UNPRIMED CD8+ LYMPHOCYTES PROMOTE THE ESTABLISHMENT OF HIV LATENCY IN CD4+ T CELLS

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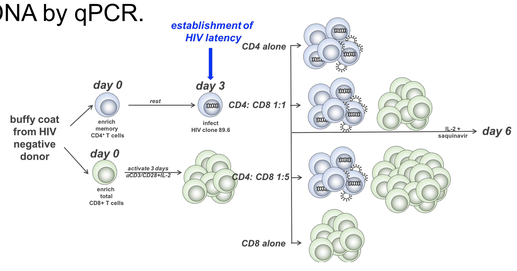
BACKGROUND

- CD8+ T cells have a complex role under ART that includes both CTL-mediated virus specific clearance of infected CD4+ T cells and non-cytolytic inhibition of virus expression.
- The effects of CD8+ T cells are synergistic in terms of reducing virus replication in the absence of ART- however, they may have divergent effects on the reservoir size.
- Our hypothesis is that CD8+ T lymphocytes suppress virus production in ART-treated HIV/SIV infection by actively inhibiting virus expression from CD4+ T cells.

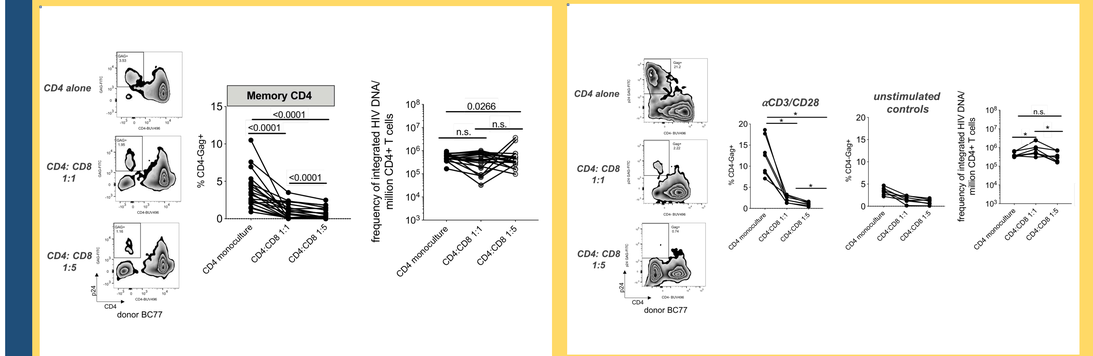
The persistence of HIV infection under ART is due to a reservoir of latently infected cells that remain indefinitely despite suppression of virus replication. Defining the mechanisms responsible for the establishment and maintenance of the HIV reservoir under ART has been the focus of efforts aimed at HIV eradication. Several studies have demonstrated that CD8+ T cells inhibit virus replication during untreated HIV/SIV infection; however, the mechanisms responsible for this antiviral effect remain poorly understood.

METHODS

- Using our primary CD4+ T cell model, we examined the impact of CD8+ T cells on the establishment of HIV latency in vitro.
- In vitro HIV infected CD4+ T cells were co-cultured with TCR activated autologous CD8+ T cells
- After 3 days, CD4+ T cells were assessed for frequency of HIV Gag expression by flow cytometry and integrated HIV DNA by qPCR.

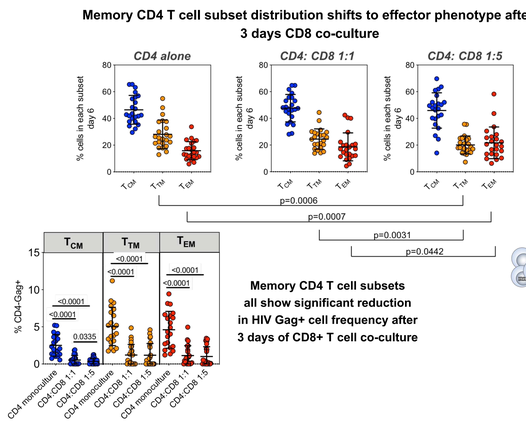


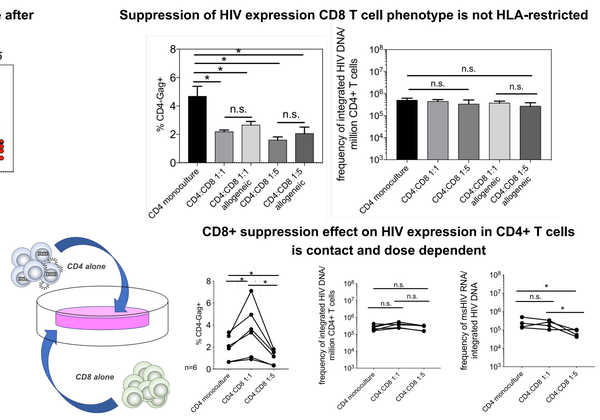
CD4+ T cells show a significant reduction in HIV expression when co-cultured in vitro with autologous CD8+ T cells in a non-cytolytic mediated mechanism.



RESULTS

- HIV expression in resting CD4+ T cells was reduced when co-cultured with autologous CD8+ T cells an average of 9-fold ($p<0.0001$) and 18-fold ($p<0.0001$) at 1:1 or 1:5 ratios
- However, we observed no significant reduction in the frequency of HIV-infected cells (n=21).
- HIV expression was also significantly reduced when HIV-infected CD4+ T cells were subsequently TCR activated and cultured in the presence of autologous CD8+ T cells, a 6-fold decrease at 1:1 target: effector ratio ($p= 0.0156$) and 14-fold decrease at 1:5 ratio ($p= 0.0156$).





CONCLUSIONS

- In vitro data using blood from HIV-naïve donors reveals a CD8 specific suppression of HIV expression in CD4+ T cells that is not due to a decrease in the frequency of infected cells
- These data support a role for CD8+ T cells in the control of HIV expression and in the establishment of latency in CD4+ T cells

Our studies demonstrated a CD8+ lymphocyte mediated suppression of HIV expression in CD4+ T cells that functions to induce the establishment as well as maintain latency in the presence of activation signaling. Understanding the mechanisms by which CD8+ lymphocytes suppress virus transcription and ultimately promote HIV latency in ART-treated HIV-infected individuals may provide critical insight to support the design HIV eradication approaches.

DISCUSSION

Is it surprising that non-cytolytic/innate CD8+ T cells suppress HIV transcription via modulation of CD4+ signaling?

- CD8+ T cells act as innate and/or non-cytotoxic anti-microbial agents (Salmonella typhimurium, Listeria monocytogenes, HSV-1)
- CD8+ T cells can mediate immune regulatory functions in the setting of autoimmunity, transplants, and anti-tumor responses

ADDITIONAL KEY INFORMATION

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