Sex Differences in Immune Function and HIV Disease

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Describe sex differences in the immune response.

Describe sex differences in the immune response to HIV infection.

Review current knowledge on the immune response to HIV and the pathophysiology of HIV disease.
Sex Differences in The Immune Response

- Sex steroids- estrogens (17β-E₂), progesterone and testosterone can differ with:
  - Gender
  - Different reproductive stages
  - The phase of the menstrual cycle
  - Effect on the innate vs. the adaptive immune response

- Different reproductive processes are influenced by the immune system:
  - Ovulation
  - Menstruation
  - Successful implantation
  - Pregnancy
Sex Differences in The Immune Response

*The Immune Response in Females is Associated With:*

- More vigorous cellular immunity (T helper and cytotoxic responses)
- More vigorous humoral immunity (antibody responses)
- A general resistance to certain infections
- A higher incidence of autoimmune diseases (estrogen enhances risk, progesterone reduces risk)
- Differing responses to injury:
  - Burns - females do worse
  - Trauma-hemorrhage - females do better:
    - Sepsis - less susceptible and higher survival rates
    - Less multi-organ dysfunction
Sex Differences in The Immune Response

Differences in the Influence of Sex Steroids Are Due to:

- Quantitative immune cell homeostasis
- Qualitative immune responses
  - Cytokine profiles
  - Balance of Th1 vs. Th2 vs. Treg lymphocyte subsets
  - Alteration in the function or activation of different cells of the immune system.
- Differences in dendritic cell differentiation & function
Sex Differences in The Immune Response

**The Influence of Sex Steroids on:**

- **Quantitative immune responses**
  - **T lymphocyte counts:**
    - Total lymphocyte counts in males are similar to females.
    - Percentage of T lymphocytes within the total lymphocyte population is lower in males as compared to females.
    - Decreased T lymphocyte counts in males as compared to females may be due to increased testosterone concentrations, since testosterone may increase apoptosis in T cells.
    - Hence females normally have more CD4 cells than men.
  - **B lymphocyte counts:**
    - No differences between males and females.
Sex Differences in The Immune Response

The Influence of Sex Steroids on:

- **Quantitative immune cell homeostasis**
  - No change in numbers of total circulating lymphocytes or variation in percentage of lymphocyte subsets during the menstrual cycle (T or B lymphocytes).
  - Post-menopausal women have a decreased total lymphocytes compared to fertile women.

- **Synthetic Hormones**:
  - OCC: no effect on absolute numbers, or percentages of lymphocytes, T cells or T cell subsets.
  - HRT in post-menopausal women: total lymphocyte count, percentage of T cells and T helper (Th) lymphocytes are decreased.
Sex Differences in The Immune Response

The Influence of Sex Steroids on:

- **Quantitative immune cell homeostasis**
  - **Monocytes**:
    - Increased in men and post-menopausal women compared to females in the follicular phase.
    - In post-menopausal women on estrogen HRT, monocytes decline.
    - Estrogen and possibly also progesterone, decreases monocyte numbers.
  - **Granulocytes**
    - Significant increase in number during pregnancy and in the luteal phase of the menstrual cycle. **Suggests a role for estrogen and progesterone to increase granulocyte numbers.**
Sex Differences in The Immune Response

The Influence of Sex Steroids on:

- **Quantitative immune cell homeostasis**

  - NK Cells:
    - NK cells are capable of killing virus-infected cells or tumour cells in the absence of prior immunization and without MHC restriction.
    - A specialized subset of NK cells in the endometrium play an important role in implantation and placentation.
    - No differences in NK cell count have been documented between males and females.
    - During the menstrual cycle, NK cells increase in the late secretory phase.
    - During pregnancy, the number of peripheral NK cells are decreased.
Sex Differences in The Immune Response

The Influence of Sex Steroids on:

- **Qualitative** immune cell homeostasis
  - Cytokine Profiles
    - No gender effect or within reproductive phases: IFN-$\gamma$, IL-4, IL-10
    - IL-2* contradictory results* between gender and within reproductive phases.
    - Greater TNF-$\alpha$ secretion and pro-inflammatory response to endotoxin challenge in females. (Critical Care Med 2007;35:1464-9)

- Balance of Th1 vs. Th2 vs. T Regulatory Lymphocyte Subsets
  - During pregnancy:
    - Decrease in the Th1 (cellular)/Th2 (humoral) ratio
    - Increased T regulatory (CD4+CD25+) cells - critical to inhibition of maternal immune responses against fetal antigens and fetal rejection.
Sex Differences in The Immune Response

The Influence of Sex Steroids on:

- **Qualitative** immune cell homeostasis
- Alteration in immune cell function or activation

**B Lymphocyte Function:**
- More vigorous humoral responses in women
- Women have higher serum levels of total IgM and IgG
- No change in Ig levels throughout menstrual cycle.
- Estrogen induces polyclonal activation, increasing IgG and IgM production.
- Testosterone inhibits IgG and IgM production.

**Granulocyte Function:**
- Estrogen decreases while progesterone increases neutrophil chemotactic activity.
- Mixed results on free radical production.
Sex Differences in The Immune Response

The Influence of Sex Steroids on:

- **Qualitative** immune cell homeostasis
- Alteration in immune cell function or activation

**Monocyte Function:**
- Cytokine production can be altered by sex hormones.
- **Monocyte TNF-α** production varies during the menstrual cycle.
- IL-12 production by monocytes is decreased during pregnancy.
- Plasma IL-6 and IL-18 levels from monocytes are increased after menopause.
- Serum IL-18 levels are increased during pregnancy.

**NK Function:**
- Estrogen and progesterone suppress NK cell activity.
- Sex hormones **do not** affect NK cell cytokine production.
Sex Differences in The Immune Response

The Influence of Sex Steroids on:

- **Qualitative** immune cell homeostasis
- Dendritic Cell Differentiation and Function
  - DCs are critical mediators of adaptive immunity, tolerance and autoimmunity.
  - DC progenitors and terminally differentiated DCs express estrogen receptor (ER).
- Evidence indicates that estrogens can:
  - Activate DCs, while progesterone inhibits DC functions.
  - Regulate the homeostasis of bone marrow myeloid and lymphoid DC precursors.
  - Regulate DC differentiation mediated by GM-CSF and Flt3 Ligand.
- Agonist and antagonist ER ligands modulate DC activation and production of inflammatory mediators.
Initial reports suggested that women with HIV disease experienced more rapid disease progression, shorter survival and poorer response to ART than men.

Subsequent research has showed that rapid disease progression was a surrogate marker for poorer access to care and later initiation of treatment (Prins M et al. AIDS 2005;19(4):357-70).

Women with HIV are more likely to:
- Be diagnosed later than men
- Begin treatment with more advanced disease.

Recent research suggests once women start therapy:
- Antiretroviral treatment works just as well in women
- Women benefit equally in terms of increased survival (Gange SJ et al. J Epidemiol Community Health 2002;556(2):153-590).
Sex Differences in the Immune Response to HIV

Meta-Analysis of Studies Published Mar 02 - Feb 07

- Little overall evidence of sex differences in the rate of HIV disease progression in recently seroconverted women and men, either before or after the introduction of HAART.
- Study again confirmed that women as a group start treatment later than men.
- Women actually seemed to have a slightly slower progression rate.
- Responded to treatment at least as well, although may have more and different side effects.

Bottom Line:

When women and men access care at the same stage of illness they have similar outcomes.
Sex Differences in the Immune Response to HIV

CD4 Cell Count

- **Women have higher CD4 cell counts** and lower HIV viral loads compared with men (Prins M et al. AIDS 2005;19(4):357-70).

- A higher CD4 cell “setpoint” following infection is due to the fact that women have a higher percentage of T lymphocytes within the total lymphocyte population compared to males.

- As a consequence it may take women longer to fall into the CD4 zone indicated for HIV treatment.

- **Sex differences in CD4 counts are most evident during early HIV infection**, then diminish as T cells decrease.

- When CD4 cells decrease to ≤ 350 cells/mm³, cell levels in women and men are similar.
Sex Differences in the Immune Response to HIV

HIV-1 Viral Load

- Women have higher CD4 cell counts and lower HIV viral loads compared with men (Prins M et al. AIDS 2005;19(4):357-70).
- Studies of viral load differences have shown:
  - Women had a 40% lower viral load than men with the same CD4 cell count (Napravnik S et al. JAIDS 2002;31(1):11-19).
- Overall, the sex difference in viral load is greater at higher CD4 cell counts and is diminished over time.
- WHIS data documented that pretreatment CD4 and HIV-1 RNA levels were not as important in clinical outcome as were reducing viral load and increasing CD4 counts to ≥ 200 cells/mm³ in response to treatment.
Sex Differences in the Immune Response to HIV

The Treatment Bottom Line:

- Early differences between women and men in CD4 cell counts and HIV viral loads do *not* have any major impact on clinical outcomes.

- Some advocates have argued over the years that HIV-infected women should start treatment at a high CD4 count or a lower viral load than men.

- There are no sex-specific differences in PHS Treatment Guidelines regarding cut-off thresholds for initiating HIV treatment.
Sex Differences in the Immune Response to HIV

Immune Responses, Pregnancy and HIV


- A recent study suggested that pregnancy seemed to protect women against disease progression:
  - During 7 yrs of follow-up the HAART era, HIV-infected women who became pregnant (most of whom took ARTs) had a lower risk of developing AIDS-defining conditions or death than those who didn’t- 8% vs. 24% even after controlling for CD4 cell counts (Tai JH et al. J Infect Dis 2007;196(7):1044-52).

- Small decreases in CD4 counts during pregnancy are common; counts return to pre-pregnancy baseline following delivery.

- Hence during pregnancy, monitor **CD4 percentage**, rather than absolute count, to assess HIV disease status.
Sex-Specific Differences in HIV Disease NOT Related to Immune Responses

Transmission

- **Women are more likely to contract HIV from an infected male partner during sex than males are from infected females. Odds range is 2x - 20x.** (Euro Study Group British Med J 1992;304(6830):809-13; Nicolosi A et al. Epidemiology 1994;5(6):570-5; Padian NS et al. Am J Epidemiol 1997;146(4):350-7; )

- A reflection of biologic susceptibility rather than immune function:
  - Vagina offers larger area of susceptible mucosal membrane for transmission.
  - Women exposed to semen for longer duration in the genital tract.
  - Young adolescent women are particularly vulnerable due to cervical ectopy.
  - Microtrauma associated with normal vaginal intercourse.
Sex-Specific Differences in HIV Disease NOT Related to Immune Responses

- **Kaposi’s Sarcoma**
  - HIV positive women are much less likely than men to develop KS.
  - Difference appears to be related to mode HIV transmission.
    - KS is highest in MSM.
    - KS incidence is lower in men with heterosexual HIV transmission and there is not much difference in KS incidence between women and men with heterosexually acquired HIV. (Biggar RJ Hematol Oncol Clin NA 1996;10(5)997-1010)

- **CMV**: women are also less likely than MSM to be infected with CMV.

- **Classic OIs** (including PCP and MAC): occur with similar frequency in women and men.
The Immune Response to HIV

Understanding the Immune System: The 1980s

- **CD4 T-lymphocytes identified as the primary target of HIV**

  OUTCOME: Lead to CD4 cell count measurements and correlation with clinical outcomes.

- Receptor for HIV cell entry: **CD4**

- Characterization of Immune Responses:
  - **Quantitative Decline:** Decline in CD4s associated with specific infectious and malignant complications.

**IT WAS ALL ABOUT THE NUMBERS!**
HIV Disease: What We Thought Then

Early

- Lymph Nodes
- Circulation

Viral Load: Low → High
CD4 Counts: Normal → Low

Late

Active HIV Replication

- Viral Factors
  - Virulence
  - Cellular tropism
  - Escape mutants

- Host Factors
  - HIV-specific immunity
  - Cellular & humoral
The Immune Response to HIV

Understanding the Immune System: The 1990s

- Identification of chemokine co-receptors for HIV
  OUTCOME: Lead to better understanding of differences in transmission & clinical disease progression.

- Receptor for HIV Cell Entry: CD4

- Co-Receptors for HIV Cell Entry:
  - CXCR4 ---> T-lymphocytes
  - CCR5 ---> macrophages
  - CXCR4 / CCR5 ---> dual tropic

- Target Cells: CD4 T-lymphocytes, macrophages, dendritic cells, thymocytes, microglia
Binding and Fusion of HIV-1 With Its Target Cell

Adapted from Montefiori and Moore, Science 283:336, 1999.
The Immune Response to HIV

**Understanding the Immune System: >2000**

- Characterization of Immune Responses:
  - **Immune Dysfunction:**
    - Quantitative- CD4 decline infectious & malignant complications
    - Qualitative- chronic activation, disorders of cytokine production & accelerated apoptosis.

  **IT’S ABOUT FUNCTION!**

- Ineffective neutralizing antibody responses
- ↓ cytotoxic responses- DTH anergy
- ↓ HIV-specific responses
The Immune Response to HIV

**Understanding the Immune System: \(>2000\)**

- Characterization of Immune Responses:
  - Immune Reservoirs: \(\Rightarrow\) Viral Latency
    - Cellular: *CD4 memory subset, macrophages*
    - Organ & Tissue:
      - Gut-Associated Lymphoid Tissue
        - spleen, lymph nodes
      - CNS
      - cervicovaginal secretions
      - seminal fluid
HIV Disease: What We Know Now

Early
- GI Tract
- LN, Spleen
- CNS
- Circulation
- Viral Load: High
- CD4 Counts: Normal

Late
- Active HIV Replication
- Viral Factors: Virulence, Cellular tropism, Escape mutants
- Host Factors: HIV-specific immunity, Cellular & humoral
- Viral Load: High
- CD4 Counts: Low
Exploiting Immune Targets in the Treatment of HIV Disease

**UNSUCCESSFUL**
- CD4 as a target: **BUST!!**
  - Soluble CD4
  - Anti-CD4 antibodies with pseudomonas exotoxin

**SUCCESSFUL**
- Entry Inhibitors:
  - CCR5 Antagonists: Maraviroc. Interferes with HIV binding to CCRF (2007). Other candidates: vicriviroc (active); aplaviroc (abandoned).
  - CXCR4 Antagonists: None successful to date. Past candidates: AMD-070.
HIV Replication Cycle

Key Limitations in The Immune Response to HIV

A Consequence of the Virus Itself

- Targeting of gut-associated lymphoid tissue
  - Rapid depletion of CD4 cells within gut mucosa following *acute infection* that *never recovers*.
- Establishment of proviral organ & tissue reservoirs *early in infection*.
  - Reservoirs are sites of low level, ongoing viral replication leading to viral resistance.
- Immune Evasion
  - Downregulation of MHC class I
  - Alteration of dendritic cell function
  - Hijacking of self membrane associated molecules with cellular budding ⇒ HIV looks like “self”.
Key Limitations in The Immune Response to HIV

A Consequence of the Virus Itself

- **Immune Escape**: a consequence of HIV’s mutability

- **Quantitative and Qualitative Immune Dysfunction:**
  - Targets the “Master Cell” of the immune response: CD4
  - Accelerated apoptosis, chronic activation
  - Dysregulation of cytokine profiles

- **Ineffective Immune Responses:**
  - Lack of functional neutralizing antibody responses
  - Preferential destruction of HIV-specific cells
  - **Epitope diversion:**
    - Dominant responses \(\Rightarrow\) ineffective in controlling virus
    - Subdominant responses \(\Rightarrow\) effectively control virus
HIV is Different

- The natural immune response to HIV is inadequate
- HIV hides from the immune system
- HIV targets and destroys the immune system
- HIV mutates rapidly

Slide Courtesy of Greg Folkers & A. Fauci, NIAID
Presentation Take Home Messages

- Profound sex differences in the immune response **DO exist.** Women have:
  - More vigorous cellular and humoral immune responses
  - Are more resistant to certain infections
  - Experience a much higher incidence of autoimmune disease

- Profound sex differences in the immune response to HIV **do NOT exist.**
  - HIV-infected women tend to have higher CD4 counts and lower viral loads early in disease but these differences:
    - Do **NOT** impact clinical outcomes
    - Diminish over time.
Presentation Take Home Messages

- Pregnancy is associated with a transient decrease in CD4 counts that is NOT associated with HIV disease progression. CD4% should be used to monitor HIV status during pregnancy.

- Every effort should be made to diagnose & treat HIV infection EARLY to counter the significant and devastating effects on the immune system established early in HIV disease.