Trained immunity in monocytes is associated with persistent Elite Controller status

442

Jéssica C. dos Santos[1], Suzanne D.E. Ruijten[1], Albert L. Groenendijk[2], Nadira Vadaq[1], Rainer Knoll[3,4], Rob ter Horst[5], Marc Blaauw[1], Louise van Eekeren[1], Willem Vos[1], Victoria Rios-Vazquez[1], Vasiliki Matzaraki[1], Jan van Lunzen[1], Leo A.B. Joosten[1,6], Mihai G. Netea[1,4], Andre J. A. M. van der Ven[1]

[1]Radboudumc, Nijmegen, The Netherlands, [2]ErasmusMC, Erasmus University, Rotterdam, The Netherlands, [3]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Bonn, Germany, [4]Life & Medical Sciences Institute, University of Bonn, Bonn, Germany, [5]The Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM), Vienna, Austria, [6]Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

BACKGROUND

The protective role of trained innate immunity in various infections is well known, but its impact on spontaneous HIV control is underexplored. The mechanisms underlying trained immunity includes transcriptional, metabolic and epigenetic changes which prompts increased production of effector molecules by monocytes. We hypothesized that trained monocytes, as induced by β-glucan, are crucial in orchestrating a beneficial antiviral immune response associated with long-term spontaneous HIV control, and is shown also in first degree relatives of HIV controllers.

METHODS

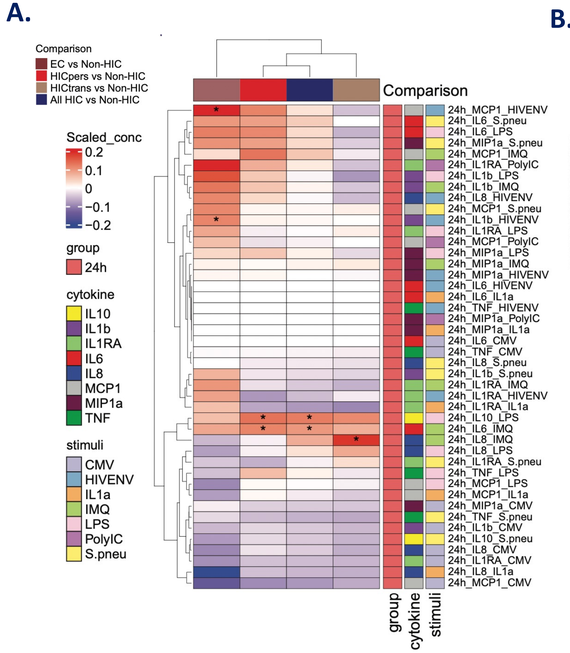
STUDY PARTICIPANTS AND EXPERIMENTAL DESIGN

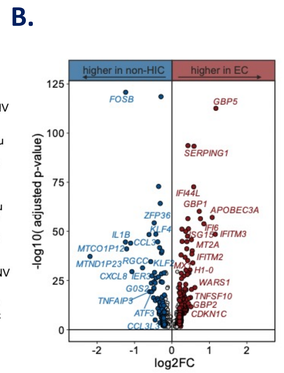
1895 people living with HIV, among which 114 HIV controllers classified as Elite controller (EC; VL <75 c/mL), viremic controllers (VC; VL <10.000 c/mL), [together defined as HIC persistent controllers (HICpers)] and transient controllers (HICtrans; lost HIV control status), were included (2000HIV study - NTC03994835). First degree family members (FAM) of HICpers and FAM-non-HIC were part of the 2000HIV-trained study (NCT04968717). We analyzed multi-omics data consisting of: 1) cytokine/chemokine production upon stimulation, 2) single-cell and bulk RNA seq expression in PBMCs, 3) circulating concentrations of β-glucans, 4) trained immunity induction through the exposure of monocytes to β-glucan and restimulation with LPS, 5) epigenomic profile using ATAC-seq.

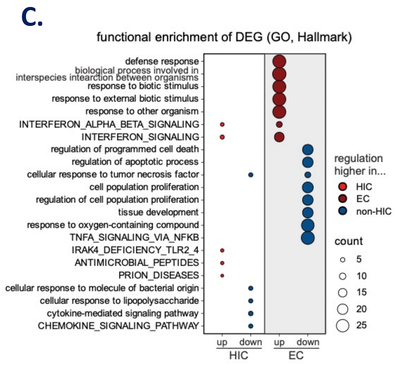
Enhanced monocyte functionality as a central player in long-term HIV control maintenance

RESULTS

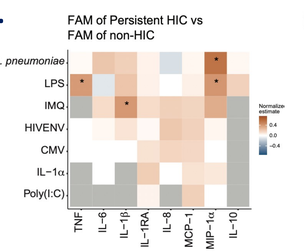
Monocytes responses of persistent controllers is increased upon stimulation and are transcriptionally characterized as less inflammatory and more antiviral

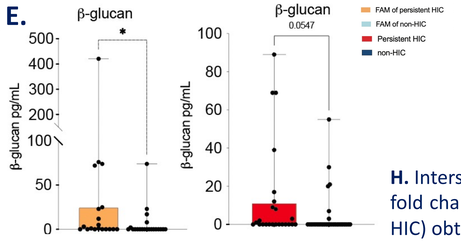






Monocytes responses of HIC and their 1st degree relatives are increased

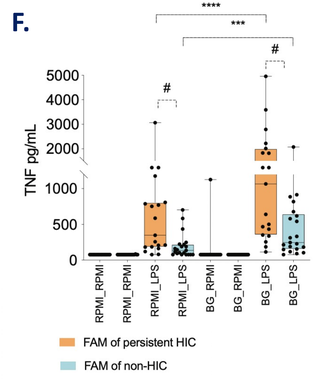


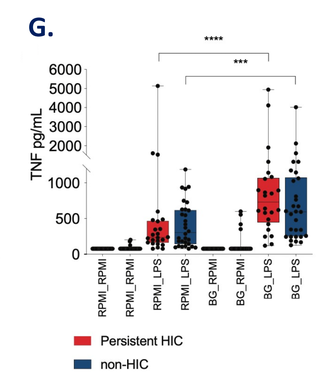


A. Differential analysis of *ex vivo* cytokine levels comparing EC (n = 20), HICpers (n = 49), HICtrans (n = 43), and all HIC (n = 92), with non-HIC (n = 1317) (*p< 0.05). **B.** Differentially expressed genes of HIC pers (n = 18), EC (n = 6) compared to non-HIC (n = 30) measured in monocytes using scRNA-seq. **C.** Functional enrichment analysis for HIC- EC-specific up- and downregulated genes.

D. Differential analysis of *ex vivo* cytokine levels comparing FAM-HICpers (n = 19) with FAM-non-HIC (n = 21). **E.** β-glucan plasma levels comparing FAM-HICpers with FAM-non-HIC and HICpers (n = 25) with non-HIC (n = 30) (*p< 0.05).

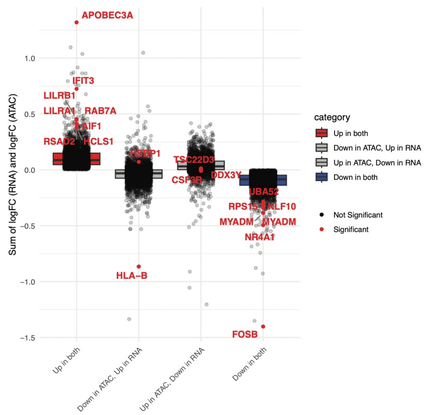
Monocytes of HIC and their 1st degree relatives have increased trained immunity





F. Training capacity of adherent monocytes from **F.** FAM-HICpers (n = 19), FAM-non-HIC (n = 21). and **G.** HICpers (n = 25) and non-HICs (n = 30) exposed to RPMI or β-glucan followed by LPS restimulation (*p< 0.05).

EC monocyte chromatin accessibility confirms trained immunity



H. Intersection of up- and downregulated genes in monocytes of EC (log fold change scRNA-seq) with differentially enriched regions (EC vs non-HIC) obtained from ATAC-seq of CD14+ cells.

ADDITIONAL KEY INFORMATION

Correspondence: jessica.dossantos@radboudumc.nl

The 2000HIV study is supported by ViiV Healthcare

www.2000HIV.com