Poster # 00230

Upregulation of Interferon Stimulated Genes Persists During Treated HIV-1 Infection

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BACKGROUND

Despite the capacity of antiretroviral therapy (ART) to suppress HIV-1, ART-treated persons living with HIV-1 and undetectable plasma HIV-1 have higher comorbidity rates than people without HIV-1, potentially due in part to chronic immune activation that persists during treatment. We previously found that certain interferon-stimulated genes (ISGs) are persistently upregulated during untreated infection and may contribute to chronic immune activation.

Here we **hypothesize** that ISGs may drive chronic immune activation during suppressive ART use. To evaluate this, we compared gene expression, including ISGs and others, in peripheral blood mononuclear cells (PBMC) from individuals with virally-suppressed HIV-1 infection after ART initiation versus uninfected controls.

METHODS



HIV-1 serodiscordant couple cohorts

vs.

n=18
Post-ART, virally suppressed, HIV-1 infected individuals

n=12
HIV-1 uninfected controls

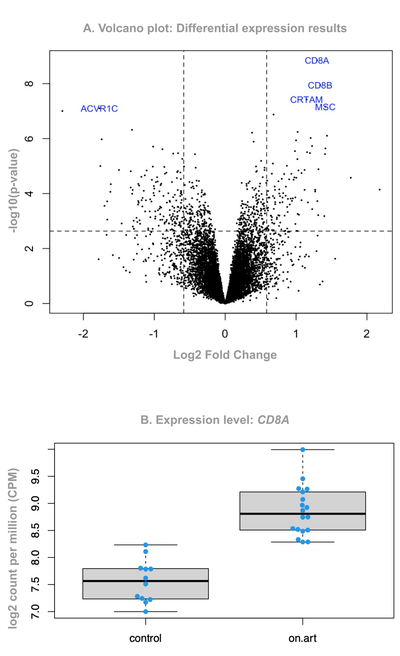
Retrieve PBMC samples, and measure genome-wide expression profile through RNA-seq

Differential gene expression: Expression level ~ groups

Gene set enrichment analysis (GSEA): MSigDB's Hallmark gene sets

RESULTS

- Overall, 594 genes were differentially expressed with FDR adjusted p<0.05, of which 254 had an absolute fold-difference>1.5. (***Figure 1A***)
- The most significant associations were for *CD8A* (***Figure 1B***) and *CD8B*, which had ~2.5-fold higher expression in post-ART participants; *CD8A* and *CD8B* facilitate cell-cell interactions involving CD8+ T cells.
- The GSEA found higher expression of genes involved in interferon-α and β responses (adj. p=7.9x10-8 and 1.5x10-13, normalized enrichment scores [NES]=2.3 and 2.4, respectively) (***Figure 2***), including ISGs such as *IFI27*, *CXCL10*, *OASL*, *IFI35,* and *MX1*(***Figure 1C***).
- Gene sets involved in immune activation, such as TNF-α signaling, inflammatory responses and allograft rejection were also enriched during treated infection (adj. p=1.0x10-8, 1.0x10-4 and 1.6x10-9, NES=2.1, 1.9, and 2.3, respectively). (***Figure 2***)



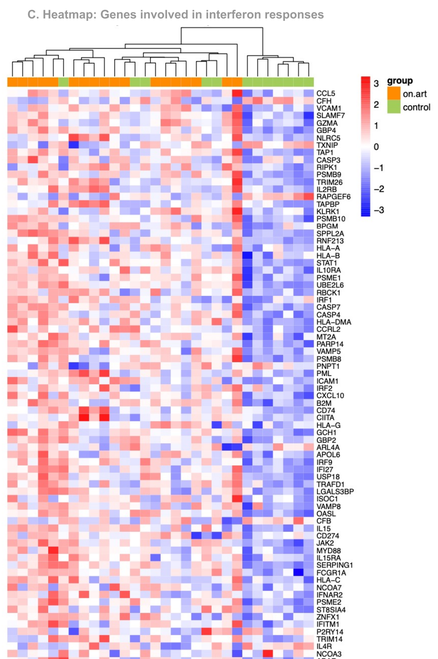


Figure 1. Gene-level results.

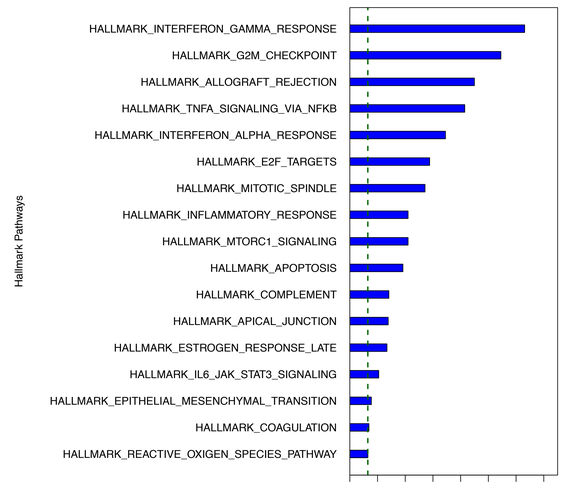


Figure 2. Pathway–level results.

CONCLUSION & DISCUSSION

We found that genes involved in immune activation, including ISGs and genes involved in CD8+ T cell responses, were enriched in virally suppressed HIV-1 infection compared to uninfected controls. Therefore, these genes are potential targets for a targeted intervention to reduce chronic immune activation during HIV-1 infection and restore a healthy immune homeostasis that could be used alongside ART.

Future studies are needed to identify biological mechanisms underlying heightened expression of ISGs and other immune activation genes, and to differentiate effects of HIV-1 replication and ART on ISG expression.

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