Cellular Immunity in Aging and HIV: Correlates of Protection

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Immune Senescence
**Correlates of Protection:**
*Targeting the appropriate immune response*

- **Live-attenuated virus vaccines**
  - Stimulate a response that is similar to natural infection

- **Killed virus vaccines**
  - Stimulate neutralizing antibodies and CD4+ T helper cells but not CD8+ cytotoxic T lymphocyte responses

- **Replication defective virus-based vaccines**
  - Stimulate CD4+ T helper and CD8+ cytotoxic T cells responses but poor neutralizing antibody titers

- **Testing responses to vaccination**
  - Serologic responses - neutralizing antibody titers or equivalent
  - Cellular immune responses
    - Measure or restimulate virus-specific T cell memory
    - T-cell proliferative capacity and correlation with serologic response

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**Antibody Response to Influenza Vaccination:**
*Correlate of Protection?*

- CHF, flu-
- CHF, flu+
- Old, flu-
- Old, flu+
- Young, flu-

![Graph](image)

Error Bars = Std Error
McElhaney et al., J Immunol 176:6333-9, 2006
**Evaluation of T Cell Responses**

**Stimulation:**
- vaccine, peptide, adjuvant
- live virus
- PMA/ionomycin
- viral peptides

**Assays:**
- ELISPOT, Proliferation
- Cytokines in PMBC Supernatants
- Granzyme B in PBMC Lysates
- Flow Cytometry

**Changes in CD8+ T cells with aging and HIV infection**

- **Non-progressive Disease**
- **Progressive HIV Disease**
- **CMV End Organ Disease**

**HIV**
- Memory CTL with costimulatory CD28
- CMV-specific effector CTL
- CMV-specific CTL > HIV or EBV-specific CTL

**Aging**
- CMV+
- ↓ IL-2 production and proliferative capacity
- Oligoclonal expansion of CMV-specific CTL are CD28-

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Changes in CD4+ T cells with aging and HIV infection

Correlates of Protection: Comparisons of HIV and Aging

- CD4+ T-cell responses in non-progressive disease
  - HIV-specific similar to EBV- and CMV-specific responses
  - IFN-γ and IL-2 production associated with non-progressive disease but decline with aging

- CD8+ T-cell responses
  - HIV-specific similar to EBV- and CMV-specific responses
  - IL-2 production and proliferative capacity maintained with non-progressive disease but decline with aging

- Chronic progressive HIV infection
  - Monofunctional T-cell response with high frequencies of virus-specific CD4+ and CD8+ T cells that secrete IFN-γ; this also occurs with aging

- Effectiveness of the virus-specific immune response
  - Depends more on the quality rather than quantity of CD4+ and CD8+ T cells
    - HIV-specific CD8+ responses in individuals exposed to HIV remain uninfected
    - HIV-specific CD4+ responses associated with virus control
    - Depletion of CD8+ results in loss of virus control and restored with repletion of CD8+ T cells
    - HIV-specific CD4+ and CD8+ preserved in long-term non-progressors

**IFN-γ: IL-10 Ratio**

*Vaccination and Infection*

- Adjusted for ACE, statin, SMWT
- A/Panama: H3N2 vaccine strain
- A/Wyoming: H3N2 circulating strain

**Grz B Response:**

*Vaccination and Infection*

- Adjusted for ACE, statin, SMWT
- A/Panama: H3N2 vaccine strain
- A/Wyoming: H3N2 circulating strain

**Weeks Post-Vaccination**

- Mean Log IFN-γ / IL-10 Ratio
- Mean Log Grz B U/mg protein

A/Pan Flu vs. No Flu:

- IFN-γ: IL-10, P<0.0001
- Error bar: std dev