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Date: November 2013
The Surfaces of Infection

**Normal Cervix**
- Low density of available CD4 T cell targets

**Normal Intestinal Mucosa**
- Majority of CD4 T cells in the body
Transmission and infection of new CD4 T cell targets

Recruitment and infection of new CD4 T cell targets

Infection of resident CD4 T cell targets
Transmission at Cervix

Recruitment and infection of new CD4 T cell targets

Transmission at Intestinal Mucosa

Infection of resident CD4 T cell targets
Damage to the GI Tract in Acute Infection

Massive loss of mucosal CD4 T cells in acute infection
Majority of loss is from lamina propria
Accounts for loss of majority of memory CD4 T cells
Th17 CD4 T cells are critical to the maintenance of mucosal epithelium, barrier function and immunity.

Th17 cells are preferentially lost from the GI tract.

Consequences of Epithelial Barrier Damage

Healthy Gut
- Tight epithelial junctions, mucus
- Anti-microbial peptides
- Secreted antibodies
- Phagocytes, neutrophils, T cells
- Cross-talk between microbes and epithelial cells and immune cells

HIV-Infected Gut
- Massive loss of CD4 T cells
- Preferential loss of Th17 cells
- Enteropathy
- 2-10x increased permeability
- Translocation of microbial products
As virus load decreases, immune activation persists

**Innate**
- **Cells**: activation of Macrophages and Dendritic Cells
- **Cytokines, chemokines**: IFNα, TNF, IL-1, IL-6, IL-8, IL-15, IL-10
- **Acute phase proteins**: Serum Amyloid A, C-Reactive Protein
- **Coagulation**: D-dimers, Tissue Factor
- **Fibrosis**: Matrix Metalloproteinase activation, collagen deposition
- **Microbial sensors**: Lipopolysaccharide Binding Protein, soluble CD14

**Adaptive**
- **T cells**: increased turnover, exhaustion, low thymic output, virus reservoir
- **B cells**: increased turnover, exhaustion, hypergammaglobulinemia

*Frequency of activated T cells is a strong predictor of disease progression*
T cell activation declines during long-term ART, but remains elevated and is associated with poor CD4 T cell reconstitution.
Causes Of Chronic Immune Activation

• HIV-induced activation of innate immune system (Bhardwaj)
  – When virus load decreases after acute phase, immune activation remains elevated
  – Virus load alone is a poor predictor disease progression (Rodriguez JAMA 2006)
  – Immune activation predicts disease progression independent of viral load (Giorgi, Deeks etc.)
  – Elite controllers who progress have increased activated CD38+ T cells (Hunt JID 2008)
  – When virus load is suppressed with ART immune activation persists and predicts progression

• Increased antigen load, bacterial overgrowth, herpes viruses (Deeks, Hunt)

• Immunologic and structural damage to gut, increased mucosal permeability, translocation of inflammatory microbial products into systemic circulation
The Gut and Immune Activation

Microbial Translocation: translocation of gut-derived microbial products to systemic circulation without overt bacteremia

- Graft vs. host disease
- Inflammatory bowel disease
- Liver disease
- Pancreatitis
- Surgery
- Alcohol
- NSAIDS

Measures of microbial translocation correlate with systemic immune activation and are predictive of clinical outcome

Can microbial translocation across gut mucosal surface cause systemic immune activation in HIV infection?
Plasma LPS and bacterial 16S rDNA levels are indicators of microbial translocation in HIV+ individuals.
LPS and Systemic Immune Activation

Plasma LPS correlates with CD8 T cell activation and plasma IFNα

Other factors in addition to LPS directly and indirectly stimulating adaptive and innate immune systems (peptidoglycan, bacterial DNA..)
Microbial Translocation and Immune Activation


A number of studies have confirmed the observations of raised measures of microbial translocation and their association with immune activation and disease progression independent of VL...
LPS Caues Immune Activation In Vivo

LPS-stimulated monocytes secrete sCD14 and shed surface CD14

Raised plasma sCD14 indicates chronic in vivo stimulation of monocyte/macrophages by LPS

“The host response” to microbial translocation
Strategies for Management of Antiretroviral Therapy (SMART)

- 5,472 HIV+ subjects at 318 sites in 33 countries
  - CD4+ T cells > 350 cells/mm³ at enrollment
  - >80% on ART

Antiretroviral strategy
- Viral suppression (VS): Continuous use of ART
- Drug conservation (DC):
  - Defer treatment until CD4+ T cells < 250 cells/mm³
  - Continue treatment until CD4+ T cells > 350 cells/mm³

- 85 subjects died, 124 had cardiovascular events, 96 had opportunistic diseases — increased in DC arm
  - Odds Ratio of death 1.8 in DC arm

IL-6, C-reactive protein and D-dimer were associated with mortality

In 700 subjects, we evaluated baseline levels of:
- Lipopolysaccharide (LPS)
- Soluble CD14 (sCD14)
- LPS core antigen-specific antibody (EndoCAb)
- Intestinal fatty acid binding protein (I-FABP) — plasma marker of enterocyte apoptosis

Each case was matched with 2 controls on age, sex, location, date of enrollment
Biomarkers indicate microbial translocation, LPS bioactivity and enterocyte damage in treated and untreated subjects.
Raised plasma LPS levels predict PB CD4 T cell decline, independently of viremia, in subjects with high plasma sCD14.
### Baseline sCD14 is a significant independent predictor of death from AIDS and non-AIDS events

#### sCD14 Levels and Mortality

**sCD14 (x10^6 pg/ml)**

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<th>Cases (pg/ml)</th>
<th>Controls (pg/ml)</th>
<th>p-value</th>
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<tr>
<td>LPS</td>
<td>32.66</td>
<td>32.56</td>
<td>0.7614</td>
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<tr>
<td>I-FABP</td>
<td>174.40</td>
<td>72.27</td>
<td>0.0967</td>
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<tr>
<td>16S rDNA</td>
<td>7.70</td>
<td>7.61</td>
<td>0.7865</td>
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<td>EndoCAb (MMU/ml)</td>
<td>128.1</td>
<td>115.1</td>
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**sCD14: OR of Death by Quartile**

- **>2.75**
- **2.35-2.75**
- **2.07-2.34**
- **<2.07 x10^6 pg/ml**

- **OR (95% CI)**

**Adjusted for IL-6, D-dimer, CRP, SAA and virus load**

**Univariate**

Sandler JID 2011
Markers of inflammation and gut barrier dysfunction predict mortality independently of CD4 count and virus load.
Possible reasons for microbial translocation:

- Altered hepatic architecture
- Kupffer cell dysfunction
- Intestinal permeability
- Bacterial overgrowth

Measured plasma LPS, sCD14, I-FABP and IL-6 in 84 subjects with varying degrees of liver fibrosis due to infection with HBV or HCV
Increased levels of I-FABP, LPS, sCD14 and IL-6 indicate enterocyte damage, microbial translocation and LPS bioactivity
sCD14 correlates with markers of inflammation, fibrosis and regeneration.
Plasma sCD14 levels predict poor clinical outcome
HIV immune activation

Gut

CD4 depletion enteropathy

Microbial translocation

Immune deficiency

Target cells

Immune activation
HIV immune activation

CD4 depletion enteropathy

immune deficiency

microbial translocation

poor pathogen control

T/Tcm Tem

target cells

immune activation

low thymic output
LT fibrosis
T/B cell dysfunction

non-AIDS morbidity and mortality

inflammation tissue damage coagulopathy

gut
non-AIDS morbidity and mortality

inflammation
tissue damage
cogulopathy

low thymic output
LT fibrosis
T/B cell dysfunction

immune deficiency

immunedeficiency

gut

CD4 depletion enteropathy

microbial translocation

poor pathogen control

ART

target cells

immune activation

CMV

???
• Chemokine receptor inhibitors:
  – maraviroc, TB-652

• Anti-infective therapy:
  – CMV, EBV, HSV, HCV/HBV

• Microbial translocation:
  – sevelamer, colostrum, rifaximin

• Enhance T cell renewal:
  – Growth Hormone, IL-7

• Anti-fibrotic drugs:
  – pirfenidone, ACEi, ARBs, KGF

• Anti-aging:
  – caloric restriction, sirtuin activators, vit. D, omega-3 fatty acids, rapamycin, diet, exercise (not recommended by me)

• Anti-inflammatory drugs:
  – Chloroquine, Hydroxychloroquine
  – Minocycline
  – NSAIDs (COX-2i, aspirin)
  – Statins
  – Methotrexate
  – Anakinra (IL-1Ra)
  – Thalidomide, lenalidomide, pentoxyfylline (weak TNF inhibitors)
  – Biologics (TNF inhibitors, IL-6 inhibitors, anti-IFNα, anti-PD1)

• Anti-coagulants:
  – warfarin, dabigatran, aspirin, clopidogrel

Combination therapy may be necessary
Therapeutic Interventions in Studies

Sevelamer: Pandrea, CROI 2013


Bovine Colostrum: Asmuth, Douek et al, AIDS 2013

IL-7: INSPIRE2 team, Sereti et al, submitted
Many Thanks To…

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