Hantaviruses

What can rodent reservoirs teach us about human disease?

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Factors Governing Emerging and Re-emerging Infectious Diseases

- Human demographics and behavior
  - Population growth, density and distribution
  - Immunosuppression
  - Sexual activity and substance abuse
- Technology and industry
  - Modern medicine
  - Food processing and handling
  - Water treatment
- Economic development and land use
  - Dam building
  - Reforestation
  - Climate change
- International travel and commerce
- Microbial adaptation and change
  - Natural variation and mutation
  - Selective pressure and development of resistance
- Breakdown of public health measures
  - Inadequate sanitation
  - Complacency
  - Vaccination rates

Adapted from Nathanson, *Viral Pathogenesis and Immunity*, 2007

Reservoirs of Zoonotic Agents

- To perpetuate, viruses must:
  - Persistently infect their reservoirs without
    - substantial pathology
    - eliciting a sterilizing immune response
  - Infect another susceptible host before
    - the immune response controls the virus
    - the host dies

Hantavirus Disease

- Two diseases with many similarities
  - Hemorrhagic Fever with Renal Syndrome (Eurasia)
  - Hantavirus Cardiopulmonary Syndrome (Americas)
- Both are thought to have immunopathologic components
  - No virus damage to the vasculature
  - Pronounced inflammatory immune response 10 to 35 days post exposure
  - The immune response is thought to be a significant contributor to hantavirus disease
- About 200,000 cases and about 10,000 deaths per year

Schmaljohn and Hjelle, *EID*, 1997

Hantaviruses

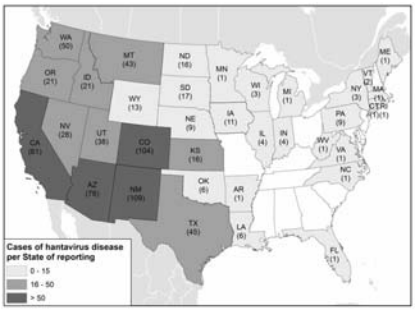
- Negative stranded RNA viruses
- Global distribution
- Enveloped
- Trisegmented
  - S - nucleocapsid (NSs?)
  - M - Gn and Gc glycoproteins
  - L - RNA-dependent RNA polymerase
- Zoonotic reservoirs (no pathology)
  - Rodents
  - Shrews
  - Moles
  - Bats

Pathogenic hantaviruses have only been found in rodents

- Reservoirs remain infected, perhaps for life, despite an immune response
- In rodent reservoirs a regulatory T cell response occurs (Easterbrook et al., *PNAS*, 2007; Schountz et al., *PNAS*, 2007)

Hantaviruses in the United States

- Sin Nombre virus (deer mouse, *Peromyscus maniculatus*)
- Black Creek Canal virus (cotton rat, *Sigmodon hispidis*)
- Bayou virus (rice rat, *Oryzomys palustris*)
- New York virus (white-footed mouse, *Peromyscus leucopus*)



Cumulative Case Count through January 2017 per State

Model Systems for the Study of Zoonotic Viruses

Mode			zoonosis research
Animal model, c (e.g., laboratory			Limited
Animal model, re (natural reservoir			imited to few species
		species-specific reagents rarely available	
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		available	

Studying immunity to zoonotic diseases in the natural host — keeping it real

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Cell

Leading Edge Review

Reservoir Host Immune Responses to Emerging Zoonotic Viruses

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Eckerle et al., *Viruses*, 2014

Hantaviruses and Their Rodent Reservoirs

Why don't reservoir rodents have pathology when infected with their hantaviruses?

Why are they unable to clear the virus?

Sin Nombre virus and the deer mouse (*Peromyscus maniculatus*)

Rodent-Borne New World Hantaviruses

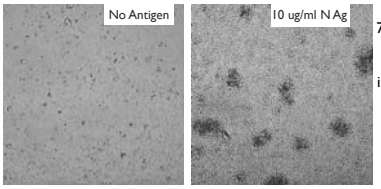
Deer mice are susceptible to Andes virus, but clear infection
(Spengler et al., PLoS One, 2013)

How do deer mouse immune responses differ to SNV and ANDV?

Experimental Design

Infected deer mice with either SNV or ANDV
Euthanize deer mice 14 days later
- Hematology (all normal, even platelets)
- Viral RNA detection
- Serology (ELISA for nucleocapsid)
- Gene expression profiling of virus-specific lymph node helper T cells (94 gene real-time PCR array)

Infect
↓ 14 days
Euthanize for lymph node cell cultures
↓ 3 days
Extract RNA

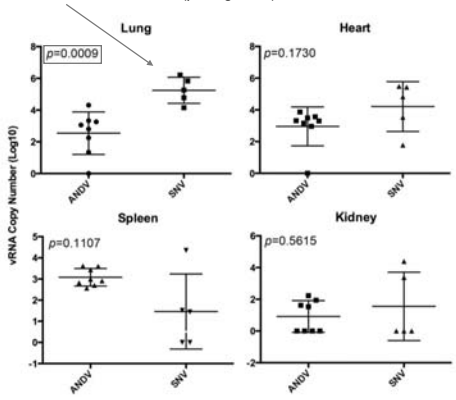


72 hour lymph node cultures from a deer mouse infected with ANDV 14 days before

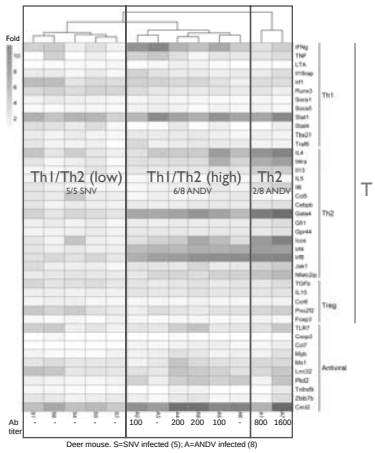
Viral Load

(per mg tissue)

Similar to levels in fatal human cases

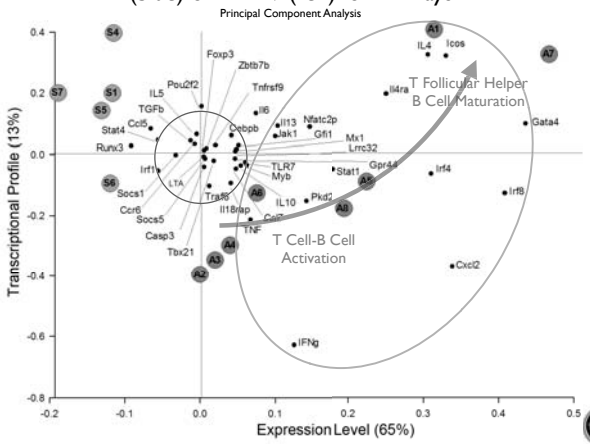


Gene Expression Cluster Analysis



Types of T cell responses

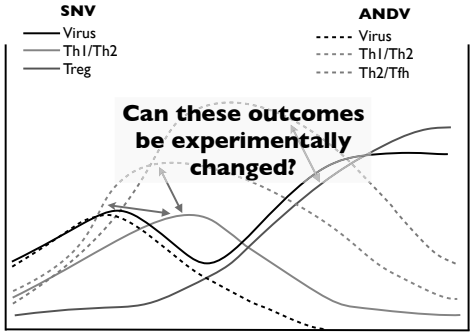
Gene Expression Profiles of Deer Mice Infected with SNV (blue) or ANDV (red) for 14 Days



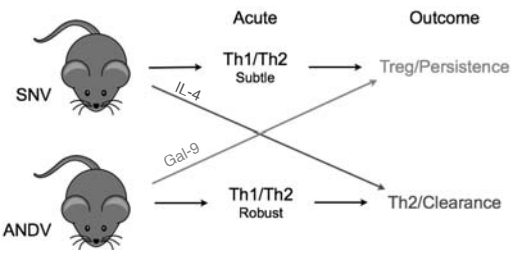
Clearance of Andes Virus Seems to be Mediated by Follicular Helper T Cells

- Follicular helper T cells are essential for robust antibody responses
  - Stimulate B cells to make antibodies
  - They facilitate class switching from IgM to IgG and IgA
  - The stimulate affinity maturation of antibodies
- The deer mouse immune response to Andes virus suggests follicular helper T cells are required for clearance of hantaviruses
  - Deer mice infected with Sin Nombre do not make a robust antibody response and remain persistently infected

An Adaptive Immune Response Model for Hantavirus Infection of Reservoirs



Altering the Outcome of Infection



Can Human Monoclonal Antibodies be used to Treat Hantavirus Disease?

- Chilean researchers examined B cells from 27 Andes virus survivors
- They identified B cells from two survivors that produced antibody that strongly neutralized Andes virus
- They genetically-engineered immortalized cells to express these antibodies in large amounts in cell culture
- Administration of these antibodies reduce mortality of hamsters infected with Andes virus to zero
- Clinical trials will begin soon
- If successful, it could be adapted to treat Sin Nombre virus infections

Garrido et al., Science Translational Medicine. 2018