Elevated Interferon Signaling in Immunological Non-Responders is Linked to anti-CMV and anti-EBV IgG

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BACKGROUND

- Immunological Non-Responders (INRs) are people living with HIV (PLHIV), who fail to reach normal CD4 T cell counts after cART treatment, despite effective viral suppression.
- INRs have increased immune activation and exhaustion, which is thought to contribute to poor immune reconstitution.
- Most PLHIV are co-infected with herpesviruses, which induce immune activation upon reactivation
- Here, we assess transcriptional signatures associated with the INR phenotype and their relationship with HIV-1 viral reservoir size and measures of herpesvirus reactivation.

Increased immune activation in Immunological Non-Responders is linked to anti-EBV and anti-CMV antibody titers

CONCLUSIONS

- Our data link anti-CMV and anti-EBV IgG titers to elevated interferon signaling in INRs.
- Increased anti-CMV IgG in INRs might reflect increased CMV reactivation, likely due to impaired cellular immunity
- These findings suggest pharmacological suppression of herpesvirus replication as a strategy to reduce immune dysregulation in INRs, which might contribute to improved CD4 T cell recovery

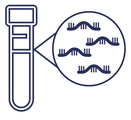
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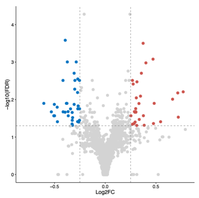
METHODS

2000HIV study



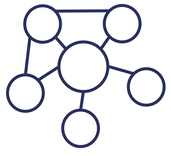


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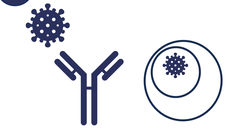
Differential expression analysis

2



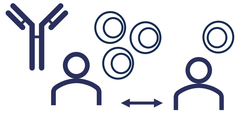
Pathway analysis (GSEA)

3



Correlate IFN-α/β signaling score with anti-herpes IgG & viral reservoir size

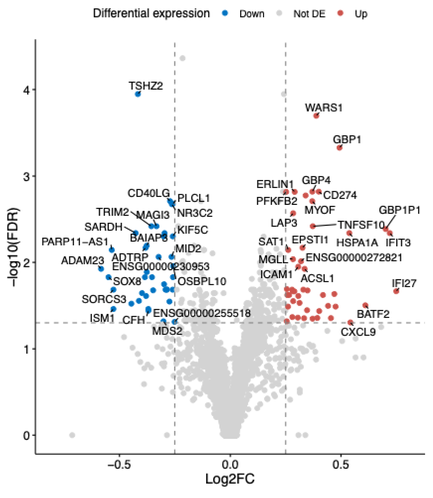
4



Compare anti-CMV IgG in INRs vs IRs

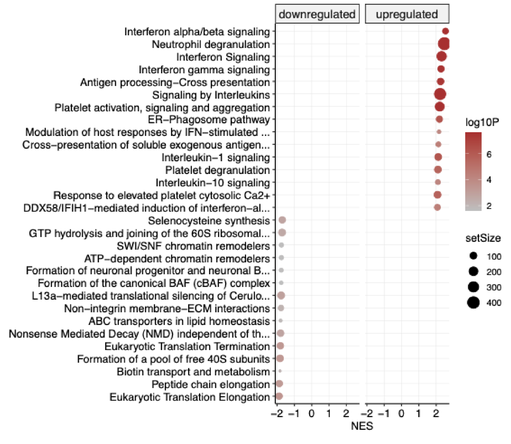
RESULTS

1. INR status is associated with differences in RNA expression



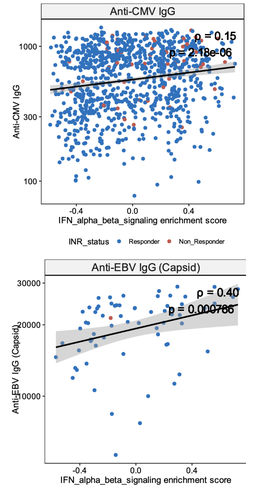
- 50 upregulated and 39 downregulated DEGs (Padj < 0.05, $\log_2$FC > 0.25)

2. Immune pathways are upregulated in INRs



- Top upregulated pathways: IFN signaling, immune activation, antigen presentation
- Top downregulated pathways: translation

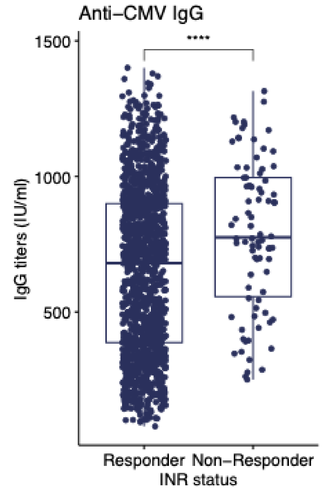
3. IFN-α/β signaling is more strongly associated with anti-CMV and anti-EBV IgG than with viral reservoir size in PLHIV



Viral variable	ρ	P-value
Total HIV-1 DNA	0.02	0.49
Intact HIV-1 DNA	0.08	0.026
Total HIV-1 RNA	0.04	0.3
Unspliced HIV-1 RNA	0.01	0.7
Anti-HSV1 IgG	0.07	0.03
Anti-HSV2 IgG	0.00	0.93
Anti-EBNA IgG	-0.04	0.74
Anti-VZV IgG	-0.06	0.63

- Only CMV/EBV seropositive individuals (93% CMV+, no difference INR vs IR; 95% EBV+ only 1 INR measured).
- This suggests that IFN-α/β signaling is driven by CMV and EBV

4. INRs have elevated anti-CMV IgG compared to IRs



The 2000HIV study is supported by ViiV Healthcare
www.2000HIV.com