HIV-1 infection is characterised by early depletion of CD161+ CD4 cells and gradual decline in regulatory T cells

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CD4 depletion is the hallmark of HIV infection
Naïve CD4 cell differentiation
Naïve CD4 cell differentiation
Naïve CD4 cell differentiation

**Intracellular pathogens**

IFN\(\gamma\) → Th1 → T Bet → IL-12 → Naïve CD4 → IL-4 → Th2 → GATA3 → Extracellular pathogens

- IL-4
- IL-5
- IL-13
- IL-25

**Extracellular pathogens**
Naïve CD4 cell differentiation

**Intracellular pathogens**
- IFNγ
- Th1
  - T Bet
  - IL-12

**Extracellular pathogens**
- IL-4
- IL-5
- IL-13
- IL-25

**Th2**
- GATA3
- IL-4

**Differentiation**
- IL-1β + IL-6 + IL-23

**Th17**
- ROR-γt
- IL-21

**Amplification**
- IL-23

**Stabilisation**
- DC

**Th17**
- IL-17A
- IL-17F
- IL-21
- IL-23

**Bacteria**
- Fungi
- Mycobacteria
Naïve CD4 cell differentiation

Intracellular pathogens

Treg
FoxP3

Naïve CD4

Immune regulation

IL-10 TGF-β

Th1

IFNγ

Tgfb

IL-12

Tbet

Differentiation

IL-1β + IL-6 + IL-23

RORγt

Th17

IL-21

Amplification

IL-23

Stabilisation

Th17

IL-17

IL-17A

IL-17F

IL-21

IL-23

DC

Extracellular pathogens

IL-4
IL-5
IL-13
IL-25

Th2

GATA3

Bacteria
Fungi
Mycobacteria
Preservation of Th17 cells in MALT of natural SIV hosts

Natural SIV hosts
- Preservation of Th17 cells
- No microbial translocation
- No immune activation

HIV-infected humans
- Profound CD4 depletion
- Loss of Th17 cells
- Microbial translocation
- Immune activation

Brenchley et al., Blood 2008; 112:2826-35.
Human interleukin 17-producing cells originate from a CD161⁺CD4⁺ T cell precursor

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CD4+CD25+ population capable of suppressing other effector cells

Prevention of autoimmunity

Immune homeostasis / self-tolerance

Tregs in HIV: no consensus

Accumulation
Inhibition of effector cells

Andersson *J Immunol* 2005
Cao, *AIDS Res Hum Ret* 2009
Weiss, *Blood* 2004

Depletion
Increase in immune activation

A poil, *JAIDS* 2005
Eggena, *J Immunol* 2005
Tregs in HIV: no consensus

Detrimental
Andersson, *J Immunol* 2005
Cao, *AIDS Res Hum Ret* 2009
Weiss, *Blood* 2004

Protective
Apoil, *JAIDS* 2005
Eggena, *J Immunol* 2005
Conference Summary

Regulatory T Cells (T<sub>reg</sub>) and HIV/AIDS: Summary of the September 7–8, 2006 Workshop

CLAIRE A. CHOUGNET<sup>1</sup> and GENE M. SHEARER<sup>2</sup>

- Differences in patient characteristics
- Varying Treg definitions
- Data analysis
- Tissues vs blood
- Cross-sectional data
Aims of this study

• To investigate the impact of HIV on diverse CD4 subsets
  – Th17 cells
  – CD161+ cells
  – Tregs
Study subjects

- 77 HIV-infected
  - Chronic infection
  - Not on ART
  - Median CD4 470 (IQR 360-668)
  - Subset followed longitudinally

- 36 HIV-uninfected
Th17 cells

Fresh PBMC

4 hours

PMA / ionomycin
Brefeldin A

Stained for CD4
Permeabilised
Intracellular IL-17
Th17 cells are depleted ten-fold in peripheral blood in HIV infection

![Graph showing comparison between HIV uninfected and infected groups, with P<0.0001.]
Th17 cells are depleted ten-fold in peripheral blood in HIV infection.

![Graph showing depletion of Th17 cells in HIV infection](image)
Do Th17 cells contribute to the antiviral effector response?

PBMC isolated

CD4 cells selected

Beads CMV EBV Gag Pol Nef Negative

IL-17

IFN-γ
Viral-specific Th17 cells are not present in HIV-infected subjects.
CD161+ CD4 cells are depleted in HIV infection
Are Th17 cells preferentially infected with HIV?

Healthy donor PBMC isolated → CD4 cells selected → Cells activated for 48h

- Stimulated with PMA/IO
- FACS for p24 and IL-17 / IFN-γ

Cells infected with virus:
- Bal
- No virus

Cells infected after 5 days
Th17 cells can be infected with HIV
Th17 cells can be infected with HIV
Th17 cells can be infected with HIV
CD161+ CD4 cells express high levels of CCR5

![Graph showing expression levels of CCR5]
CD161+ CD4 cells can be infected with CCR5-tropic HIV
CD161+ CD4 cells can be infected with CCR5-tropic HIV
Summary

- Th17 cells depleted 10-fold in HIV-infected individuals
- Profound depletion even in subjects with high CD4 counts suggests early depletion
- Viral-specific Th17 cells not found
- CD161+ Th17 precursors depleted
- Th17 cells and CD161+ CD4 cells infected with HIV, but not preferentially
Definition of Tregs
Definition of Tregs

Healthy control

HIV-infected subject

CD3+CD4+CD25^{hi}FoxP3^+
Tregs are depleted in peripheral blood in HIV infection

P=0.08
Tregs are depleted in peripheral blood in HIV infection.
Tregs decline during disease progression in HIV infection

![Graph showing correlation between change in CD4 and change in Tregs]
Decline in Tregs is associated with increase in immune activation

\[ R = -0.33 \]
\[ P = 0.030 \]
Summary

• Tregs are depleted in HIV infection in both cross-sectional and longitudinal analysis

• Decline in Tregs is associated with increased immune activation
Conclusions

• Both Th17 cells and Tregs are depleted in HIV infection
• Loss of Th17 cells may enable mucosal translocation and immune activation
• Depletion of CD161+ CD4 cells may prevent Th17 reconstitution
• Tregs decline gradually during disease progression
• Loss of Tregs may enable immune activation to proceed unchecked
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