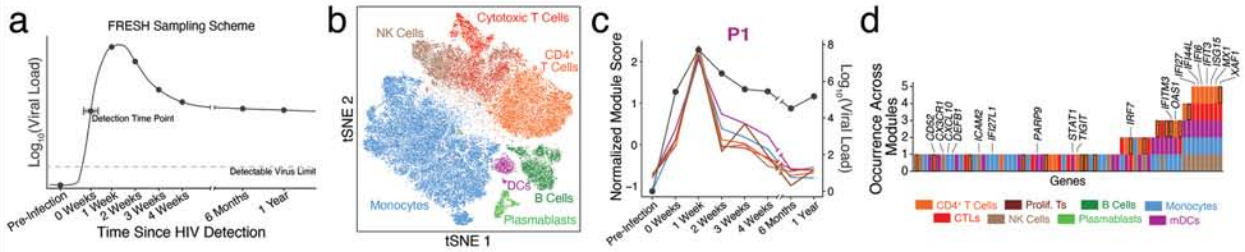


Viral load trajectories of longitudinally monitored individuals in the FRESH Study

The FRESH Study[1] provides a unique opportunity to study **multicellular immune dynamics** of host responses in hyper-acute HIV infection with the advancement of **single-cell RNA-Sequencing (scRNA-Seq)** technologies.

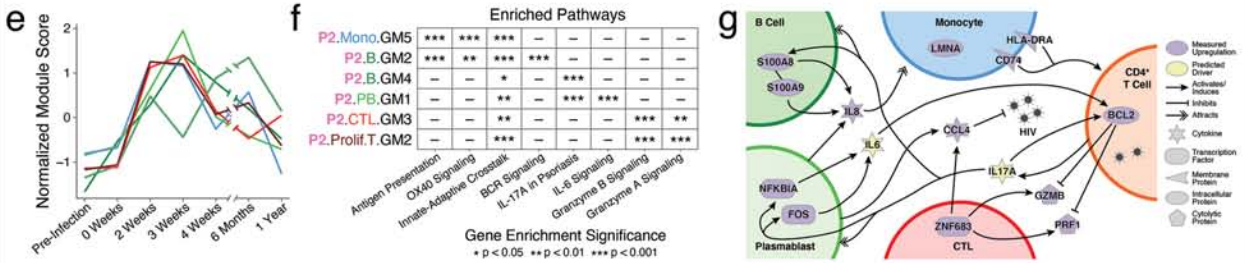


Multicellular Immune Dynamics Revealed by scRNA-Seq

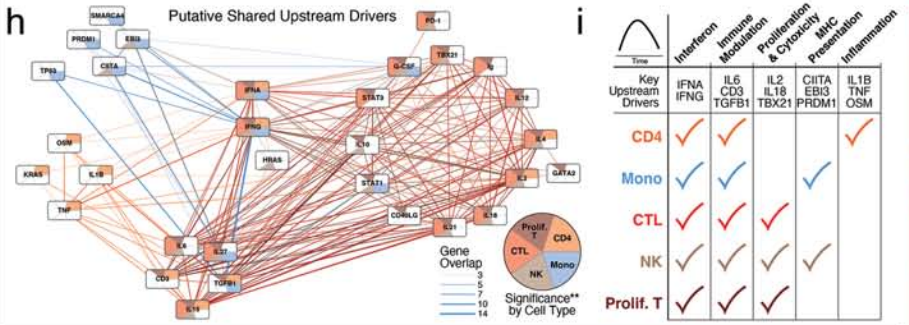


(**a,b**) Longitudinal PBMC samples from four FRESH participants were processed by Seq-Well[2], inclusive of pre-infection timepoints for a total of >59,000 single cells. (**c**) **Multicellular gene module discovery** identifies interferon-responsive gene programming in several different cell types aligning with peak viremia. (**d**) With cell-subset resolution, we annotate **which genes are cell-type specific or shared across multiple lineages** in response to interferon.

[2]Gierahn et al., 2017

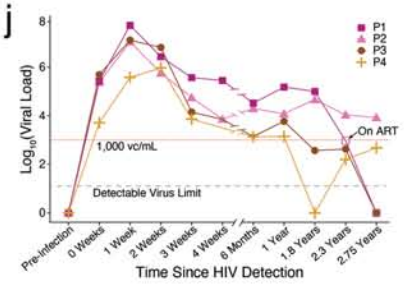


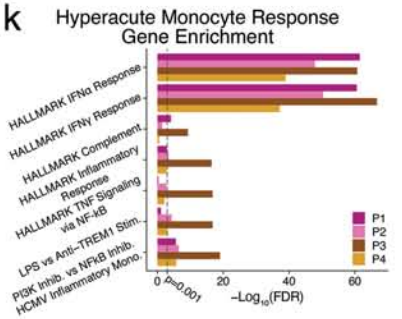
(**e**) Clustering temporal module scores across all gene modules reveals modules with **similar expression dynamics across multiple cell types**. (**f**) Gene set enrichment analysis identifies distinct cellular programming across different cells. (**g**) Linking gene expression between cells nominates a putative **cell-cell signaling network with temporal resolution** in HIV infection. Here, IL-8/IL-6 production by B cells may play a role in preventing cytolytic killing of infected CD4+ T cells.

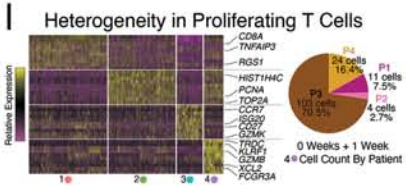


(**h**) Network of shared upstream drivers in acute HIV infection across all four individuals in multiple cell types. (**i**) We summarise how different cells respond to complex stimuli. **Surprisingly, only CD4+ T cells are predicted to respond to pro-inflammatory signals.**

Cell Subsets that Associate with Future Control of HIV







(**j**) Two participants studied (P3 & P4) develop natural control of HIV in chronic infection. (**k**) Comparing genes upregulated immediately after infection in **monocytes** highlights a **poly-functional subset** unique to P3. (**l**) Unsupervised clustering of **proliferating** cytotoxic T cells reveals a subset of **NK cells** associated with P3 & P4. These cells **precede the acute CD8+ T cell expansion** in time.

Acknowledgements & Contact Info

We would like to thank the FRESH clinical team and study participants for enabling us to learn from the critical first moments of HIV infection.

The complete expression matrix and associated R code are available online: *http://shaleklab.com/resource/immune-dynamics-of-acute-hiv-infection/*

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