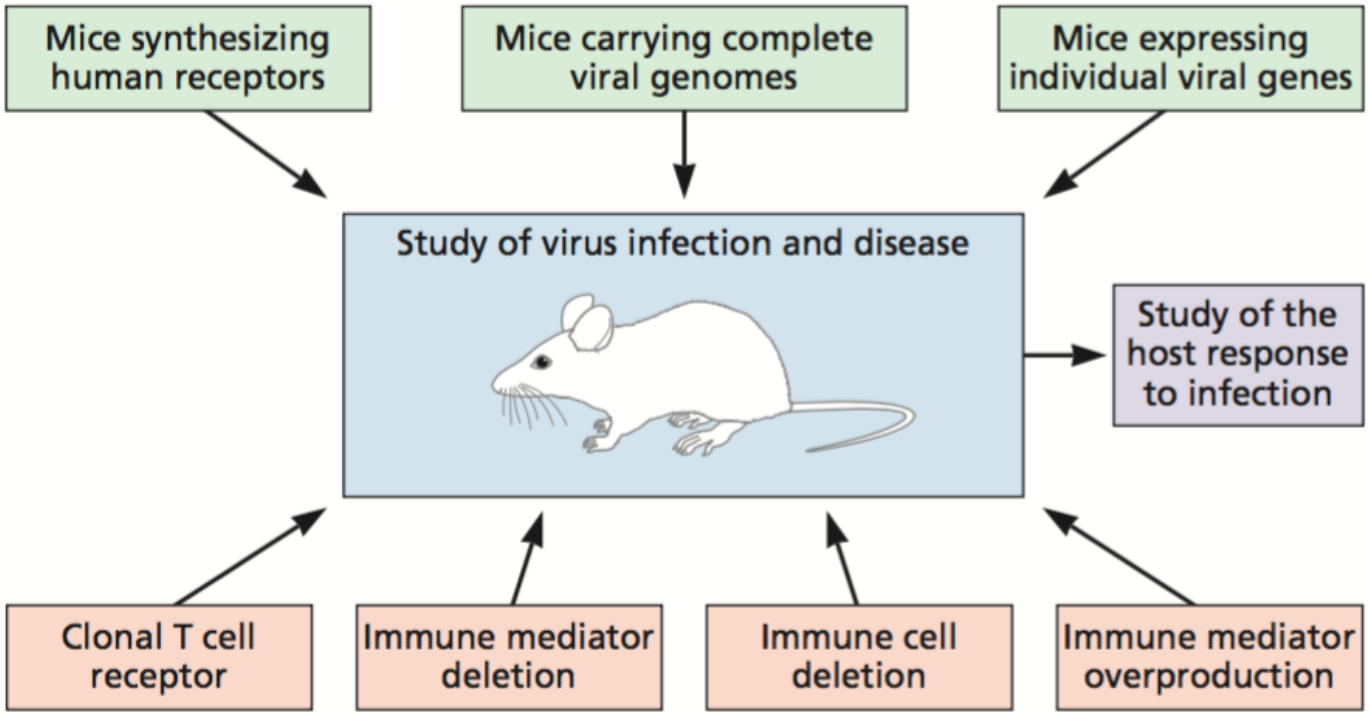
Mechanisms of pathogenesis

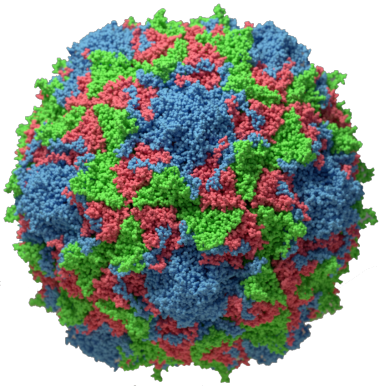
Lecture 15
Biology 3310/4310
Virology
Spring 2017

We have met the enemy and he is us.
–Walt Kelly

Animal models: Mice lie, monkeys exaggerate



- Human viruses in animals
- Animal viruses that resemble human infection



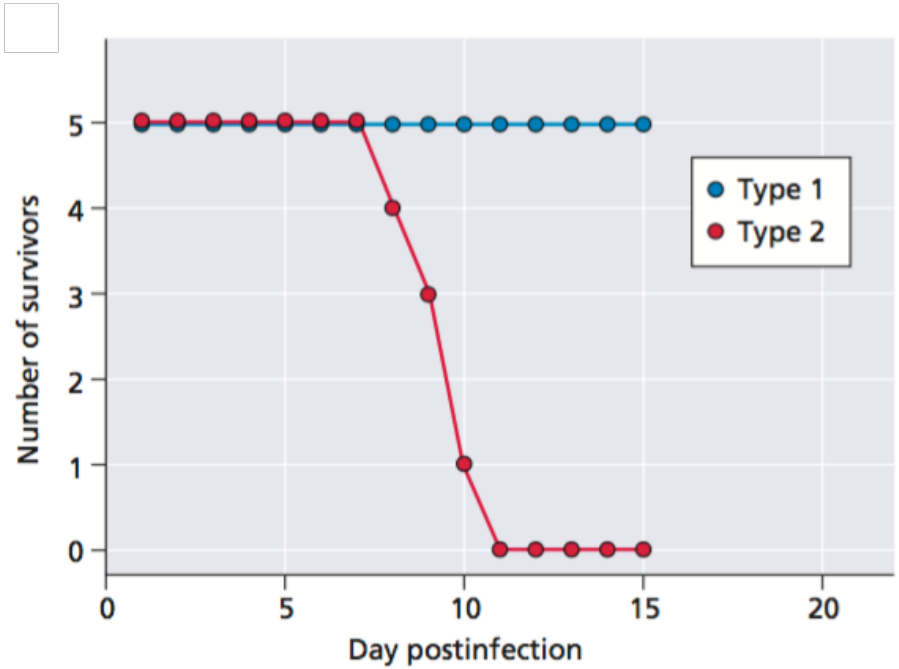
PVR

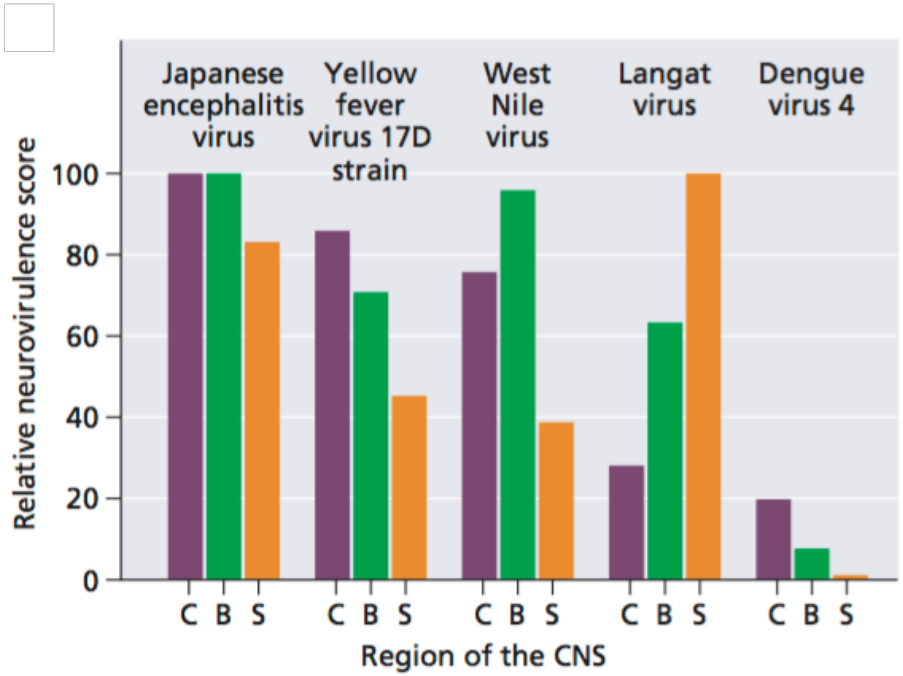
PVR-Tg

Viral virulence

- Capacity of a virus to cause disease in a host
- Virulent vs avirulent or attenuated virus
- Virulence can be quantitated:
  - Mean time to death
  - Mean time to appearance of symptoms
  - Measurement of fever, weight loss
  - Measurement of pathological lesions (poliovirus); reduction in blood CD4+ lymphocytes (HIV-1)

Measuring viral virulence



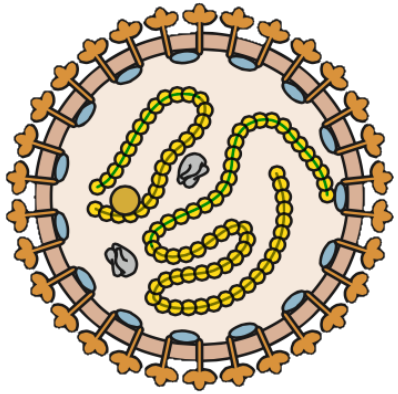


Principles of Virology, ASM Press

Viral virulence is a relative property

- Influenced by dose, route of infection, species, age, gender, and susceptibility of host
- Cannot compare virulence of different viruses
- For similar viruses, assays must be the same

Virulence depends on route of inoculation



Lymphocytic choriomeningitis virus

Dose	Route	Outcome
100,000 PFU	Intraoperitoneal	Survival
1 PFU	Intracranial	Death

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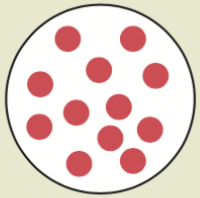
Which statement about viral virulence is wrong?

A. It can be influenced by dose, route of infection, species, age, gender, and susceptibility of host
B. It can be quantitated by measurement of fever
C. Ebola virus is more virulent than human papillomavirus
D. It is the capacity of a virus to cause disease in a host
E. When comparing virulence, the assays must be the same

Viral virulence

- Major goal of virology is to identify viral and host genes that determine virulence
- Virulence genes usually identified by mutation: a virus that causes reduced or no disease in a specified system

Identifying virulence genes

Virus	Growth in cell culture	Effect on mice	Virulence phenotype
Wild type		 Reproduction	Neurovirulent
Mutation leading to a general defect in reproduction		 Poor reproduction	Attenuated
Mutation in a gene specifically required for virulence		 Poor reproduction	Attenuated

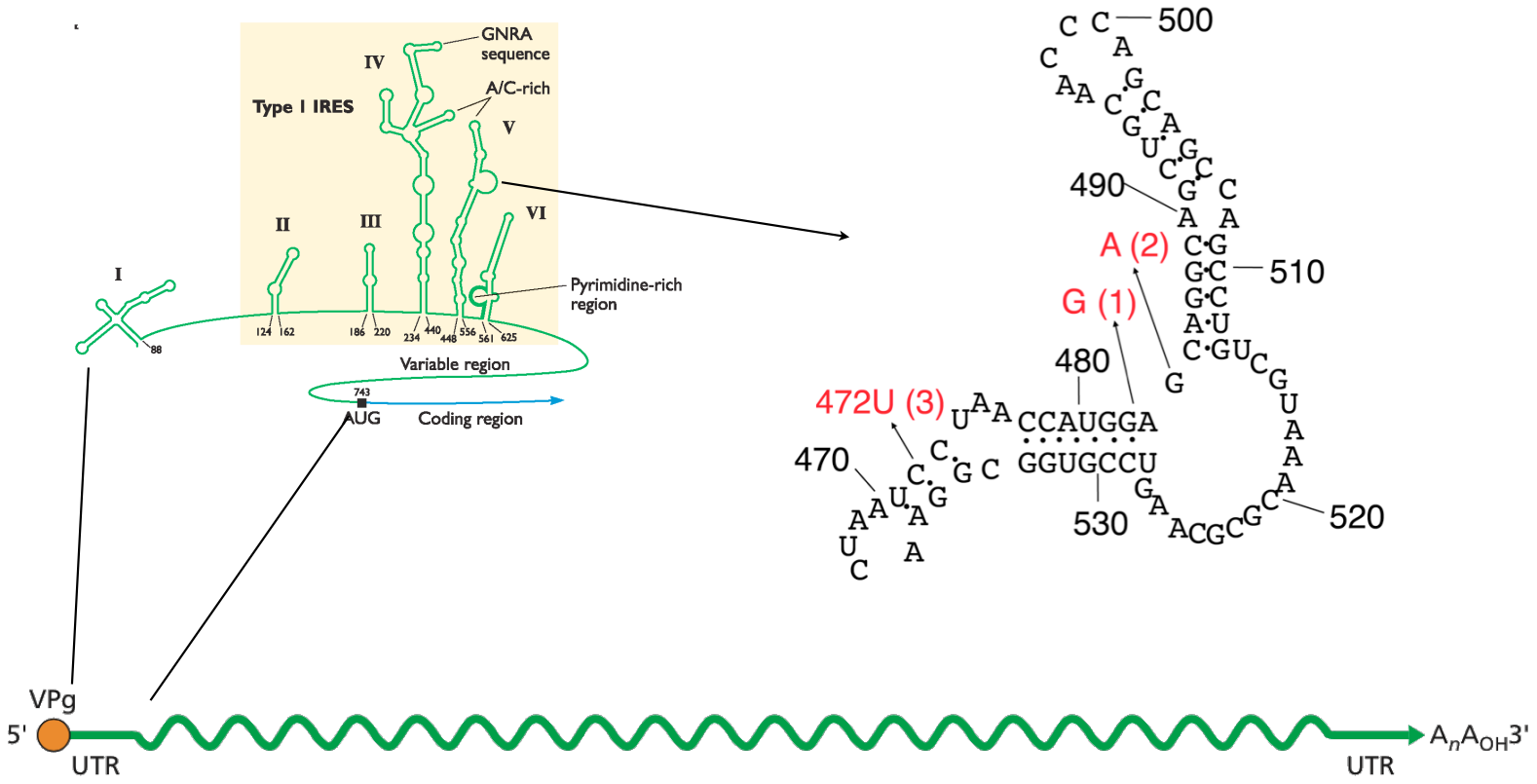
Principles of Virology, ASM Press

Viral virulence genes

- Viral replication
- Invasiveness
- Tropism
- Modify the host defense mechanisms
- Enable the virus to spread in the host
- Intrinsic cell killing effects

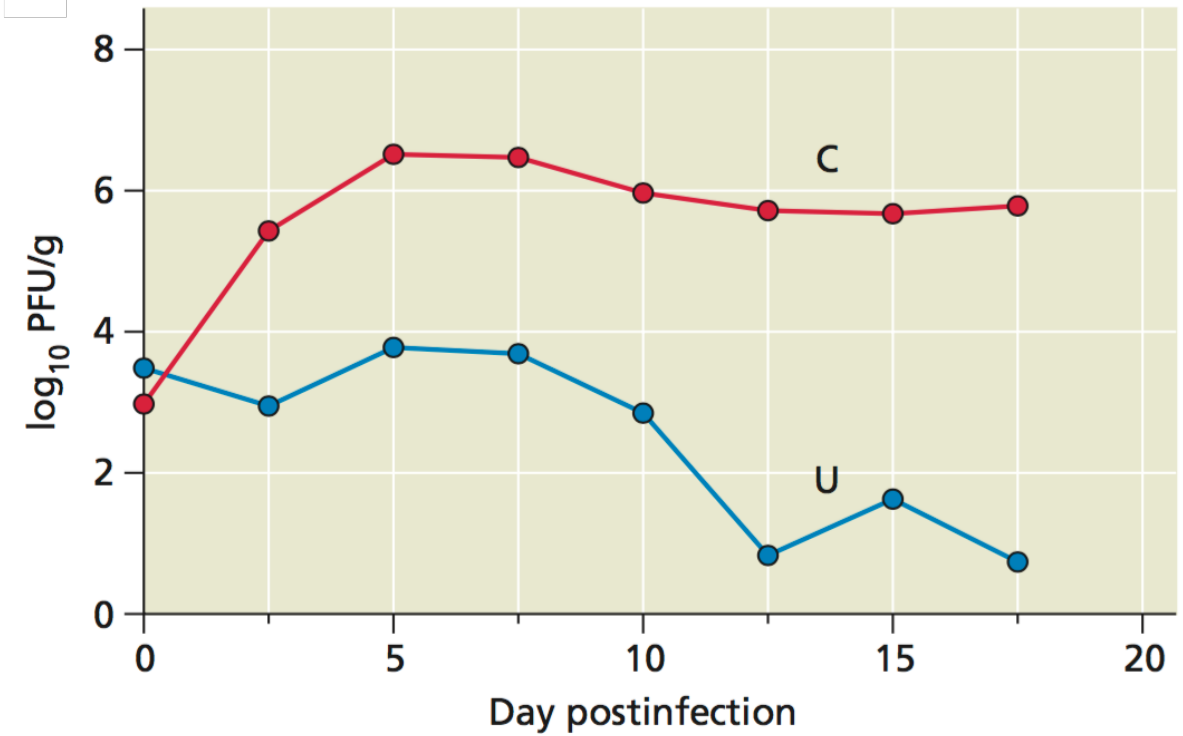
Virulence determinants may not encode proteins

Sabin vaccine strains of poliovirus contain a mutation in the 5'-noncoding region that reduces neurovirulence



Poliovirus replication in mouse brain

Virus	Base at 472	LD_{50}
PRV7.3	U	$>2 \times 10^7$
PRV8.4	C	9×10^3



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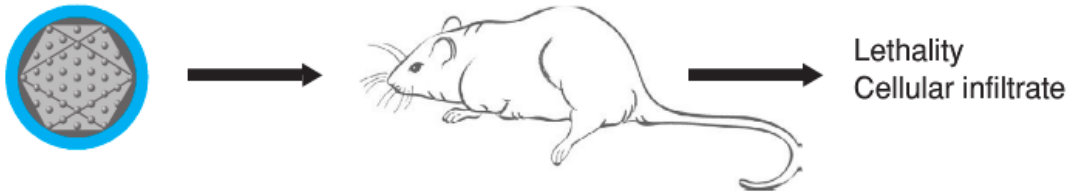
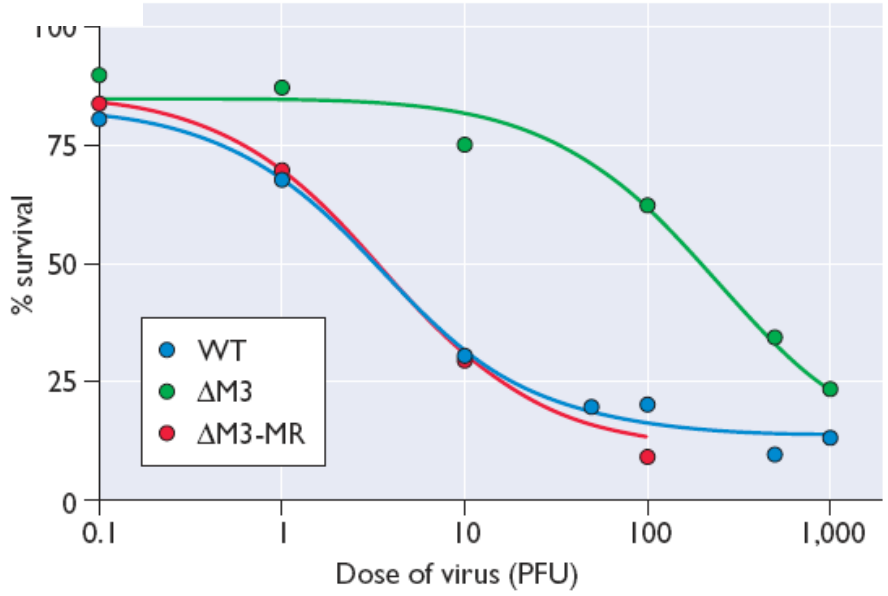
Gene products that modify host defense

- Immune modulators
  - Apoptosis, autophagy, intrinsic proteins (Apobec3G)
  - *Virokines* and *viroceptors*
  - Complement binding proteins
  - Modifiers of MHC I, II pathways
- Often not required for growth in cell culture

Viral virulence genes





Gammaherpesvirus 68 M3 gene encodes a chemokine receptor

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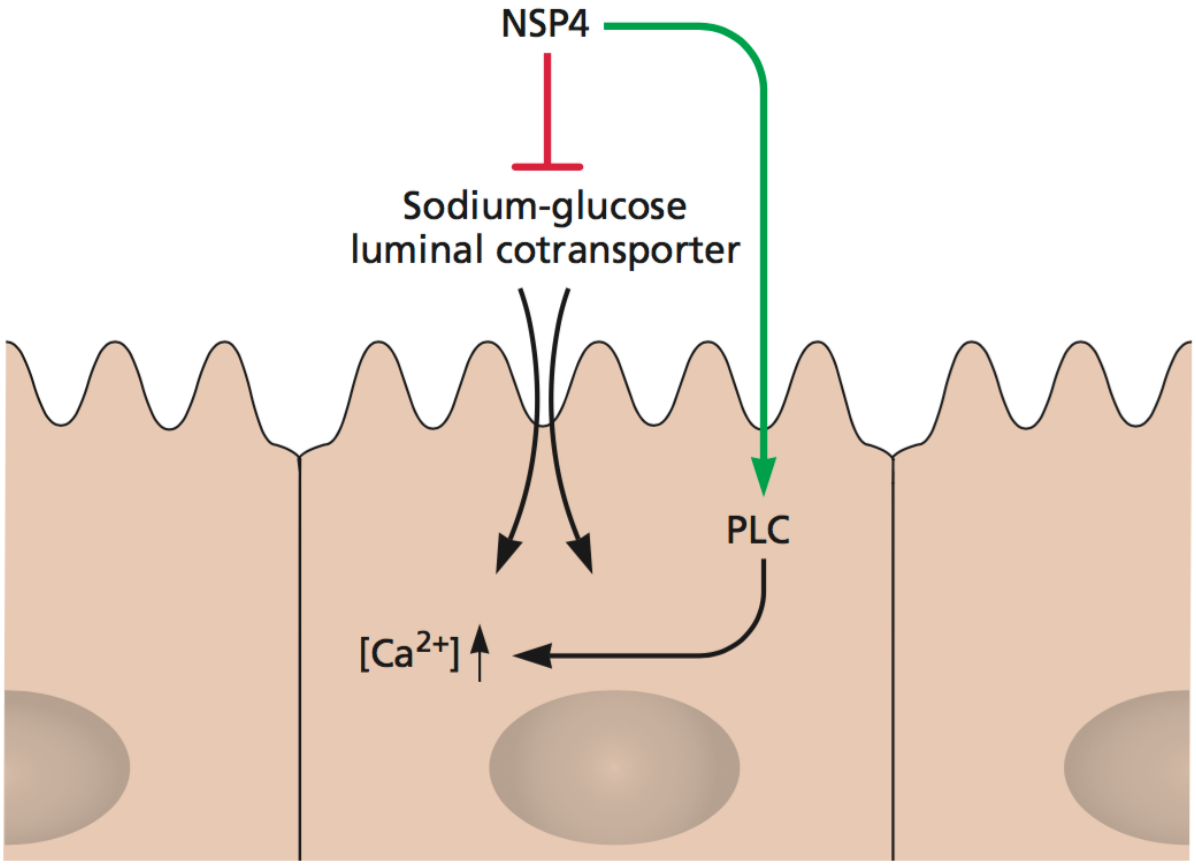
Toxic viral proteins

NSP4 nonstructural glycoprotein of rotaviruses: viral enterotoxin



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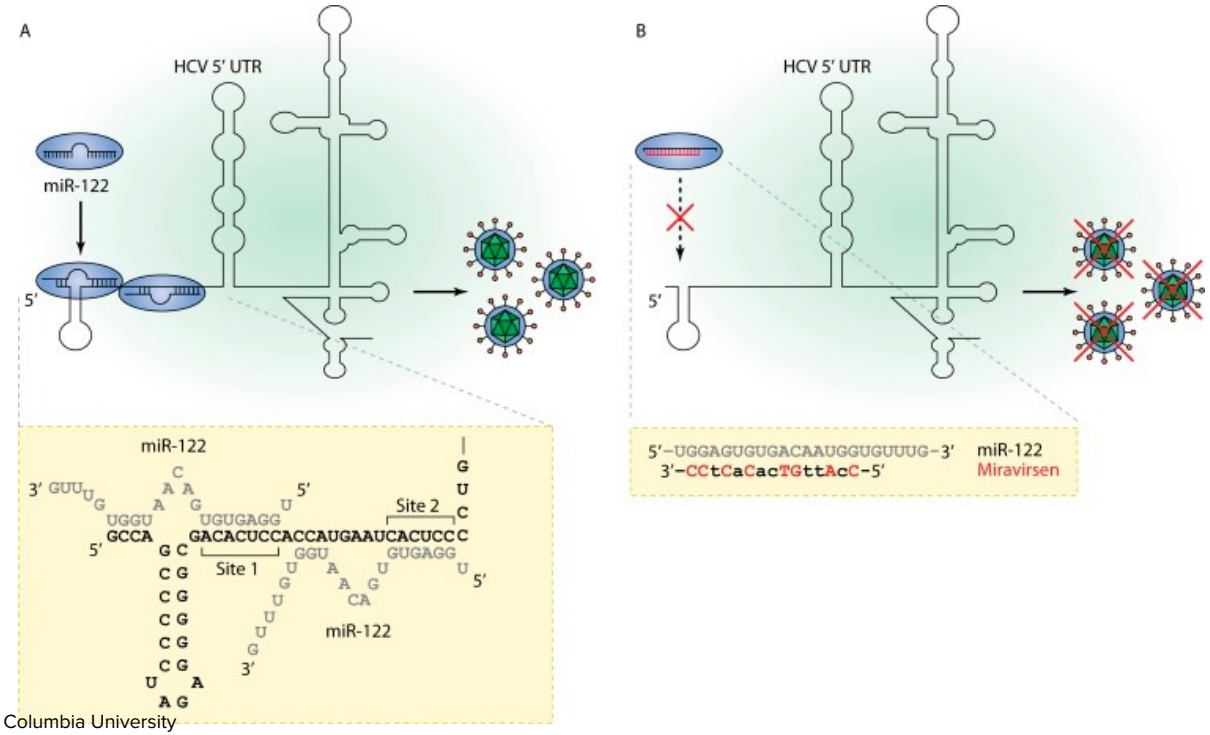
miRNAs

- miR-122, liver-specific miRNA required for HCV replication
- Anti-miR-122 reduces HCV RNA in humans



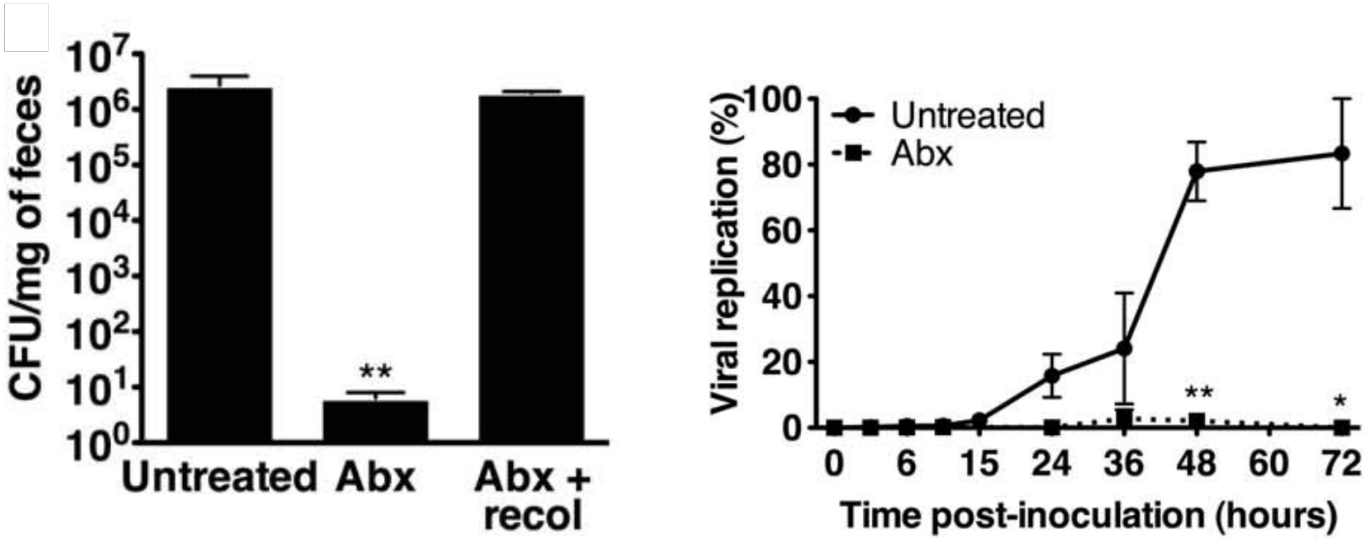
J. Cell Biol. Vol. 199 No. 3 407–412

Mechanisms of cell injury by viruses

- Cytolytic viruses: cytopathic effects (apoptosis, necrosis, pyroptosis)
- Viroporins
- Viral inhibition of host protein and RNA synthesis, leads to loss of membrane integrity, leakage of enzymes from lysosomes, cytoplasmic degradation
- Syncytium formation by enveloped viruses (parainfluenza, HIV)

Role of the microbiome in viral replication

Poliovirus infection of TgPvr mice



DOI: 10.1126/science.12110

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Which statement about determinants of viral virulence is incorrect:

A. Virulence genes can encode viral proteins
B. Virulence genes can encode cellular proteins
C. They are the same in all viruses
D. They can be found in untranslated regions
E. They may encode immune modulators

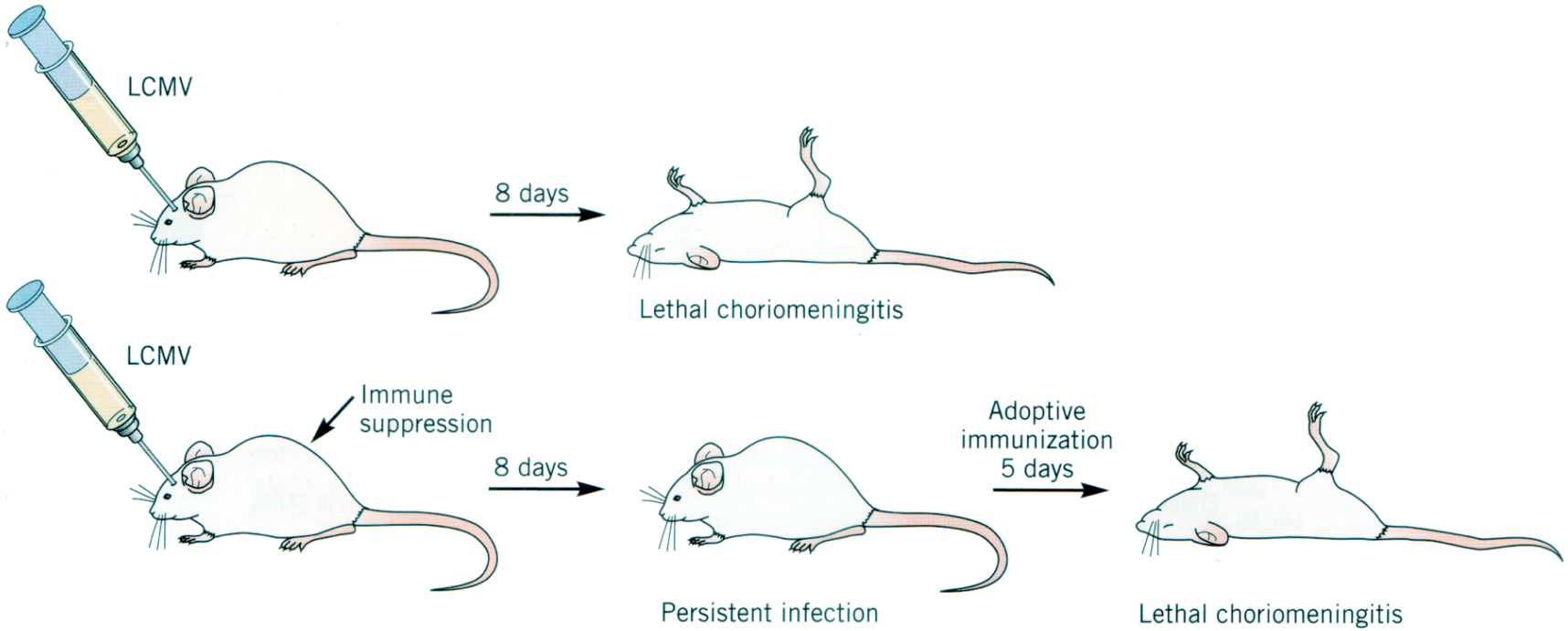
Immunopathology: Too much of a good thing

- Clinical symptoms of viral disease (fever, tissue damage, aches, pains, nausea) are a consequence of host response to infection
- Non-cytopathic viruses: disease is usually a consequence of the immune response

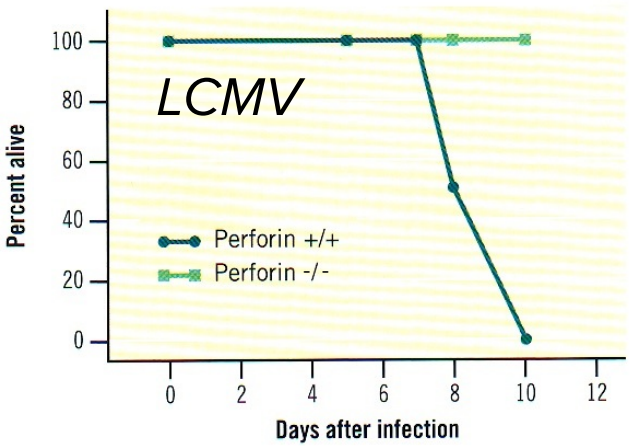
Immunopathology

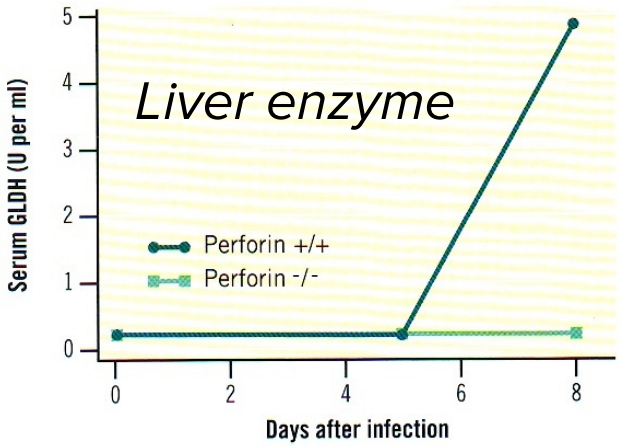
Mechanism	Virus
$CD8^+$ T cell mediated	Coxsackievirus B HIV-1 Hepatitis B virus
$CD4^+$ T cell mediated - Th1	Measles virus Herpes simplex virus
$CD4^+$ T cell mediated - Th2	Respiratory syncytial virus
B cell mediated (antibody)	Dengue virus

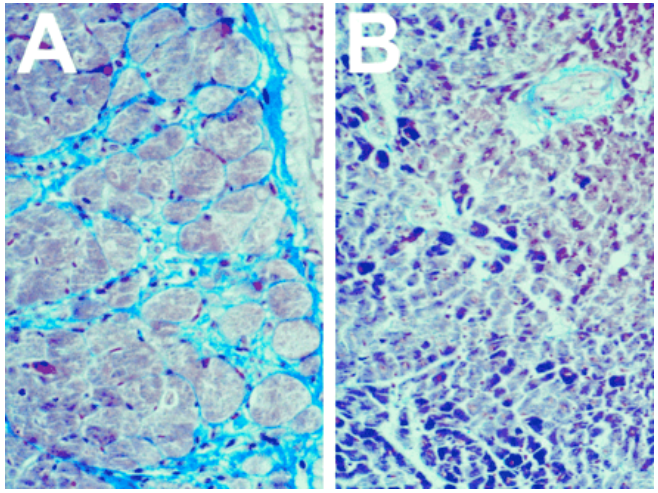
Viral disease mediated by CD8$^+$ CTLs



Lesions associated with CD8 cells





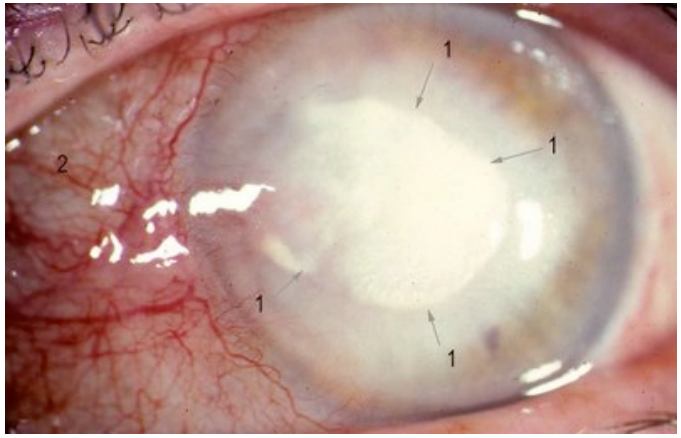


Lesions associated with CD4+ T cells

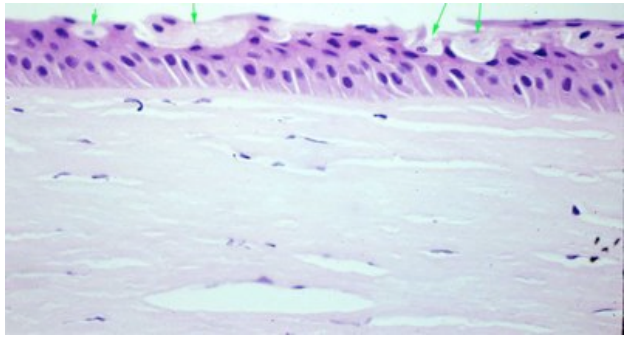
- Elaborate more cytokines than CD8+ T cells, and recruit and activate many nonspecific effector cells
- Most recruited cells are neutrophils and mononuclear cells, which are protective but cause tissue damage
- Immunopathology caused by release of proteases, reactive radicals, and cytokines (e.g. Tnf-α)

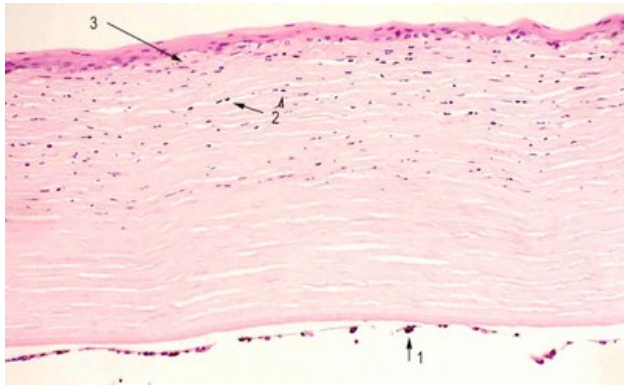
Lesions associated with CD4+ T cells

- Herpes stromal keratitis, one of the most common causes of blindness in developed countries; almost entirely immunopathological ($CD4^+$ Th1 cells)
- Repeated infections cause opacity and reduced vision



Lesions associated with CD4+ T cells

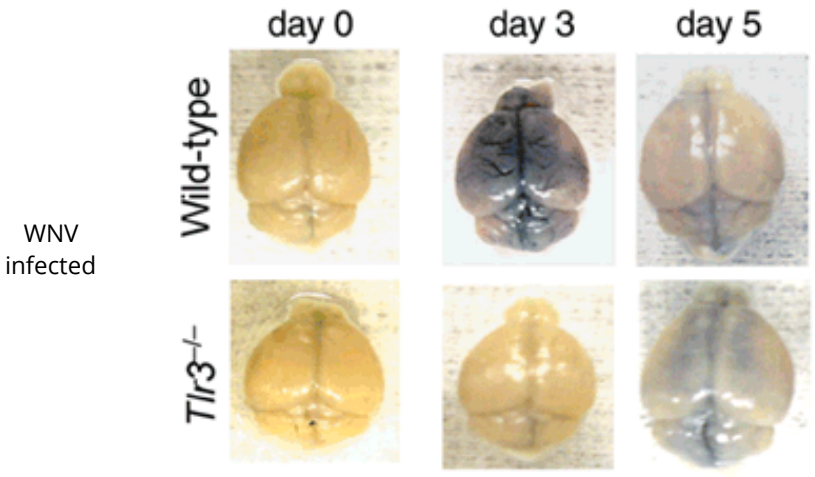




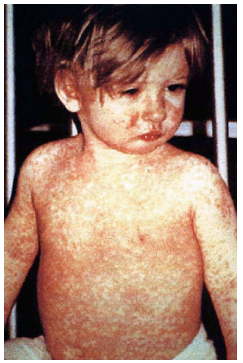
- Virus replicates in corneal epithelium, but $CD4^+$ Th1 inflammation restricted to underlying uninfected stromal cells
- Stromal cells damaged by secreted cytokines produced by infected cells in corneal epithelium

TLR3 and West Nile virus encephalitis

- Tlr3$^{-/-}$ mice more resistant to WNV lethal infection, have impaired cytokine production
- TNF-α compromises blood-brain barrier

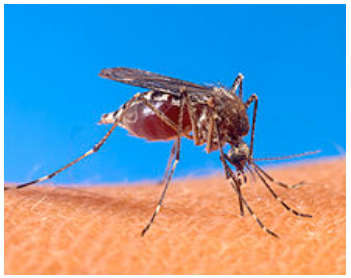


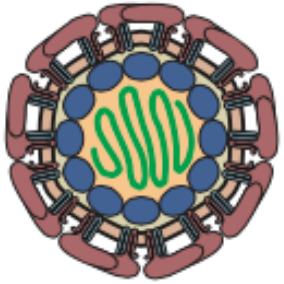
Poxes and rashes



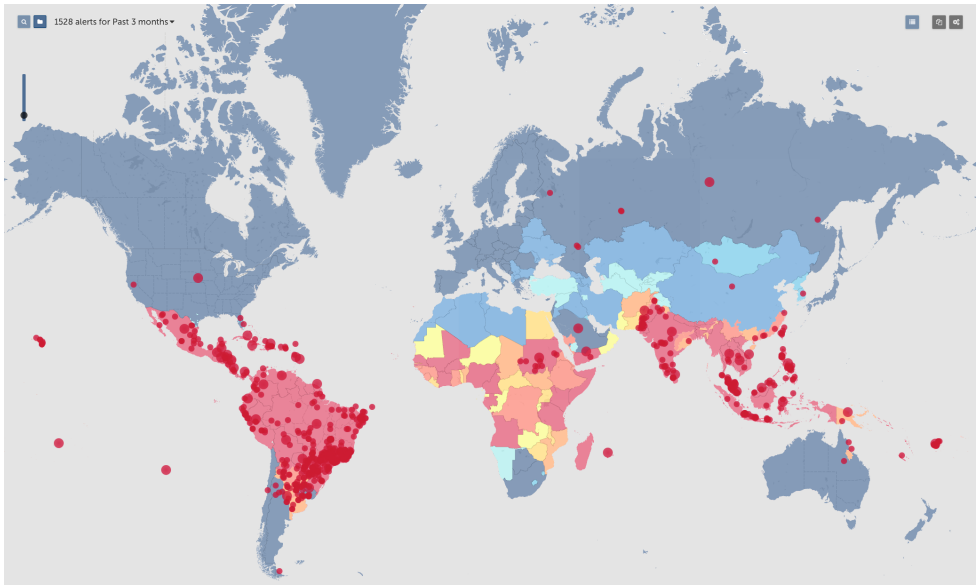
- Many virus infections produce characteristic rash (measles, smallpox, varicella zoster)
- Th1 cells and macrophages activated by original infection home in on infected foci in skin
- These cells produce cytokines such as IL-2 and IFN-ϒ
- Cytokines act locally to increase capillary permeability, influx of T cells

Dengue fever (breakbone fever)

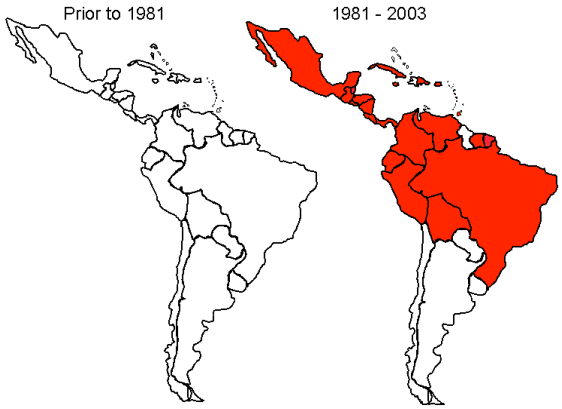




- Dengue virus, transmitted mainly by *Aedes aegypti*
- Endemic in the Caribbean, Central and South America, Africa and Southeast Asia - billions at risk
- 400 million infections/year
- Second only to malaria among insect-borne diseases



American Countries with laboratory confirmed dengue hemorrhagic fever, prior to 1981 and from 1981 to 2003

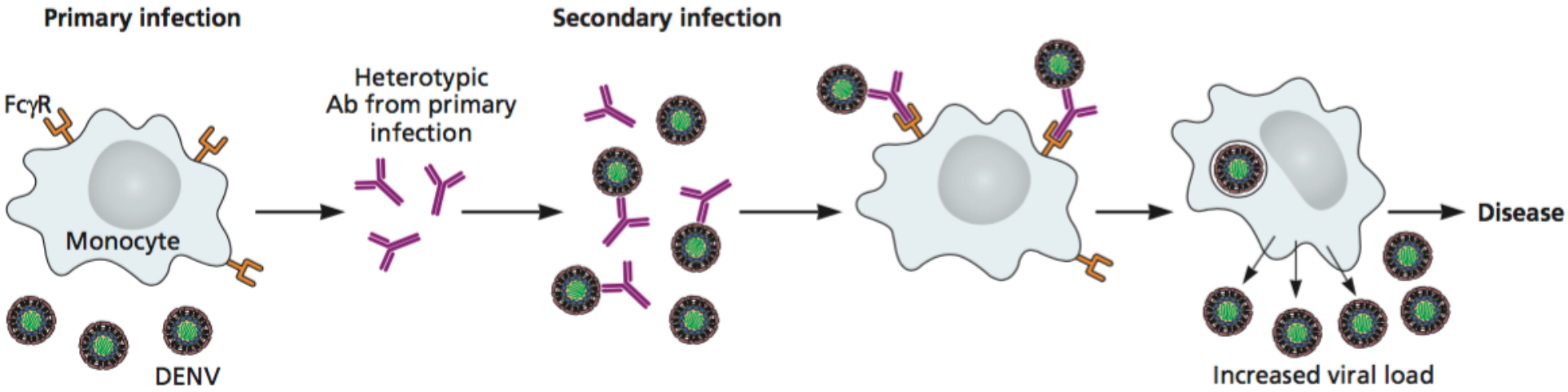


Source: WHO/PAHO/CDC, Aug. 2004

Dengue fever

- Primary infection asymptomatic or *acute febrile illness with severe headache, back and limb pain and rash. Severe aches and pains in the bones.*
  - Normally self-limiting, patients recover in 7-10 days
  - In 1/14,000 primary infections: dengue hemorrhagic fever, life threatening disease
  - Internal bleeding leads to fatal dengue shock syndrome
- Antibodies to virus made; four serotypes, no cross-protection

Dengue fever



After secondary dengue infections, incidence of hemorrhagic fever and shock syndrome 1/90 and 1/50

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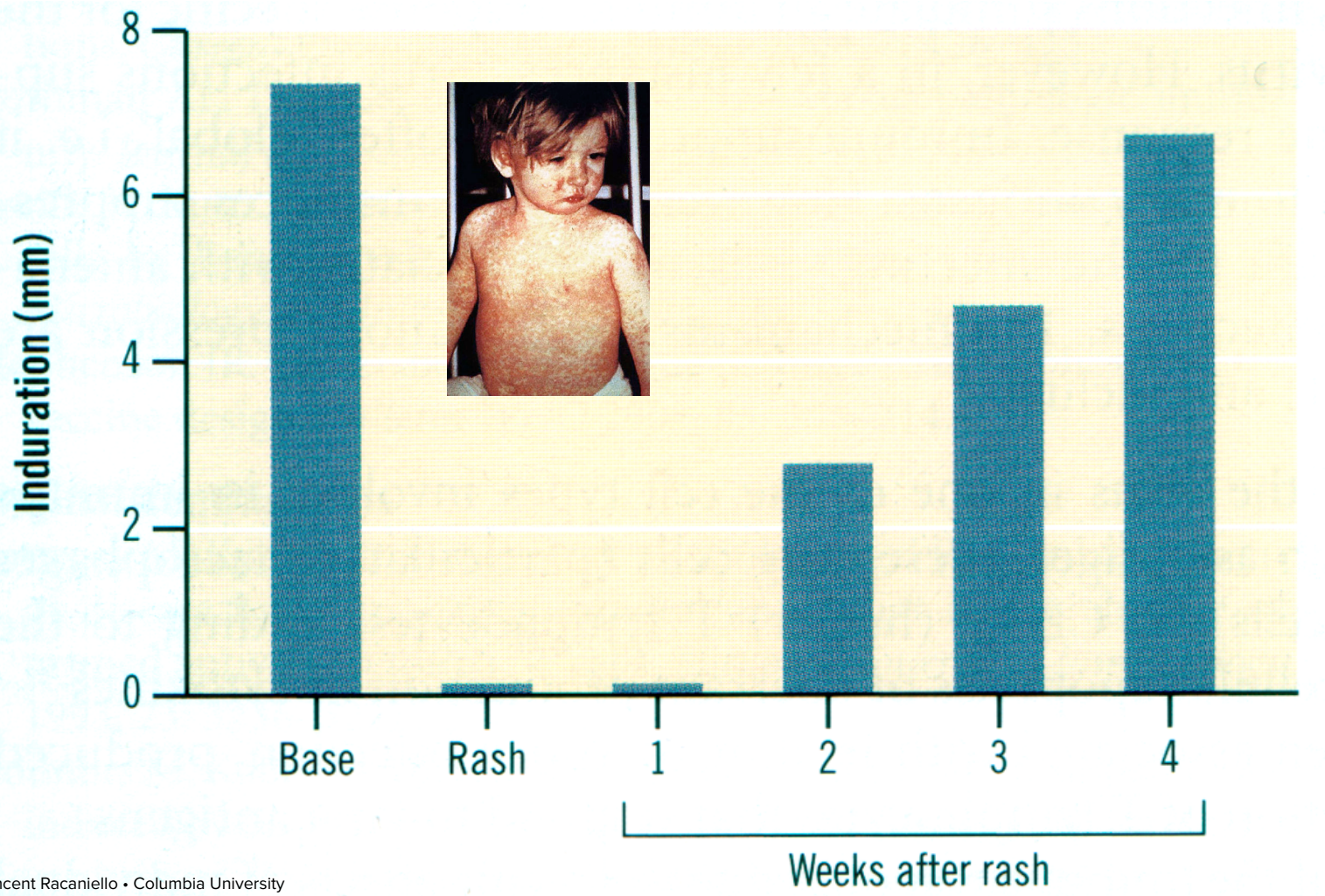
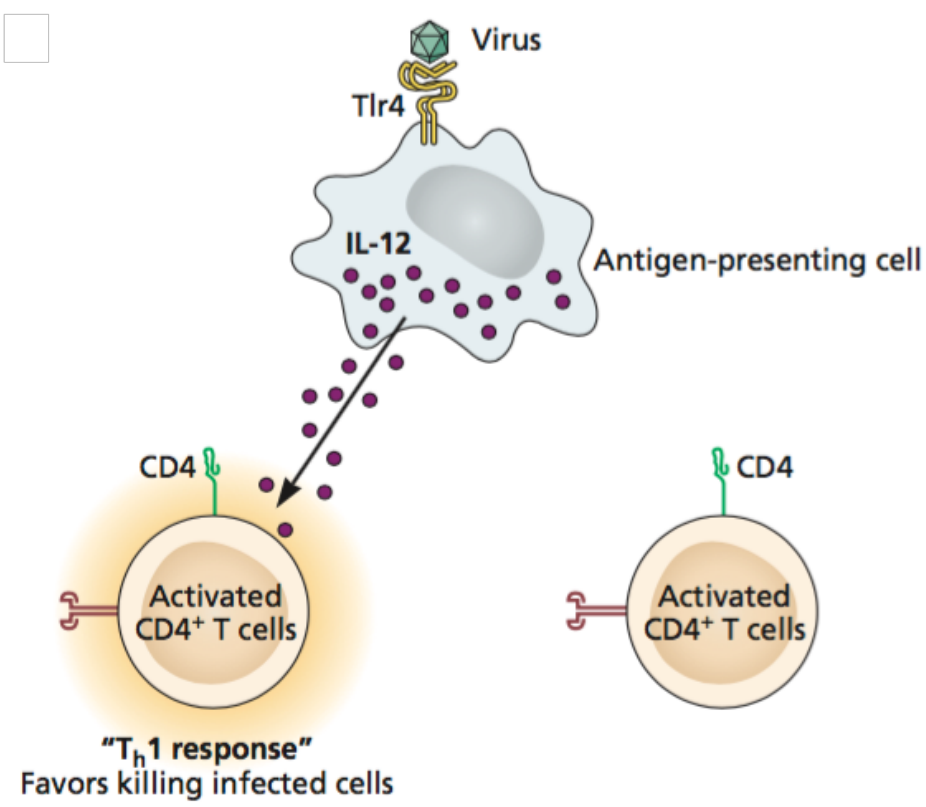
Immunosuppression

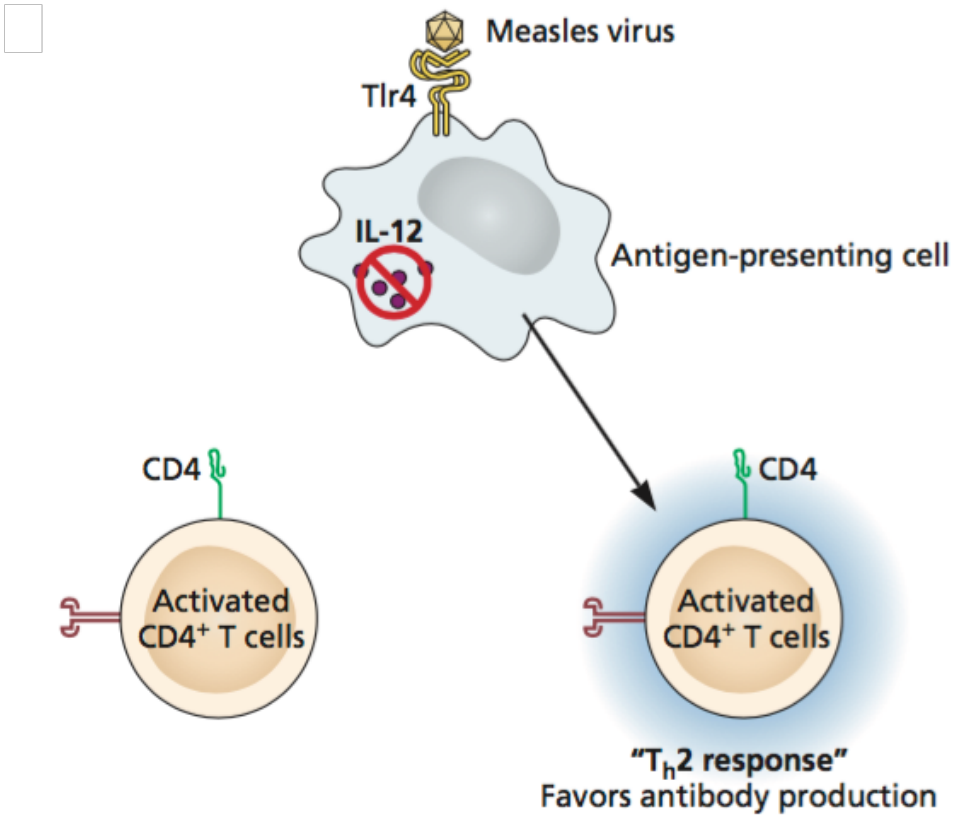
- Global reduction of the immune response caused by virus infection
- Mechanisms
  - Replication in one or more cells of immune system
  - Perturbation of cytokine homeostasis and intracellular signaling
  - Viral proteins acting as viroceptors or virokines (immune modulators)

Immunosuppression during measles infection



Measles virus immunosuppression





Examples of immunosuppression

Virus	Disease	Cells infected	Manifestation
Measles	Measles	Monocytes, DC Thymic epithelial cells	Reduced T cells Enhanced infections
Rubella	Rubella	Lymphoid cells	Persistent rubella infection
HIV	AIDS	CD4+ T cells monocytes	Opportunistic infections Neoplasia

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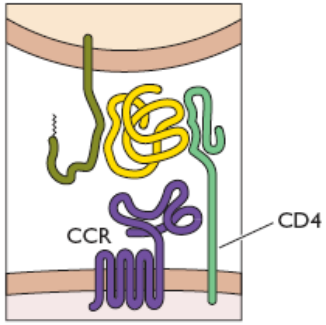
Which of the following is an example of B-cell mediated immunopathology?

1. $CD8^+$ T cells that cause tissue damage
2. Poxes and rashes
3. Dengue shock syndrome
4. HIV-1 associated opportunistic infections
5. All of the above

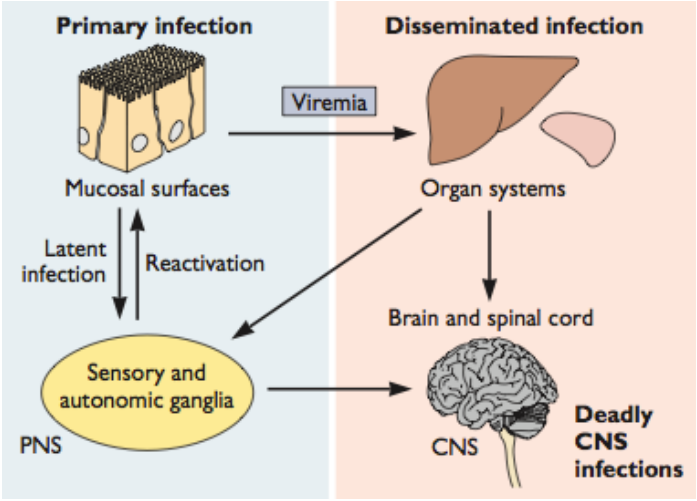
Host genes that determine susceptibility



- Ccr5-delta32 mutation protects vs HIV-1 infection
- Present in 4-16% of European descent
- Stem cell therapy cured German AIDS patient
- HIV gets the zinc finger: http://www.virology.ws/2014/03/19/hiv-gets-the-zinc-finger/

Host genes that determine susceptibility

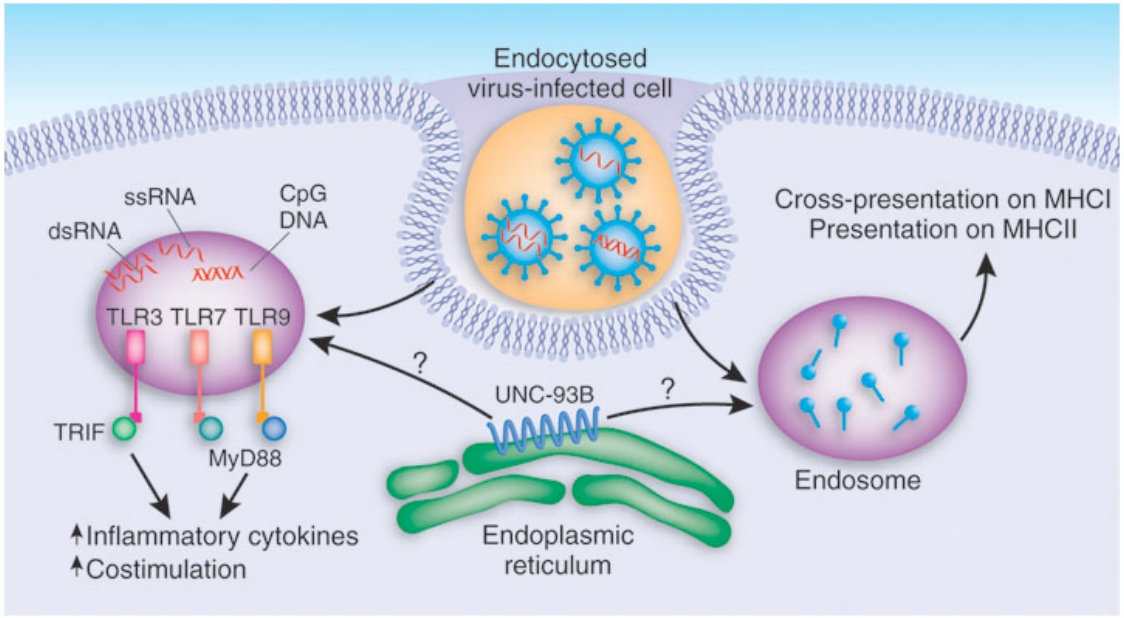
Herpes simplex encephalitis



- Rare and potentially fatal CNS infection, ~1 case/250,000/yr
- 70% mortality if untreated
- Two peaks of incidence: 6 mo - 3 yr (primary infection) and >50 yr (reactivation from latency)

Human determinants of susceptibility

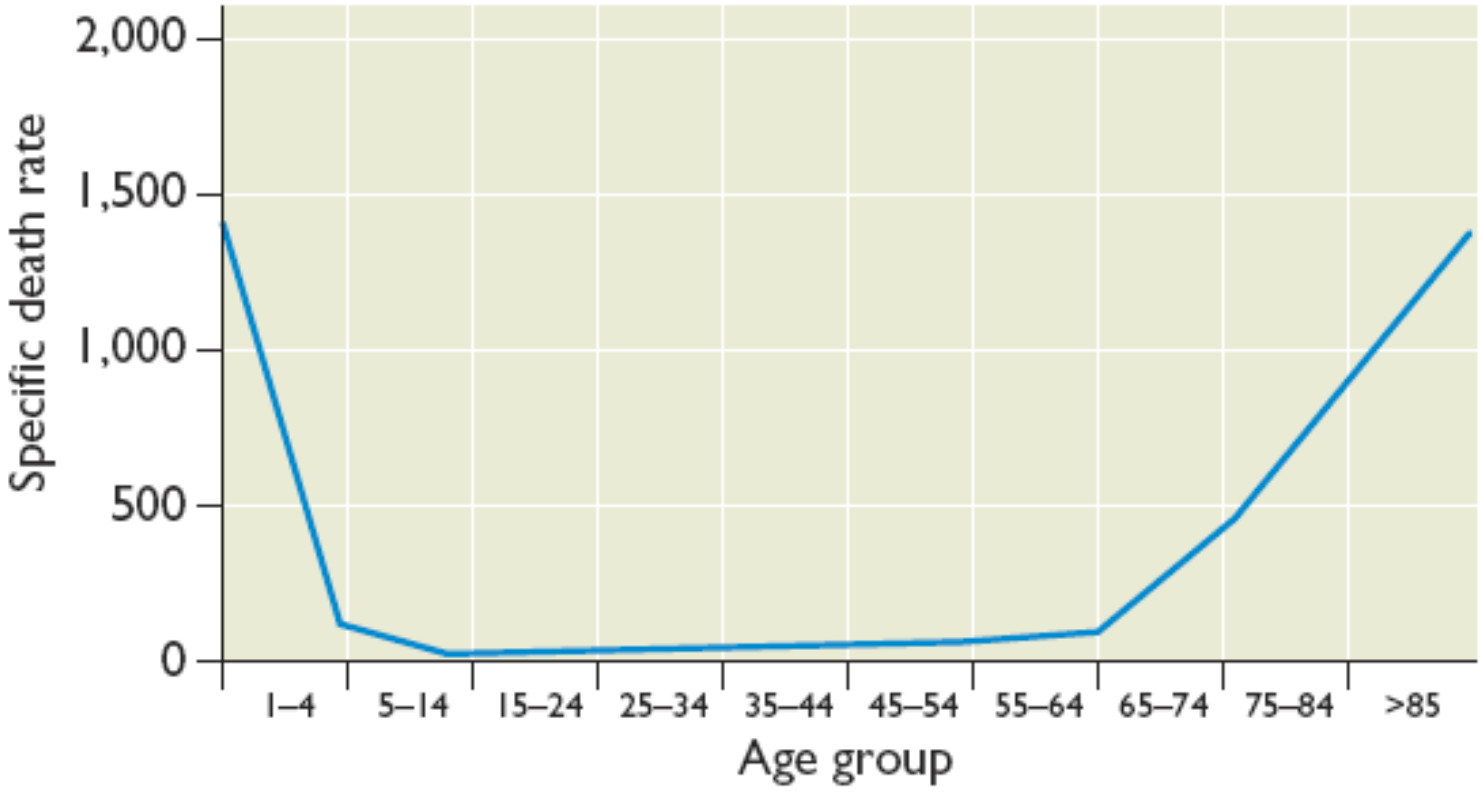
- GWAS, SNPs
- Mutations in *TLR3*, *UNC-93B*, TRIF or TRAF3 predispose human carriers to HSV encephalitis



Other determinants of susceptibility: Age

- Very young and very old humans most susceptible to disease
- Young - immaturity of immune response; greater freedom from immunopathology
  - LCM i.c. adult mice lethal; infant mice survive (T cell response)
- Old - less elastic alveoli, weaker respiratory muscles, diminished cough reflex

Influenza, US, 1911-1915



Other determinants of susceptibility

- Males slightly more susceptible to viral infections than females
- Pregnancy: hepatitis A, B, E, influenza more lethal, polio more common
- Malnutrition increases susceptibility because physical barriers and immune response are compromised
  - Why measles is 300 times more lethal in developing countries than Europe, N. America

Other determinants

- Cigarette smoking increases susceptibility to respiratory infections
- Air pollution increases respiratory disease
- Stress causes increased susceptibility