Persistent Infections

Lecture 17
Biology W3310/4310
Virology
Spring 2014

*Paralyze resistance with persistence*
—W O O D Y H A Y E S
Acute vs persistent infections

- Acute infection - rapid and self-limiting
- Persistent infection - long term, life of host
- Stable, characteristic for each virus family
- Most persistent infections probably begin as an acute infection
General patterns of infection

- **Acute infection**
  - Rhinovirus
  - Rotavirus
  - Influenza virus

- **Persistent infection, smoldering**
  - Lymphocytic choriomeningitis virus

- **Persistent infection, latent**
  - Herpes simplex virus

- **Persistent infection, slow**
  - Measles virus SSPE
  - Human immunodeficiency virus
  - Human T-lymphotropic virus
Persistent infections

• Occur when primary infection is not cleared by immune response
• Virions, protein, genomes continue to be produced
• Viral genomes may remain after proteins are not detected
Persistent infections

- No single mechanism
- When cytopathic effects are absent and host defenses are reduced, persistent infection is likely
- Viral immune modulation
# Persistent human infections

<table>
<thead>
<tr>
<th>Virus</th>
<th>Site(s) of persistence</th>
<th>Consequence(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Adenoids, tonsils, lymphocytes</td>
<td>None known</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>B cells, nasopharyngeal epithelia</td>
<td>Lymphoma, carcinoma</td>
</tr>
<tr>
<td>Human cytomegalovirus</td>
<td>Kidneys, salivary gland, lymphocytes, (^a) macrophages, (^a) stem cells, (^a) stromal cells (^a)</td>
<td>Pneumonia, retinitis</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Liver, lymphocytes</td>
<td>Cirrhosis, hepatocellular carcinoma</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Liver</td>
<td>Cirrhosis, hepatocellular carcinoma</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>CD4(^+) T cells, macrophages, microglia</td>
<td>AIDS</td>
</tr>
<tr>
<td>Herpes simplex virus types 1 and 2</td>
<td>Sensory and autonomic ganglia</td>
<td>Cold sore, genital herpes</td>
</tr>
<tr>
<td>Human T-lymphotropic virus types 1 and 2</td>
<td>T cells</td>
<td>Leukemia, brain infections</td>
</tr>
<tr>
<td>Papillomavirus</td>
<td>Skin, epithelial cells</td>
<td>Papillomas, carcinomas</td>
</tr>
<tr>
<td>Polyomavirus BK</td>
<td>Kidneys</td>
<td>Hemorrhagic cystitis</td>
</tr>
<tr>
<td>Polyomavirus JC</td>
<td>Kidneys, central nervous system</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Central nervous system</td>
<td>Subacute sclerosing panencephalitis, measles</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Central nervous system</td>
<td>inclusion body encephalitis</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Sensory ganglia</td>
<td>Progressive rubella panencephalitis</td>
</tr>
</tbody>
</table>

\(^a\)Proposed, but not certain.
The cytotoxic T lymphocyte response
Modulation of MHC I proteins
CTL escape mutants

- Herpes simplex virus
- Hepatitis C virus
Killing activated T cells

- When CTL engages an infected cell, the CTL may die instead of the target
- An example of viral defense
Reduced immune surveillance

- Cells and organs differ in degrees of immune defense
- CNS, vitreous humor of eye, areas of lymphoid drainage devoid of initiators and effectors of immune response
- Could be damaged by fluid accumulation, swelling, and ionic imbalances of inflammation
- Persistent infections of these tissues are common
Infection of immune cells

- Many viruses infect cells of the immune system
- HIV infection of CD4 T cells, monocytes, macrophages, dendritic cells
Measles virus

• *Paramyxoviridae*

• No known animal reservoir

• One of most contagious human viruses

• 158,000 deaths globally in 2011 - preventable

• Lifelong immunity after infection

• Causes systemic immunosuppression (Week 3, S2)
SSPE

- Subacute sclerosing panencephalitis, a progressive, degenerative encephalitis
- After measles, 1/million contract SSPE
- 6-8 yr incubation
- Viral nucleoprotein particles detected in brain, but no infections virus produced
- Genomes spread between synaptically connected neurons
Polyomavirus persistence

- Infected for life
- Variety of organs - kidney, intestine, respiratory tract
- 100,000 particles/ml in urine
- Unknown mechanisms of persistence
- PML
- TWiV #250 - Wookie viruses twiv.tv/2013/09/15/twiv-250-wookie-viruses/
Hepatitis B virus

- Transmitted by exposure to blood (childbirth, transfusion, sex, drug use, nosocomial)
- Main target is hepatocyte
- 95% of adults, 5-10% newborns resolve acute infection
Hepatitis B virus

- ~350 million worldwide have chronic HBV
- Transmission
- Hepatocellular carcinoma
Chronic HBV

- Virus is not cytopathic for hepatocytes
- CTL kill infected hepatocytes
- During chronic infection, fibrosis leads to cirrhosis, liver failure
- HCC develops after 20-30 yr of chronic (often asymptomatic) infection
Hepatitis C virus

- + strand RNA virus, *Flaviviridae*
- Transmitted by exposure to contaminated blood (sex, drug use), during birth
- 2.2% of human population (185 million) infected
HCV

- **Acute infection**: usually asymptomatic or typical signs of hepatitis

- **Chronic infection**: high level viremia

![Diagram of HCV infection outcomes]

- Acute infection: 60-85% chance of spontaneous resolution or progression to chronic infection
- Chronic infection: 5-20% chance of developing cirrhosis after 25 years, with an annual progression rate of ~7%
  - Cirrhosis leads to progressively worse liver function:
    - Slowly progressive liver failure
    - Decompensation
    - HCC (Hepatocellular Carcinoma)
HCV

- HCV clearance associated with IFN-λ3 alleles (GWAS)
- Multiple immune modulation mechanisms
Latent infections - general properties

- Viral gene products that promote productive replication are not made or found in low concentrations.
- Cells harboring the latent viral genome are poorly recognized by the immune system.
- Viral genome persists intact so that productive infection can be initiated to spread infection to new hosts.
State of the genome

- Non-replicating DNA in a dividing cell
  - HSV, VZV in neurons
- Autonomous self-replicating DNA in dividing cell
  - EBV, CMV, HPV, HBV, KSHV
- Integrated into host chromosome, replicates with host
  - Parvovirus, HHV6
HSV infections

• US >80% seropositive with genomes in PNS
• Millions carry latent viral genomes in nervous system without symptoms
• 40 million experience recurrent herpes disease
• HSV-1, HSV-2
• A well-adapted pathogen
HSV primary infection of ganglia

Sensory and sympathetic ganglia can be infected
• Viral genome silenced, coated with nucleosomes
• Multiple copies of episomal viral DNA remain in nucleus
• No further replication needed to persist - neurons do not divide
• Herpes is forever - drugs and vaccines cannot cure a latent infection
Latency associated transcript

- Only LATs, miRNAs made in latently infected neurons
- No proteins translated from LATs
- RNA silencing to maintain viral genome in latent state
- Host contribution
Reactivation

- Small number of neurons in ganglion reactivate
- Virions appear in mucosal tissue innervated by latently infected ganglia, blisters ensue (not always)
- This is how infection is transmitted (intimate contact)
- Immune response is too slow (viral antagonism) to prevent shedding
- Some reactivate every 2-3 weeks; others never
Triggers of reactivation

- Sunburn (UV), physical or emotional stress, nerve damage, hormonal imbalance, steroids
- Stimulate production of viral proteins needed to activate viral transcription program
- Immediate early proteins: ICP0 can reactivate
Epstein-Barr virus

- 95% of US adults are seropositive and carry genome
- Genome resides in B lymphocytes
- Most are infected at an early age, are asymptomatic
- Causal agent of:
  - Infectious mononucleosis
  - Human cancers (Hodgkins lymphoma, nasopharyngeal carcinoma, Burkitt’s lymphoma)
EBV primary and latent infection

- **Primary infection**
  - Saliva
  - Oropharynx
  - Epithelium
  - Dermis

- **Persistent infection**
  - Lymphoid tissue and peripheral blood

**Infectious mononucleosis**

- B cells are essential for EBV latency

- **EBNA-1**
  - Latently infected, resting memory B cells

- **EBNA**
  - Reactivated EBV-infected B cell

- **LMP-1**
  - EBV-infected B-cell clast

- **LMP-2**
  - EBV-infected B cell

**Blood vessel**

- Cytotoxic T cell
- Natural killer cell

**Resting B cell**

- EBV-infected B cell clast

**Lytic EBV-infected B cell**

EBV primary and latent infection

- EBV primary and latent infection

Principles of Virology, ASM Press
EBV latency

- Viral DNA is self-replicating episome, associates with nucleosomes in B cells
- Produces limited repertoire of viral genes
- B cells home to bone marrow and lymphoid organs
- Not killed by CTLs or antibody unless reactivation occurs (modulation of MHC)
When B cells divide?

- Episomal viral genome must replicate to be distributed to daughter cells
- EBV DNA has two origins of replication
  - Ori Lyt is used for lytic replication: high copy #
  - Ori P is used for episomal replication in latently infected cells: low copy #
Varicella-zoster virus (VZV)
VZV

- 99% adults infected pre-vaccine, 30% develop zoster, 2/3 >50 years of age
- Latency: Episomal viral DNA, 2-9 genomes in 1-7% of neurons
- Viral gene expression is restricted, IE, E, L genes
- Factors that trigger reactivation from neurons are unknown
Cytomegalovirus (HCMV)

- High seroprevalence (50-99%) globally
- Transmitted by respiratory routes (virus in saliva), urine, sex
- Replicates in peripheral blood leukocytes, endothelial cells
HCMV

- Persistent shedding of virus in saliva and urine for months to years
- Resolved by cellular immune response, but latently infected myeloid cells remain in bone marrow (precursors of monocytes, macrophages, dendritic cells)
- Risk of transmission during organ transplantation
- Virus crosses placenta, can cause congenital defects, death
HHV-6, HHV-7

- Agents of exanthem subitum, mild childhood rash (sixth disease)
- >85% of adults have antibody to both viruses
- Horizontal infection through respiratory secretions, parent to child
- Infects lymphoid, endothelial, liver, CNS, salivary cells
HHV-6 integration

- In some cell types viral DNA integrates into telomeres
- About 1% of transmission acquires HHV-6 via germline
- Plausible strategy for latency and transmission
Estimated burden of chronic viral infection in humans

Virus

Estimated number of infected individuals (millions)

HTLV1  HDV  HIV  Adenovirus  GBV-C  KSHV  HCV  Papilloma  HBV  HSV-2  HSV-1  AAV  Polyoma BK  Polyoma JC  CMV  EBV  VZV  HHV-6  HHV-7  Anellovirus  ERV