HIV & Inflammation: Clues to Prevention Paradox

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Inflammation: Modulator of Mucosal Defense

- What is inflammation?
- What role does it play in HIV prevention?
- Is it friend or foe?
- Can it be exploited to promote protection?
What is inflammation?

- **Protective** tissue response marked by recruitment of WBCs, release of cytokines, chemokines, and antimicrobial proteins
- Serves to eliminate offending agent and damaged tissue
- Chronic inflammation associated with HIV progression
Inflammation and HIV Acquisition

- Transmitting viral load
- Stage of HIV infection
- Virulence
- Tropism (R5>X4)
- Target cells (#; activation)

Epithelial barrier
- Protective mediators
- Microbiota
- Host genetics (CR5Δ32)

Haase A, Nature 2010
Mucosal Mediators of “Inflammation”
Protective or Facilitators of HIV

- **Protective:**
  - Directly inhibit HIV infection
  - Maintain epithelial barrier
  - Promote healthy vaginal flora
  - Promote innate immune responses

- **Facilitators:**
  - Recruit and activate immune target cells
  - Activate NFκB pathways to promote HIV replication
  - Disrupt epithelial barrier
  - Interfere with innate responses
Cytokines/Chemokines

- Activators: Enhance HIV infection
  - TNFα, IL-1, IL-6, IL-12, chemokines
    - Activate NF-κB, which binds to HIV LTR to initiate or increase viral transcription.
    - Recruit and activate immune target cells

- Suppressors: Inhibit HIV infection
  - IFNα: Antiviral activity, suppresses RT
  - RANTES, MIP1α, MIP1β: inhibit co-receptor binding
  - IL-10: Inhibits HIV replication
  - IL-13: Down modulates CCR5 expression
Antimicrobial proteins

- **Defensins:**
  - Inhibit HIV in vitro (HBDs and HNP1-3)
  - BUT also recruit immune cells and induce inflammatory responses

- **SLPI**
  - Anti-inflammatory
  - Direct antiviral activity (?)
  - Higher levels associated with reduced HIV acquisition/transmission

- **Lactoferrin**
  - Direct inhibitory activity in vitro
  - BUT “alarmin”: recruits and activates immune cells
Mucosal inflammation and HIV

- Increased risk of transmission
  - IL-1β and IL-8 associated with higher cervicovaginal HIV-1 RNA concentrations, even after controlling for plasma viral load and vaginal microbial cofactors

- Increased risk of acquisition
  - Higher viral set point
  - Lower CD4 count

Roberts, L et al JID 2012 205(2): 194
Factors associated with ↑ HIV Risk

- Sex
- STI
  - HSV, HPV, Bacterial STD, Trichomonas
- BV
  - Decrease SLPI
  - Increase IL-1β
- Pregnancy
- Adolescents
- Depot medroxyprogesterone
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Sex/Semen and Mucosal Inflammation

- Buffers protective acidic pH
- Enriched in cytokines/chemokines
- Triggers MIP-3α, GM-CSF, MCP-1, IL-6, and IL-8 from genital tract epithelial cells
- Induces TNFalpha

Lisco, A et al JID 2012; 1:97-105
Sex Increases Immune Targets

- Women who had sex within 3 days had higher cervical CD3+ (76 ± 4%) and CD4+ T lymphocytes (58 ± 6%) compared to women who last had sex >3 days prior to evaluation (CD3+ 54 ± 6%, CD4+ 39 ± 4%).

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HPV

- HPV associated with increased HIV risk*
- ? Mechanisms
- Compared concentrations of immune mediators in CVL from HIV-negative women with high risk HPV positive (HRHPV+) CIN-3 (n=37), HRHPV+ CIN-1 (n=12), or PAP negative controls (n=57).

*Smith-McCune KK et al PLoS One 2010; 5:e10094
Cervical Dysplasia Associated with Lower “Protective” and “Higher” Inflammatory Mediators

Mhatre et al, under review
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Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies

Julius Atashili\textsuperscript{a,b}, Charles Poole\textsuperscript{a}, Peter M. Ndumbe\textsuperscript{b}, Adaora A. Adimora\textsuperscript{a} and Jennifer S. Smith\textsuperscript{a}

- Possible mediators
  - Loss of H2O2 (directly virucidal)
  - Activation of CD4 by alkaline pH
  - Upregulation of cytokines that promote local HIV replication (TNF-alpha, IL-1 beta)
  - Direct stimulation of HIV expression from T cells/monocytes by BV-associated bacteria

Atashili 2008
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Critically, BV has also been independently associated with increased risk of HIV transmission to uninfected male partners

Cohen C, IAS Rome, 2011
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Pregnancy Associated with ↓ HBDs
and Higher “Inflammatory” Cytokines
Measurement individual mediators may not capture complex interactions

- “Functional assays”
  - Measure antimicrobial activity of secretions collected by swab or lavage
    - HIV
      - ??
    - HSV-2
      - Correlates with concentrations of HNP1-3, IL-8, Lf
    - E.coli
      - Proteomic studies suggest that this activity is mediated by host proteins and proteins secreted by Lactobacillus
Inflammatory Cytokines May Disrupt the Epithelial Barrier

Intact mucosal epithelium is impervious to HIV-1

Disrupted epithelium allows HIV-1 across to infect target cells

Apical well
Cells in polarized system
Basolateral well
Microbicides may disrupt this barrier directly or by increasing inflammatory cytokines.
Putting it all together..

- Factors associated with increased HIV risk characterized by increases in inflammatory cytokines, increase in activated immune target cells, and lower levels of protective mediators.

- Similar mucosal environment observed prior to HIV seroconversion; higher inflammatory mediators associated with higher viral set point.
  - CAPRISA 002
  - CAPRISA 004
But this is only a snap-shot

- Association is not causality
- Inflammatory signaling cascades are complex
- Some inflammation is protective
  - Primes innate immune responses
- Too much may increase HIV risk
  - MTN 001 data
    - Higher levels in U.S. vs. Durban participants
    - Lower levels after 6 wks vaginal TFV
    - Is this protective or facilitating HIV infection??
Interventions?

- Directly block inflammation
  - Must be fine-tuned
  - Not disrupt ability of mucosa to respond appropriately to other pathogens
  - Ex. Glycerol monolaurate blocks DC/T cell recruitment by blocking MIP3a responses (Haase et al)
Interventions

- Treat/prevent underlying causes
  - STD rx efforts have failed to reduce risk of HIV transmission or acquisition
  - May reflect persistent inflammation
    - Ex. Activated T cells persist after resolution of genital herpes lesions
  - Vaccines may hold greater promise

- Augment natural host defenses
  - INFs, TLR agonists, recombinant defensins
  - Double-edged swords
Future Directions: Knowledge Gaps

- Assessment of inflammatory status complex
- Measurements of individual mediators may not tell the whole story
  - Need to consider complex interactions between mediators/signaling cascades/downstream events
  - Functional assays may provide more comprehensive measure but biological significance of measures unclear
- Inflammation & Microbicide Trials
  - Inflammation increases HIV risk in both placebo and rx arms
  - BUT may interfere with drug activity
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Mohak Mhatre
Gaps in Knowledge that Impact Prevention Efforts: PrEP and Vaccines

- What are the driving forces that enable virus to establish infection?
- How much virus is needed to transmit?
- What accounts for R5 viruses predominating?
- What are the first cells infected & what allows that infection to be amplified and disseminated?
- How do site specific differences in mucosal immunity impact HIV risk and prevention?

- Vagina, ectocervix: (Type II mucosa)
  - Stratified squamous epithelia
  - Sparse submucosal immune cells
  - IgG predominant immunoglobulin

- Endocervix and gut: (Type 1 mucosa)
  - Simple columnar
  - pIgA receptor; IgA predominates
  - MALT