Gut immunity and HIV

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The gut in HIV infection

It is much simpler to study peripheral blood lymphocytes

BUT

70-to-80% of immune cells are in the GI tract
The gut in acute HIV infection: background concepts

- HIV penetrates intestinal lining and/or is transported to gut epithelium

- Gut-associated lymphoid tissue (GALT)
  Largest lymphoid organ in body
  Includes:
  - Peyer’s patches
  - solitary lymphoid follicles
  - activated T cells

The gut mucosa expresses the α4β7 integrin

**CD4+ T cells much more abundant in gut than in peripheral blood; must of these cells are CCR5+ memory cells**
Concentration of CCR5+ CD4+ T cells in peripheral blood, lymph nodes, and gut in humans

HIV disease progression: immune activation, microbes, and leaky gut. Douek D, Topics in HIV Medicine, 2007
CD4+ T cells depletion in the GI tract during primary HIV infection

- Up to 80% within 2-4 weeks

- CD4+ T cells depletion occurs sooner and is more pronounced in gut than in peripheral tissues
Immune depletion in the gut

Uninfected

HIV-infected

There is a marked reduction in mucosal lymphoid tissue in acute infection

HIV Infection Rapidly Depletes Gut Effector Memory CD4+ T Cells


Brenchley, et al. JEM 2004
CD4+ T cells depletion in the gut

Uninfected  Acute infection  2y on HAART

Mehandru et al., PLoS Med 2006
CD4+ T cell depletion in peripheral blood, mesenteric lymph nodes (LN), inguinal LN, and jejunum after simian immunodeficiency virus infection of macaques

HIV disease progression: immune activation, microbes, and leaky gut. Douek D, Topics in HIV Medicine, 2007
A Tale of Two Monkeys

Rhesus
PATHOGENIC INFECTION

Sooty Mangabey
NON-PATHOGENIC INFECTION
Does HIV directly infect the gut?

YES

Gut cells express the $\alpha 4 \beta 7$ integrin
HIV-1 envelope protein binds to and signals through integrin $\alpha_4\beta_7$, the gut mucosal homing receptor for peripheral T cells

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Infection with human immunodeficiency virus 1 (HIV-1) results in the dissemination of virus to gut-associated lymphoid tissue. Subsequently, HIV-1 mediates massive depletion of gut CD4$^+$ T cells, which contributes to HIV-1-induced immune dysfunction. The migration of lymphocytes to gut-associated lymphoid tissue is mediated by integrin $\alpha_4\beta_7$. We demonstrate here that the HIV-1 envelope protein gp120 bound to an activated form of $\alpha_4\beta_7$. This interaction was mediated by a tripeptide in the V2 loop of gp120, a peptide motif that mimics structures presented by the natural ligands of $\alpha_4\beta_7$. On CD4$^+$ T cells, engagement of $\alpha_4\beta_7$ by gp120 resulted in rapid activation of LFA-1, the central integrin involved in the establishment of virological synapses, which facilitate efficient cell-to-cell spreading of HIV-1.
HIV-1 gp120 binds to α4β7 expressed on gut cells

The interaction between α4β7 and gp120 activates LFA-1

Activated LFA-1 binds to ICAM-1, establishing immunovirologic synapses that facilitate the rapid spread of HIV
Do the gut alterations seen in HIV infection influence the immune response?

Alterations in the gut permeability allow the penetration of gut microbiota in the peripheral blood.

**MICROBIAL TRANSLOCATION FROM THE GUT IS INVOLVED IN DRIVING IMMUNE ACTIVATION**

Immune activation is (probably) responsible for progression to AIDS.
Plasma LPS levels are a quantitative indicator of microbial translocation.

Increased plasma LPS levels in HIV+ individuals

Brenchley et al., J Exp Med, 2004
Human Toll-Like Receptors (TLRs) Permit Rapid Host Defense Responses to a Broad Array of Microbial Motifs

Microbial TLR Ligands Activate CD4+ T Cells to Enter Cell Cycle and CD8+ T Cells to Express CD69

Activated CD4+ T cells enter cell cycle

Activated CD8+ T cells express CD69
What effect does HAART have on these parameters?
Persistence of HIV in Gut-Associated Lymphoid Tissue despite Long-Term Antiretroviral Therapy

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(See the editorial commentary by Yuki and Wong on pages 640–2.)

Human immunodeficiency virus (HIV) persists in peripheral blood mononuclear cells despite sustained, undetectable plasma viremia resulting from long-term antiretroviral therapy. However, the source of persistent HIV in such infected individuals remains unclear. Given recent data suggesting high levels of viral replication and profound depletion of CD4+ T cells in gut-associated lymphoid tissue (GALT) of animals infected with simian immunodeficiency virus and HIV-infected humans, we sought to determine the level of CD4+ T cell depletion as well as the degree and extent of HIV persistence in the GALT of infected individuals who had been receiving effective antiviral therapy for prolonged periods of time. We demonstrate incomplete recoveries of CD4+ T cells in the GALT of aviremic, HIV-infected individuals who had received up to 9.9 years of effective antiretroviral therapy. In addition, we demonstrate higher frequencies of HIV infection in GALT, compared with PBMCs, in these aviremic individuals and provide evidence for cross-infection between these 2 cellular compartments. Together, these data provide a possible mechanism for the maintenance of viral reservoirs revolving around the GALT of HIV-infected individuals despite long-term viral suppression and suggest that the GALT may play a major role in the persistence of HIV in such individuals.
Collagen Deposition Limits Immune Reconstitution in the Gut

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(See the editorial commentary by Read and Sorensen, on pages 653–4.)

Despite suppression of human immunodeficiency virus (HIV) replication by antiretroviral therapy, reconstitution of CD4+ cells is variable and incomplete, particularly in gut-associated lymphatic tissues (GALT). We have previously shown that immune activation and inflammation in HIV-infected and simian immunodeficiency virus–infected lymph nodes result in collagen deposition and disruption of the lymphatic tissue architecture, and this damage contributes to CD4+ cell depletion before treatment and affects the extent of immune reconstitution after treatment. In the present study, we compared collagen deposition and the extent of depletion and reconstitution of total CD4+ cells and subsets in peripheral blood, lymph nodes, and inductive and effector sites in GALT. We show that CD4+ cell depletion in GALT correlates with the rapidity and greater magnitude of collagen deposition in this compartment, compared with that in peripheral lymph nodes, and that although treatment does not restore CD4+ cells to effector sites, treatment in the early stages of infection can increase CD4+ central memory cells in Peyer patches.
Are other parameters of gut health e.g. gut microbiota and flogistic (inflammatory) indexes altered in asymptomatic HIV infection?
The Normal Gut Microbiota is Impaired Even in Asymptomatic HIV-Infected Adults with High CD4 counts

Reduced levels of beneficial bacteria

- Reduced levels of beneficial bacteria
  - Bifidobacteria
  - Lactobacilli

Increased levels of pathogenic microorganisms

- Increased levels of pathogenic microorganisms
  - Pseudomonas
  - Candida

Gori A et al (JCM, 2008 and submitted)
CALPROTECTIN

- *Calprotectin* - a protein found in plasma and stool - is a useful marker for inflammatory bowel disease (IBD)

- *Calprotectin* is elevated in IBD (normal values $<50\text{mg/kg}$)
Increased levels of Intestinal Inflammation in Asymptomatic HIV-Infected Adults with High CD4 counts

Calprotectin *Baseline values (ITT)*

- 51% > 50 mg/kg
- 34% > 100 mg/kg
- 9% > 250 mg/kg

*Significant GI inflammation*

*Healthy*

Gori A et al (JCM, 2008 and submitted)
COPA trial: Study Design

Synergistic prebiotic mixture of:

**scGOS:** low molecular weight Galacto-Oligosaccharides from lactose  
**lcFOS:** high molecular weight Fructo-Oligosaccharides from chicory  
**pAOS:** Acidic oligosaccharides (pectin hydrolysate) from citrus fruit

- Treatment-naïve HIV-positive asymptomatic individuals
- CD4+ T-cell counts 400-800 cells/μl
- Plasma HIV-1 RNA 1,000-65,000 copies/ml
  - Randomized, double-blind, placebo-controlled
    1. Placebo
    2. Single dose of scGOS/lcFOS/pAOS (15 g/day)
    3. Double dose of scGOS/lcFOS/pAOS (30 g/day)
- 12 weeks of supplementation (+ 4 weeks follow up)
- Samples (blood, feces) collection at baseline and after 12 weeks
scGOS/IcFOS/pAOS mixture well tolerated by and safe in HIV-1 patients

No major effect
on absolute CD4$^+$ T-cell or on
HIV viral load
scGOS/IcFOS/pAOS Improves the Gut Microbiota of HIV-1-Infected Asymptomatic Adults
scGOS/IcFOS/pAOS Improve the Gut Microbiota of HIV-1-Infected Asymptomatic Adults

*Clostridium histolyticum* cluster

- **Control**: Baseline
- **Single dose**: Baseline, Week 12
- **Double dose**: Baseline, Week 12

Statistical significance:
- *p* < 0.001
- *p* = 0.011
- *p* = 0.009
scGOS/lcFOS/pAOS reduces CD4⁺/CD25⁺ activated T Lymphocytes in HIV-1-infected Asymptomatic Adults
scGOS/IcFOS/pAOS increases NK cell activity in HIV-1-infected Asymptomatic Adults
Conclusions

- CD4+ T cells are depleted in the gut within few days of HIV infection
- The resulting passage of bacteria and bacterial products from the gut to the periphery results in immune activation
- Impaired CD4+ cell counts and non-suppressed viremia persist in GUT of HIV-infected patients despite HAART
- Impaired gut health (gut microbiota, gut inflammation) is observed at early stages of infection in asymptomatic patients
- Improvement of gut flora and of immune markers is seen in HIV-infected asymptomatic, HAART-naïve patients receiving scGOS/IcFOS/pAOS
Der Mensch ist was er isst

or

Man is what he eats

L. Feuerbach, 1862
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