Of mice and men: HIV-induced CD38 expression on CD8+ T lymphocytes contributes to mitochondrial dysfunction and chronic inflammation despite antiretroviral therapy

P. MATHUR, S. KOTTILIL, B. ATKINSON, A. HEREDIA, A. GHOSH

Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA

INTRODUCTION

- Antiretroviral treatment (ART) has increased the life expectancy of people with HIV (PWH), however, comorbidities are higher in PWH than HIV-negative individuals.
- This is partly due to accelerated cellular aging, a consequence of CD38 expression, mitochondrial dysfunction, and inflammation.
- However, the role of CD38-expressing T cells on accelerated cellular aging in PWH is not completely understood.

AIM

- To evaluate the role of CD38 in T cell function in PWH.

METHODS

- The proportion of cytotoxic CD38+ CD8+ T lymphocytes from peripheral blood mononuclear cells (PBMCs) of PWH and HIV negative-individuals was measured.
- PBMCs from PWH on ART were cultured with or without HIV gag-specific peptide stimulation and cytokine production was detected by flow cytometry.
- Mitochondrial function from T cells of PWH on ART and HIV-negative (healthy) donors was compared using mitochondrial-specific dyes.
- Last, we generated a humanized (NSG) mouse model and infected mice with HIV (Bal strain) to determine the proportion of CD38+ T cells and cytokine production.

RESULTS

- Mean CD38 expression on CD8 T cells was significantly different between PWH not on ART (n=485), PWH virally-suppressed on ART (n=291), and HIV-negative individuals (n=119) (Figure 1).
- In PWH on ART, HIV gag-specific peptide stimulation of CD8+ T cells significantly increased CD38 expression and augmented secretion of IFNγ+ and TNFα+. There was a higher expression of CD38 among CD8+ T cells that produced IFNγ and TNFα (Figure 2).
- T cells in PWH have altered mitochondrial function (Figure 3).
- HIV-infected NSG mice had T cell changes consistent with HIV infection, a higher proportion of CD38+ T cells with an activated phenotype, and significantly higher levels of inflammatory cytokines (Figure 4).

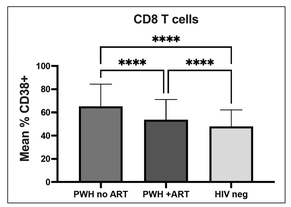

Figure 1. (A) Mean %CD38+CD8+ T lymphocytes from a longitudinal cohort of PWH on and off ART and HIV-negative individuals. Statistical significance was tested by Kruskal-Wallis test with post hoc analysis (Dunn's Multiple comparison test) and Mann-Whitney test. ****, p value< 0.0001.

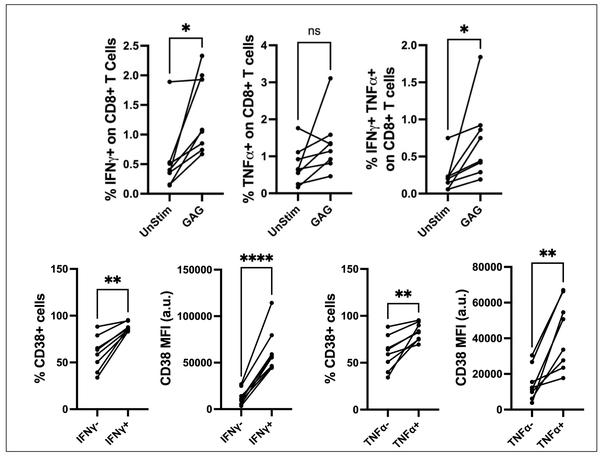

Figure 2 (right). Intracellular cytokine production and change in CD38 expression on CD8+ T lymphocytes in response to HIV gag-specific peptide stimulation among 8 PWH on ART. Statistical significance was tested by paired t test. *, p value< 0.05; **, p value< 0.005; ****, p value< 0.0001; ns – not significant.

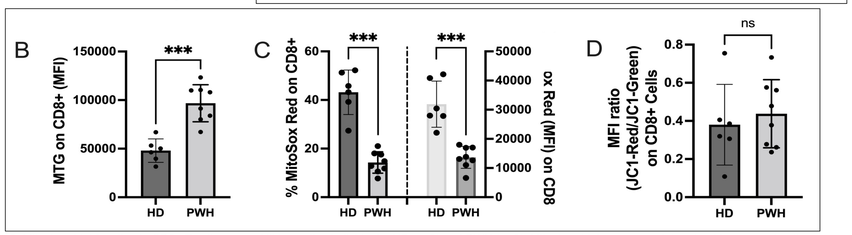

Figure 3. Mitochondrial function in CD8+ T cells among HIV-negative individuals (HD, n=6) and PWH (n=8). Mitochondrial mass was determined by measuring the mean fluorescence intensity (MFI) of mitotracker green (MTG) among CD8+ T lymphocytes. Frequency of mitochondrial superoxide positive lymphocytes and level of mitochondrial superoxide (MFI) were determined by staining the CD8+ T lymphocytes with mitosox red dye. Mitochondrial membrane depolarization was determined by the red to green ratio of MFIs of mitochondrial membrane potential-dependent dye JC-1 among the CD8+ T lymphocytes. Statistical significance was tested by Mann-Whitney test. ***, p value< 0.005; ns – not significant.

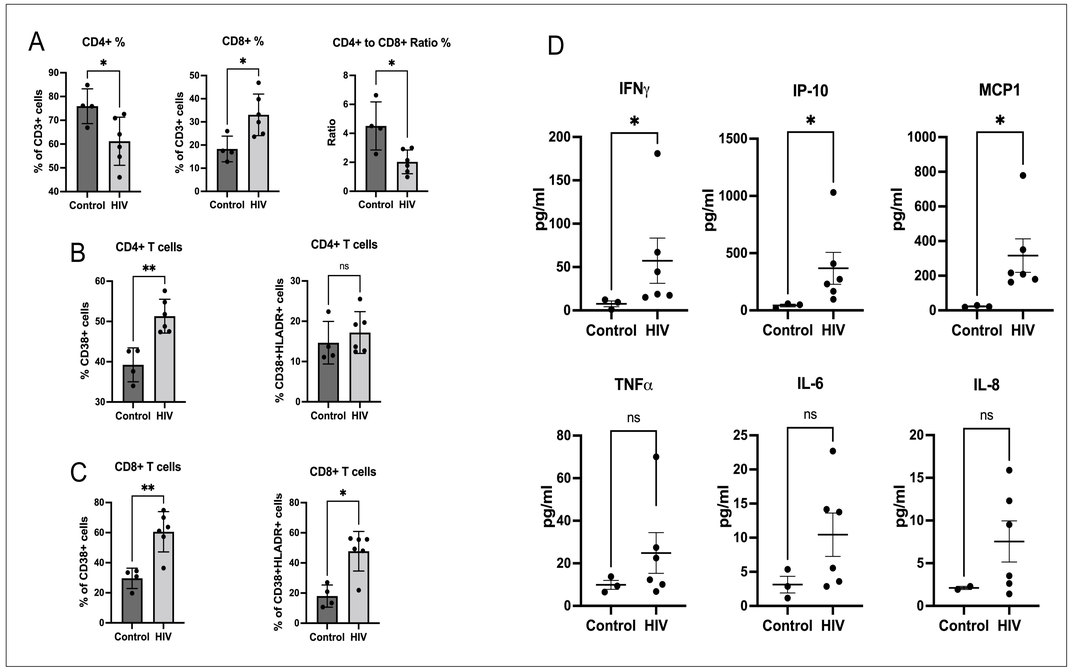

Figure 4. (A) Frequency of CD4+ and CD8+ T lymphocytes and comparison of ratio of the frequencies of CD4+ to CD8+ T cells between control and HIV infected humanized mice. Statistical significance determined by Mann-Whitney test. (B) Frequency of CD38+ and CD38+HLADR CD4+ (B) and CD8+ (C) T cells in HIV- infected humanized mice compared to control. Statistical significance determined by Mann-Whitney test. (D) Cytokine measurements of HIV-infected humanized mice and controls. Statistical significance was tested by independent t test. *, P value< 0.05; **, P value< 0.01; ns – not significant. HLADR= Human Leukocyte Antigen – DR isotype, IFN=Interferon, IP=Inducible Protein, MCP=Monocyte Chemoattractant Protein, TNF=Tumor Necrosis Factor, IL=Interleukin.

CONCLUSIONS

- A high number of CD38-expressing CD8+ T cells persist in PWH despite viral suppression by ART.
- In vitro, T cells of PWH have altered mitochondrial function, and HIV-specific stimulation augments CD38 expression on CD8+ T cells and contributes to a proinflammatory response.
- These findings translate to a humanized mouse model, where HIV infection upregulates CD38 expression and cytokine production.
- Hence, CD38 may be one of the driving factors for a chronic, inflammatory state, ultimately accelerating cellular aging and the risk of comorbidities in PWH.
- Pharmacological targeting of CD38 may provide a strategy to reduce end-stage organ disease in PWH.

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CONTACT INFORMATION

Poonam Mathur, pmathur@ihv.umaryland.edu