Cell-mediated immunity to influenza in mice: T-cell specific responses that correlate with protection

DHHS, NIH, NIAID, LVD

Protective immunity to influenza in mice

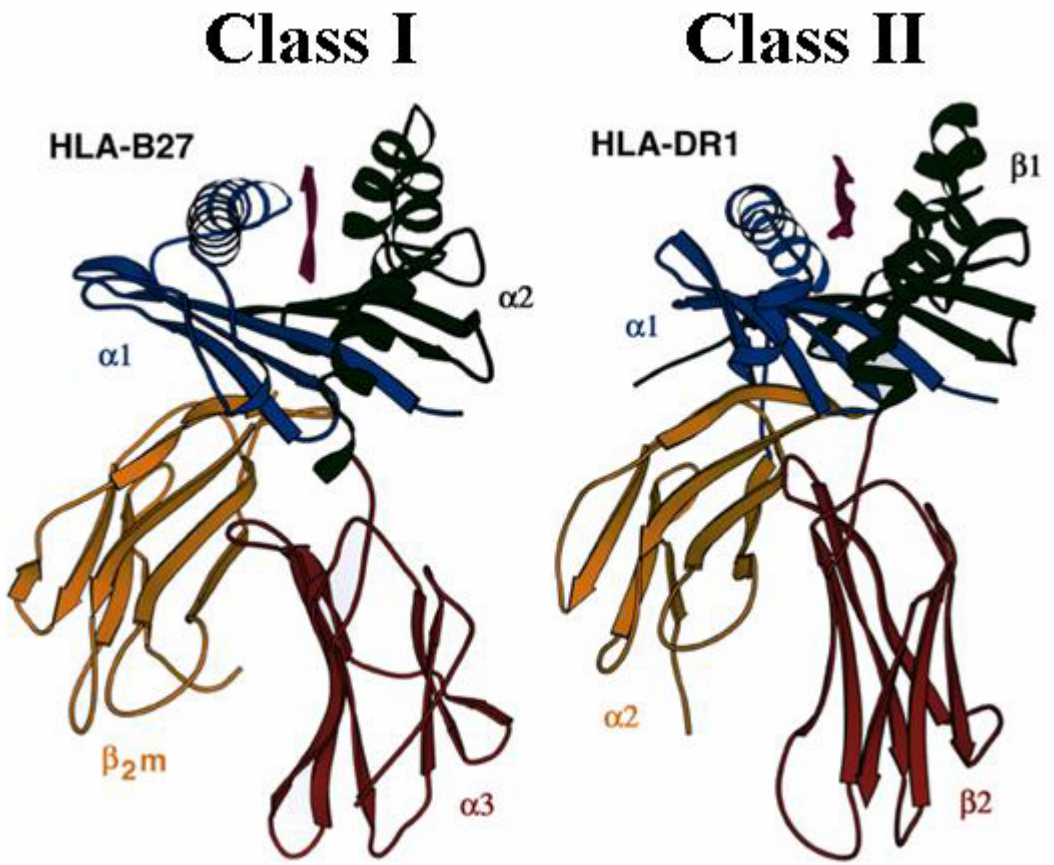
- **Ideal: Immunize for specific neutralizing antibodies to the virus**
- **Cell-mediated immunity can provide “protection” against morbidity and mortality.**
- **For optimal immunity: Immunization should generate memory from all effector arms of the immune system**

Why focus on T-cell immunity in influenza infection?

Responses can be heterosubtypic

T cell recognition and specificity

T cells recognize antigen in association with molecules encoded by the major histocompatibility complex (MHC)



CD8+ T-cell responses to influenza are characterized by

Immunodominance Hierarchies

- **T-cells respond to only a tiny fraction of the potential peptide determinants encoded by the virus genome**
- **The immunogenic determinants are ordered into highly reproducible hierarchies based on the magnitude of cognate CD8+ T cell responses**

Immunodominant determinants can be found in any influenza protein

- Dependent upon antigen presentation
  - Peptide ability to bind MHC class I
  - Ability to be processed
- T-cell precursor frequency
- For heterosubtypic immunity, there has been more emphasis on the internal proteins in part due to their greater conservation.

T-cell mediated “protection” reduced - weight loss, mortality, days to death, virus titers, and/or histopathology

- CD8+ T-cells can not completely prevent infection
- Best expectation: limit or attenuate morbidity or mortality

T-cell immunity can “protect”

- **Homo- and hetero-subtypic immunization with or without depletion of cell populations or using knock out/deficient mice**
- **Immunization to internal proteins**
- **Bulk T cell transfers**
- **Transfer of T cell lines or clones**

CD8+ T cell responses correlate with anti-influenza protection

- **All of the immunodominant specificities tested can be protective**
  - **Some have been shown to also be detrimental and/or have associated immunopathology**
- **Multiple function, repertoire diversity or higher avidity T-cells may provide optimal memory generation and/or protection but has not been rigorously demonstrated for influenza**
- **The precursor frequency associated with “protection” has not been examined – Essentially there is no value such as the 1:40 as there is for HI or 1:80 as discussed for microneutralization.**

Innate Immunity Issues

- **Is there innate memory to influenza and what is its role in heterosubtypic immunity?**
- **Are there aspects of the innate response that together with measurements of the adaptive immune response would give a better idea of the correlates of immunity? Such as natural killer cells, cytokine or chemokine levels following vaccination**
- **Most inbred mouse models examined lack MX.**