Genetic regulation of immune responses to CMV in spontaneous HIV controllers

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BACKGROUND

- HIV controllers (HICs) spontaneously control an HIV infection without requiring ART
- We previously showed that SNPs associated with lower odds of HIC in the MHC region upregulate IL-1β and TNF-α response to CMV pp65
- Here, we further investigate how these SNPs regulate pro-inflammatory responses to CMV and the role of these responses in HIV control

SNPs associated to lower odds of spontaneous HIV control in the MHC region upregulate pro-inflammatory memory responses to CMV pp65

METHODS

Participants:

- 2000HIV cohort: 1895 virally suppressed PLHIV
- 2000HIV-TRAINED cohort: 61 virally supressed PLHIV (31 HICs) & 45 HIV- first degree family members

Methods:

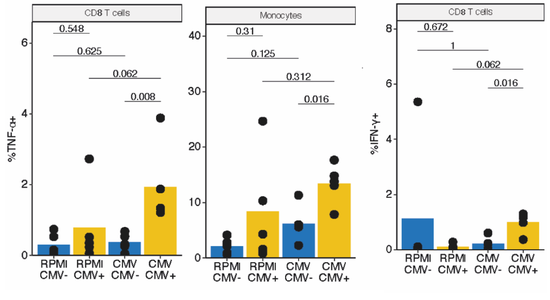
- Intersection of top SNPs associated with HIV control and cytokine response to CMV with eQTL summary statistics from 2000HIV cohort ($P < 0.01$)
- Intracellular cytokine staining upon 4h stimulation with CMV pp65 peptide pool in 5 CMV+ and 5 CMV- PLHIV.
- 24h stimulation of PBMCs with CMV pp65 peptide pool, IFN-γ measured in supernatant
- Genetic association study in the MHC region with CMV serostatus in 87 CMV- and 1180 CMV+ PLHIV of European ancestry
- *Ex vivo* PBMC stimulation with 13 stimuli for 24h or 7 days, production of 12 cytokines in supernatant measured by ELISA. Unsupervised hierarchical clustering of spearman correlations

RESULTS

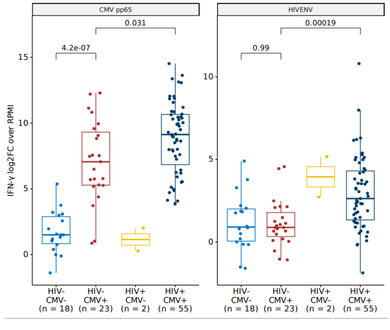
HIV control risk SNPs upregulate TNF-α and IL-1β responses to CMV, and regulate expression of classical HLA genes and lncRNAs in the MHC locus

	GWAS HIC		*cytQTL CMV response*		
rsID	*P-value*	*OR*	*P-value*	*β*	*Prioritized genes*
Top SNP IL-1β	$1.1 \cdot 10^{-4}$	0.3	$4.15 \cdot 10^{-8}$	0.28	*AL662844.4, ATP6V1G2, DDR1, HLA-B, HLA-C, TCF19*
Top SNP TNF-α	1.6 · 10-3	0.23	$8.4 \cdot 10^{-6}$	0.32	*AL645933.2, CCHCR1, DDAH2, HCG27, HLA-B*

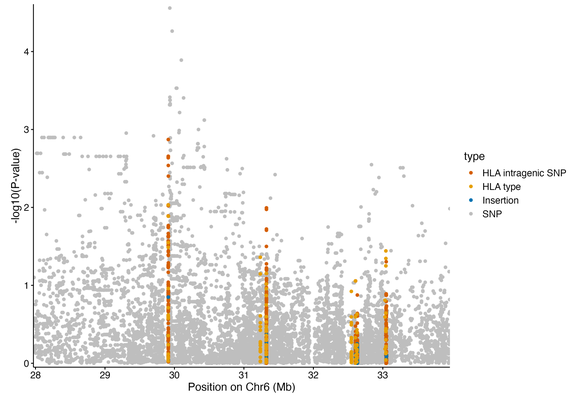
The inflammatory memory response to CMV pp65 is mediated by CD8 T cells and monocytes



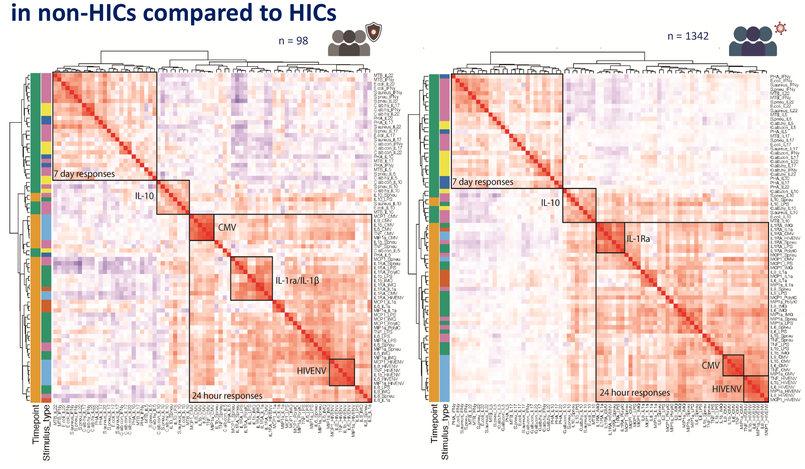
Increased memory responses to CMV pp65 in PLHIV vs healthy controls



Genetic variants in the MHC region do not strongly associate with CMV serostatus



Pro-inflammatory responses to CMV pp65 and HIVENV cluster more closely in non-HICs compared to HICs



CONCLUSIONS

- SNPs associated with reduced odds of HIC in the MHC locus upregulate pro-inflammatory memory responses to CMV pp65
- This suggests that CMV-driven inflammation is unfavourable for HIV control

ADDITIONAL KEY INFORMATION

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www.2000HIV.com