IL-21 reduces residual inflammation and virus persistence in ART-treated SIV-infected rhesus macaques

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Implications of residual chronic immune activation in HIV-treated patients

Residual Inflammation

- Higher than expected
- Stable over time
- Strong prognostic importance
- Associated with HIV persistence

HIV persistence and replication

non-AIDS-related overall morbidity

Inflammation in treated HIV disease is:

Currier J.S. AIDS conference 2012
Contributors to chronic immune activation

HIV replication & Immune response to the virus; Immunomodulatory functions of viral proteins

Immune response to reactivated infections

Loss of mucosal integrity

Loss of lymphoid tissue structure

Pro-inflammatory Milieu

Homeostatic Proliferation

Altered balance of CD4+ T cell subsets

Th17
Tcm

Tfh
Treg
Tem

Towards an HIV cure
people focused on science driven

Paiardini & Muller-Trutwin, Immunol Rev 2013
IL-17 and IL-22 producing cells are critical for the mucosal immune functions

- Important for anti-bacterial/fungal immunity and epithelial integrity
- Neutrophil recruitment
- Proliferation of GI enterocytes
- Production of tight junction proteins
- Production of anti-bacterial defensins

- If not properly regulated, Th17 pro-inflammatory activity may result in tissue damage
Depletion of intestinal Th17 cells is associated with progression to AIDS

- Th17 & Th22 cells are preferentially depleted in pathogenic HIV and SIV infections (Brenchley, 2008; Cecchinato, 2008; Raffatellu, 2008; Campillo-Gimenez, 2010; Li, 2011; Singh, 2012; Klatt, 2012; Kim, 2012)

- Th17 cells are preserved in nonpathogenic SIV infection of natural hosts as well as in HIV Elite controllers and LTNP (Brenchley, 2008; Favre, 2009; Brandt, 2011; Salgado, 2011; Ciccone, 2011)

- Depletion of Th17 cells is associated with microbial translocation, chronic immune activation, and disease progression (Raffatellu, 2008; Cecchinato, 2008; Gordon, 2010)

- Effective CD4 T cell restoration in gut-associated lymphoid tissue of HIV-infected patients is associated with increased Th17 cells (Macal, 2008)

- SIV replication in rhesus macaque is limited by the size of the preexisting Th17 cell compartment (Hartigan-O'Connor, 2012)

Can we modulate the levels of intestinal Th17 cells in vivo?
**Interleukin (IL)-21 functions**

**Rationale**

- Th17 cell generation is severely impaired in the absence of IL-21 (Nurieva, Nature 2007; Korn, Nature 2007; Yang, Nature 2008)
- IL-21 shows promise in multiple myeloma and renal cell carcinoma trials to improve CD8 and NK cell functions (Davis, Clin Cancer Res 2009; Rasmussen, Br J Clin Pharmaco 2010; Steele, Br J Cancer 2012).

**Further rationale comes from our previous studies**

H. Søndergaard, Tissue Antigens, 2009
Study design

16 RMs, 8 ART+IL-21 & 8 ART alone; age/sex matched; 8 A01+, all B08- & B17-

Does IL-21 improve the partial reconstitution of intestinal Th17 and Th22 cells achieved with ART?

Does it limit residual immune activation/inflammation?

Would this impact on residual viremia and/or size of the latent SIV reservoir?
cART is very effective in suppressing SIV replication in RMs

Limit of detection 60 copies/mL; undetectable values plotted at half LOD
Improved homeostasis of Intestinal IL-17 and IL-22 producing cells

IL-21 Treated

Controls
IL-21 limits intestinal T cell activation

CD4 T cells

CD8 T cells
IL-21 limits intestinal T cell proliferation

Similar reduction found in CD4 and CD8 T cell activation in blood
IL-21 limits plasma residual viremia

Repeated measures analyses: percentages of RMs with undetectable viremia over time is significantly higher in IL-21 treated animals than controls (P=0.03)

Limit of detection: 3 copies/mL (Jeff Lifson)
IL-21 reduces cell associated SIV DNA in rectal tissues

Jeff Lifson
Conclusions

IL-21 administration in ART-treated, SIV-infected RMs:

- Is safe and significantly improves reconstitution of intestinal IL-17 and IL-22 producing CD4 T cells
- Results in a more rapid and pronounced reduction of residual activation in blood and intestinal T cells
- Limits residual viremia in plasma and cell associated SIV-DNA in rectal tissues

To explore IL-21 as a potential immunotherapeutic agent for HIV infection
OPEN QUESTIONS – WORK IN PROGRESS

- Did IL-21 reduce the levels of soluble markers of inflammation?
- Did IL-21 reduce the size of the latent SIV reservoir?
- How the achieved results impact on viral rebound following ART interruption?
- How the achieved results impact on immune activation following ART interruption?
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