Viral virulence

Lecture 15
Biology W3310/4310
Virology
Spring 2015

Serious illness doesn’t bother me for long because I am too inhospitable a host.
—Albert Schweitzer
Animal models

- Mice with new receptors
- Mice with complete viral genomes
- Mice expressing individual viral genes

Study of virus infection and disease

- Clonal T-cell receptor
- Immune mediator deletion
- Immune cell deletion
- Immune mediator overproduction

- Study of the host response to infection

- Human viruses in animals
- Animal viruses that resemble human infection
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)
Viral virulence

A

Number of survivors

Day postinfection

Type 1
Type 2

B

Relative neurovirulence score

Japanese encephalitis virus
Yellow fever virus 17D strain
West Nile virus
Langat virus
Dengue virus 4

Region of the CNS

C
B
S

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*

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000 PFU</td>
<td>Intraoperitoneal</td>
<td>Survival</td>
</tr>
<tr>
<td>1 PFU</td>
<td>Intracranial</td>
<td>Death</td>
</tr>
</tbody>
</table>
Which statement about viral virulence is wrong?

1. It can be influenced by dose, route of infection, species, age, gender, and susceptibility of host
2. It can be quantitated by measurement of fever
3. Ebola virus is more virulent than human papillomavirus
4. It is the capacity of a virus to cause disease in a host
5. 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

<table>
<thead>
<tr>
<th>Virus</th>
<th>Growth in cell culture</th>
<th>Effect on mice</th>
<th>Virulence phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td><img src="Image" alt="Replication" /></td>
<td><img src="Image" alt="Replication" /></td>
<td>Neurovirulent</td>
</tr>
<tr>
<td>Mutation leading to a general defect in replication</td>
<td><img src="Image" alt="Poor replication" /></td>
<td><img src="Image" alt="Poor replication" /></td>
<td>Attenuated</td>
</tr>
<tr>
<td>Mutation in a gene specifically required for virulence</td>
<td><img src="Image" alt="Poor replication" /></td>
<td><img src="Image" alt="Poor replication" /></td>
<td>Attenuated</td>
</tr>
</tbody>
</table>
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

Attenuated Sabin vaccine strains of poliovirus contain a mutation in the 5’-noncoding region that reduces neurovirulence.
Poliovirus replication in mouse brain

<table>
<thead>
<tr>
<th>Virus</th>
<th>Base at 472</th>
<th>LD$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRV7.3</td>
<td>U</td>
<td>&gt;$2 \times 10^7$</td>
</tr>
<tr>
<td>PRV8.4</td>
<td>C</td>
<td>$9 \times 10^3$</td>
</tr>
</tbody>
</table>
Gene products that modify host defense

- Immune modulators
  - Apoptosis, autophagy, proteins (Apobec3G)
  - *Virokines* and *viroceptors*
  - Complement binding proteins
  - Modifiers of MHC I, II pathways
- Often not required for growth in cell culture
Gammaherpesvirus 68 M3 gene encodes a chemokine receptor
Toxic viral proteins

NSP4 nonstructural glycoprotein of rotaviruses: viral enterotoxin
Regulation of virulence by a cellular protein: TRIM5α

- Old world monkeys are not infected by HIV-1
- Virions enter but encounter a block before RT
- Restriction mediated by species-specific protein TRIM5α that acts on the viral capsid
miRNAs

• miR-122, liver-specific miRNA required for HCV replication

• Anti-miR-122 reduces HCV yield in chimpanzees
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
Should we make viruses more virulent?

- Highly lethal in genetically resistant mice (strong cell response)
- Suppressed memory response

+ IL-4 gene → Mice
The obsession with viral virulence

Influenza Surveillance: 2014–2015 H1N1 “Swine”-Derived Influenza Viruses from India

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http://dx.doi.org/10.1016/j.chom.2015.02.019

The 2014-2015 H1N1 outbreak in India has reportedly led to 800 fatalities. The reported influenza hemagglutinin sequences from India indicate that these viruses contain amino acid changes linked to enhanced virulence and are potentially antigenically distinct from the current vaccine containing 2009 (Cal0709) H1N1 viral hemagglutinin.

- Limited sequences available from outbreak
- 2014 isolate has HA D225N change ‘associated with serious illness’
- Unknown if this strain is still in circulation
Go to:

m.socrative.com
room number: virus

Which statement about determinants of viral virulence is incorrect:

1. Virulence genes can encode viral proteins
2. Virulence genes can encode cellular proteins
3. They are the same in all viruses
4. They can be found in untranslated regions
5. They may encode immune modulators
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

![Bar graph showing induration (mm) over weeks after rash onset.](image)
Measles virus immunosuppression

- Dendritic cells and monocytes are infected, antigen-presenting activity compromised
- Circulating T lymphocytes are decreased by 50%
- Aberrant cytokine responses: IL-4 and IL-10 increased, skews Th1 to Th2 and reducing macrophage activation

![Diagram of Th1 vs Th2 response and immune cross-regulation by cytokines](attachment:diagram.png)
# Examples of immunosuppression

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
<th>Cells infected</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Measles</td>
<td>Monocytes, DC Thymic epithelial cells</td>
<td>Reduced T cells Enhanced infections</td>
</tr>
<tr>
<td>Rubella</td>
<td>Rubella</td>
<td>Lymphoid cells</td>
<td>Persistent rubella infection</td>
</tr>
<tr>
<td>HIV</td>
<td>AIDS</td>
<td>CD4+ T cells monocytes</td>
<td>Opportunistic infections Neoplasia</td>
</tr>
</tbody>
</table>
Host genes that control host susceptibility to viral disease

- *flv* gene of mice determines susceptibility to flavivirus
- *flv* encodes 2′-5′-oligo(A) synthetase
Human determinants of 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/
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
Influenza severity and IFITM3

- IFITM3 is an ISG encoding a transmembrane protein
- Essential for controlling influenza morbidity and mortality in mice
- Humans hospitalized with severe influenza are enriched for a mutation in IFITM3 gene

IFITMs also inhibit dengue, HCV, Ebola
Virus susceptibility mapping to MHC
Virus susceptibility mapping to MHC

![Graph showing virus susceptibility mapping to MHC for H-2<sup>a/a</sup> and H-2<sup>a/b</sup> mice.](image)
Elite controllers

- Long-term nonprogressors: low HIV loads without antiretrovirals
- Multiple traits responsible
- Associated with specific MHC I alleles (HLA-B57)
Viral co-infections: HIV-1 and HSV-2

- HSV-2 enhances HIV infection of Langerhans cells
- HSV-2 stimulates production of antimicrobial peptides by epithelial cells
- AMP LL-37 enhances HIV-1 infection of LCs
- LL-37 up-regulates HIV-1 receptors CD4 and CCR5
Which of the following are examples of SNPs that control susceptibility to viral disease?

1. Viral co-infections
2. Ccr5-delta32
3. Mutations in tlr3 that predispose to herpes simplex encephalitis
4. The flv gene
5. All of the above
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
Age exceptions

- Poliovirus, mumps virus, measles virus infections milder at young age; better balance of protective and pathogenic immune response at this age?

- 1918 influenza pandemic lethal for very young, very old, and unexpectedly for young adults 18-30 yr old
Perhaps lacked protective immunity which would be conferred by previous infection with related virus
Other determinants

- 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
  - For this reason, 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