The MHC-II Processing and Presentation of HIV-1 Antigens

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Introduction

Human immunodeficiency virus type 1 (HIV-1) is a lentivirus of the Retroviridae family. Having first been identified in 1983 (1)—two years after the characterization of acquired immunodeficiency syndrome (AIDS), a condition that results from untreated HIV-1 infections (1)—HIV-1 continues to pose an unwavering global health threat. Notably, in 2020, an estimated 680,000 people across the globe died from HIV-1-related causes (2).

While the advent of antiretroviral therapy (ART) has significantly reduced the aforementioned figure, ART is by no means a silver bullet: importantly, it cannot target host cells that serve as latent HIV-1 reservoirs once the pathogen integrates its genome into those of infected cells, thus ensuring that infections cannot be eradicated (3). Furthermore, ART only manages infections—it does not prevent them. For this reason, much research has been conducted investigating potential HIV-1 vaccines. This effort, however, has largely proven fruitless given that no fully approved or licensed HIV-1 vaccine currently exists (4). In light of this information, our lab investigated major histocompatibility complex class II (MHC-II)-restricted HIV-1 antigen presentation, a topic on which literature is scant (5). Specifically, our lab addressed presentation among $CD4^+$ T cells and dendritic cells (DCs), the latter being a classical professional antigen-presenting cell (APC).

Background

In further detail, our lab investigated MHC-II-restricted HIV-1 antigen presentation among monocyte-derived DCs (MDDCs) and activated $CD4^+$ T cells. We chose these cell types for several reasons:

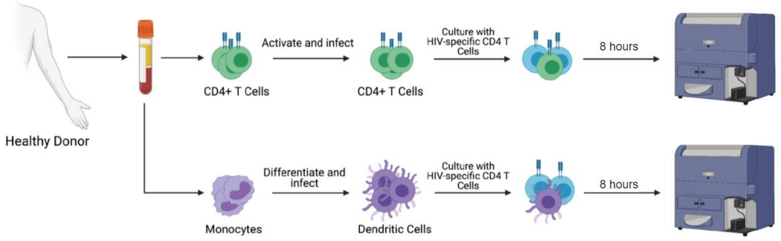
$CD4^+$ T Cells
1. Primary characteristic of HIV-1 infection is infection and depletion of $CD4^+$ T cells themselves
2. Activated CD4s express both MHC-II and CD86 (5)
3. Both *in vitro* and *in vivo*, activation of $CD4^+$ T cells is required for viral replication (6)
4. $CD4^+$ T cells that function as APCs can induce hyporesponsiveness in other $CD4^+$ T cells (7)
5. $CD4^+$ T cell anergy has been observed during HIV-1 infection (8)

DCs
1. Are conventionally known to present antigen to and activate $CD4^+$ T cells (9)
2. Express both CXCR4 and CCR5 alongside minor amounts of CD4 required for HIV-1 infection (10)
3. Can trans-infect $CD4^+$ T cells in the context of an HIV-1 infection (11)

HIV-1 Peptide
- The chosen HIV-1-specific peptide is gag293, a p24 (gag protein) epitope to which the experimental (F5, hereinafter referred to as the HIV-specific TCR) TCRs have specificity (12)

Methods

In summary, both CD4s and DCs are infected with various strains of HIV-1 or cultured with gag293 peptide and then presented to (non-infected) antigen-specific responding CD4s prior to flow staining and analysis:



Cell Sample Isolation and Anonymization
- All cell samples are isolated and anonymized by the Penn Human Immunology Core (HIC)

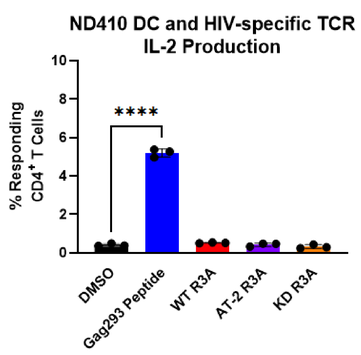
Presenting $CD4^+$ T Cell Activation
- T cells are activated with irradiated K562 cells expressing CD64, CD86, and OKT3, a murine aCD3 antibody (13)

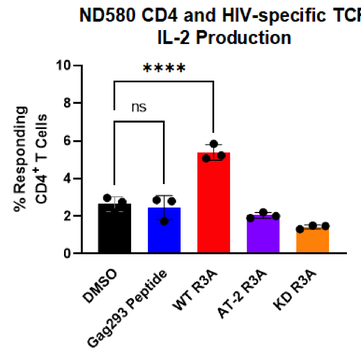
Monocyte Differentiation
- The utilized DCs are derived from monocytes using interleukin-4 (IL-4) and granulocyte-macrophage colony-stimulating factor (GM-CSF)

Conditions (Including Experimental HIV-1 Virions)
- HIV-1 virions: WT R3A (wild type), AT-2 (WT R3A chemically inactivated with aldrithiol-2), and KD (WT R3A K574D fusion-deficient mutant)
- Other conditions: Working DMSO and gag293 peptide

Donor Matching
- APCs and responding CD4s in each condition originate from the same donor

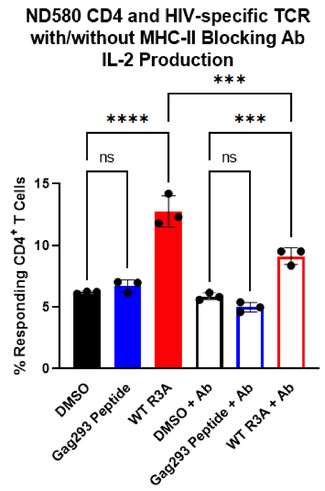
Results





The above graphs are from different experiments

Results (Continued)



One-way ANOVA: p<0.05 (*), p<0.01 (**), p<0.005 (***), p<0.001 (****)
The phrase "normal donor" is initialized as ND

Conclusions and Discussion

- $CD4^+$ T cells present gag293 peptide derived from infectious WT R3A virus, but not that originating from the extracellular environment or derived from any other tested HIV-1 virions
- Presentation of gag293 peptide among CD4s appears to be MHC-II dependent
- DCs present gag293 peptide originating from the extracellular environment, but not that derived from either infectious WT R3A virus or any of the other tested HIV-1 virions

Given that only one antigen (p24) and one of its epitopes (F5) were investigated herein, further research addressing other gag epitopes and non-gag HIV-1 antigens is warranted to more comprehensively understand the landscape of HIV-1 antigen processing and presentation.

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