

CD4⁺CD25^{hi} T regulatory cell dynamics during acute and chronic HIV-1 infection

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Background

What are natural T regulatory cells?

Subset of CD4⁺ T lymphocytes that express the transcription factor, foxp3

Phenotype: CD4⁺, CD25^{hi}, other markers (memory markers like CD45RO and CD62L, CTLA-4, GITR)

Activity: Suppressive function. Major role in preventing autoimmunity

Role of T regulatory cells in infections: a fine balance

Leishmania: T regs allow persistence of parasite at site of infection, thus long term immunity¹

Pneumocystis carinii: T regs allow persistence of parasite, and inhibit extent of inflammation²

However, in HSV: T regs impair the protective antiviral effects of CD8 T cells against viral challenge³

Role in HIV pathogenesis: largely unknown

T regs suppress HIV T cell-specific responsiveness^{2,4,5}

Decreased T regs in HIV infection result in chronic state of hyperactivation⁶

HIV-specific T reg suppressor activity is associated with immune competency⁷

Methods

Study subjects: included (i) recently infected individuals with HIV-1 (n=47) (documented negative HIV-1 EIA within previous 12 months, or presence of a non-reactive "detuned" EIA at enrollment

(ii) those with chronic HIV-1 (n=13) (documented HIV-1 infection for >2 years)

(iii) Healthy uninfected donors (n=18)

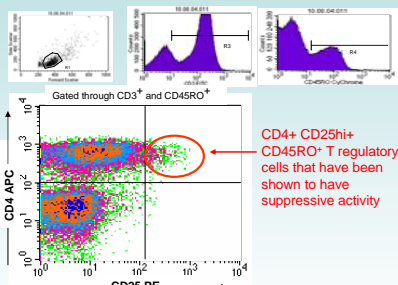
Flow cytometry: Fresh or frozen peripheral blood mononuclear cells (PBMCs) were immunostained with the following monoclonal antibodies: CD3 FITC, CD4 APC or PE/Cy5.5, CD25PE, CD45RO APC or Cychrome, and flow cytometric analyses was done on four-color FACSCaliber.

PCR: After immunostaining, cells were sorted into T cell subsets (T regs, CD4⁺ CD25⁺ memory T cells) Following RNA extraction and cDNA synthesis, samples were amplified using human foxp3 primers, or HIV-1 gag primers. Real-time PCR was performed and expression of foxp3 or HIV-1 gag was normalized to gapdh expression in each sample.

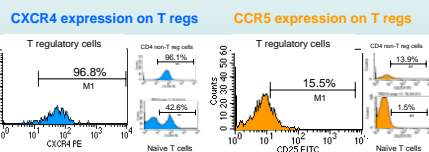
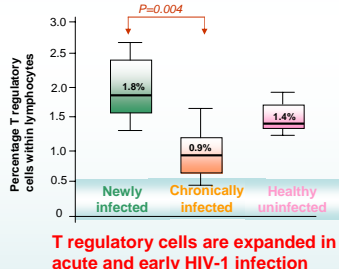
Statistics: Paired t test, ANOVA, linear regression methods (SPSS v.10.0)

Results

Flow cytometric analysis of T regulatory cells

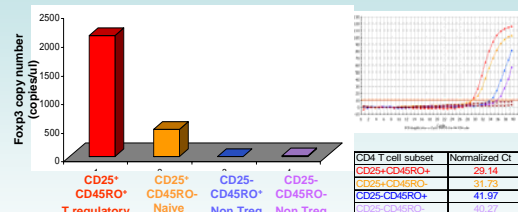


Distribution of T regulatory cells within the lymphocyte subset among different populations

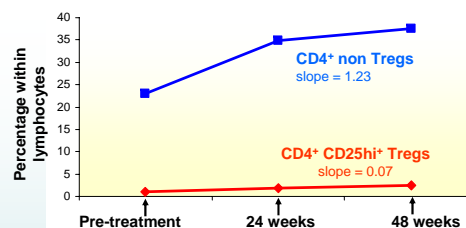


T regulatory cells express similar levels of the chemokine receptors CCR5 and CXCR4 as memory CD4⁺ T cells

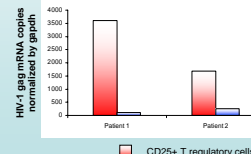
Foxp3 expression in CD4⁺ T cell subsets



Recovery of T regulatory and CD4⁺ T cells with HAART in early HIV-1 infection

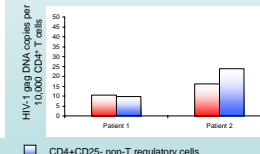


Productive HIV-1 mRNA infection



CD25⁺ T regulatory cells show higher levels of productive HIV-1 infection

Integrated proviral HIV-1 DNA



Provirial HIV-1 DNA levels are similar in CD25⁺ T regulatory cells and CD4⁺ non-T regulatory cells

Conclusions

- Naturally-occurring foxp3-expressing T regulatory cells can be phenotypically expressed as CD3⁺CD4⁺CD45RO⁺CD25^{hi} T cells.
- CD4⁺CD25^{hi} T regulatory cells are expanded in acute HIV-1 infection and may likely play a role in suppressing activation of CD4⁺ T cells and decrease the targets for infection and viral replication.
- In new HIV-1 infections, as HAART is initiated and immune reconstitution occurs, T regulatory cells increase modestly (slower recovery than CD4⁺ T cells). Thus CD4⁺CD25^{hi} T regulatory cells may play a role in further suppressing activation of target CD4⁺ T cells, therefore contributing to faster CD4⁺ T cell recovery.
- CD4⁺CD25^{hi} T regulatory cells appear to be sites of active infection and replication of HIV-1 to a larger extent than naïve CD4⁺ T cells.
- CD4⁺CD25^{hi} T regulatory cells have high and comparable levels of chemokine receptors CCR5 and CXCR4; thus T regulatory cells are also potential targets for HIV-1 infection.

References

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