Persistent Infections

Lecture 17
Biology 4310
Virology
Spring 2020

Paralyze resistance with persistence
—WOODY HAYES
Acute vs persistent infections

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

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

**Latent**
- Herpes simplex virus types 1 and 2

**Persistent: asymptomatic**
- Lymphocytic choriomeningitis virus
- JC virus

**Persistent: pathogenic**
- Human immunodeficiency virus type 1
- Human T-lymphotropic virus
- Measles virus SSPE
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>Burkitt's lymphoma, Hodgkin's disease</td>
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<tr>
<td>Human cytomegalovirus</td>
<td>Kidneys, salivary gland, lymphocytes, macrophages, stem cells, stromal cells</td>
<td>Pneumonia, retinitis</td>
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<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>
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<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 inclusion body encephalitis</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Central nervous system</td>
<td>Progressive rubella panencephalitis</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Sensory ganglia</td>
<td>Zoster (shingles), postherpetic neuralgia</td>
</tr>
</tbody>
</table>

*Proposed but not certain.*
The cytotoxic T lymphocyte response
Modulation of MHC I system

Viral and cellular peptides

Ubiquitin-dependent proteolysis

Proteasome

Cytotoxic T lymphocyte

CD8

T cell receptor

Infected cell

Endoplasmic reticulum

Golgi apparatus

Lysosome

mCMV gp48

HIV Nef

mCMV m152

Adenovirus E3 gp 19kDa

hCMV US3

EBV EBNA-1

hCMV US6

hCMV US11, US2

β2-microglobin

MHC class I heavy chain

Group A adenoviruses
CTL escape mutants

- Herpes simplex virus
- Hepatitis C virus

Changes may also affect proteasomal processing
Killing activated T cells

- When CTL engages an infected cell, the CTL may die instead of the target
- An example of viral defense
- A normal cell process to limit immunopathology

HIV, CMV induce FasL on infected cell surface
• 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 (eye, high FasL)
• Could be damaged by fluid accumulation, swelling, and ionic imbalances of inflammation
• Persistent infections of these tissues are common
Persistence of Ebola Virus in Ocular Fluid during Convalescence


SUMMARY

Among the survivors of Ebola virus disease (EVD), complications that include uveitis can develop during convalescence, although the incidence and pathogenesis of EVD-associated uveitis are unknown. We describe a patient who recovered from EVD and was subsequently found to have severe unilateral uveitis during convalescence. Viable Zaire ebolavirus (EBOV) was detected in aqueous humor 14 weeks after the onset of EVD and 9 weeks after the clearance of viremia.
Infection of immune cells

- Many viruses infect cells of the immune system
- Measles virus infection of APCs
- HIV infection of CD4 T cells, monocytes, macrophages, dendritic cells
Which of the following are features of persistent infections?

A. They last the lifetime of the host  
B. Viral immune modulation is involved  
C. Immune cells may be infected  
D. They may occur in areas of reduced immune surveillance  
E. All of the above
Measles virus

- *Paramyxoviridae*
- One of most contagious human viruses
- 114,900 deaths globally in 2014 - preventable
- Lifelong immunity after infection
- A classic acute virus infection
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

**WuKipolyomavirus**

**Avipolyomavirus**

**Orthopolyomavirus**
Polyomavirus persistence

- Infected for life, high seropositivity in human populations
- Variety of organs - kidney, intestine, respiratory tract
- 100,000 particles/ml in urine
- Unknown mechanisms of persistence
- Progressive Multifocal Leukoencephalopathy (PML)
- TWiV #250 - Wookie viruses microbe.tv/twiv/twiv-250-wookie-viruses/
Hepatitis B virus

- Transmitted by exposure to blood (childbirth, transfusion, sex, drug use, tattooing, nosocomial)
- Main target is hepatocyte
- 95% of adults, 5-10% newborns resolve acute infection
VIRAL HEPATITIS B IN THE WORLD

- 257m Global
- 115m Western Pacific
- 60m Africa
- 39m South-East Asia
- 21m Eastern Mediterranean
- 15m Europe
- 7m Americas
Hepatitis B virus pathogenesis

A  Acute Hepatitis B

B  Chronic Hepatitis B

ALT = alanine transaminase
Chronic HBV

- Virus is not cytopathic (!) for hepatocytes
- CTL kill infected hepatocytes
- T cell exhaustion may lead to T cell dysfunction (persistence)
- 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, tattooing, during birth)
- 71 million infected globally
Persistence via multiple immune modulation mechanisms
Opioid crisis has led to increase in HCV infections in US
Go to:

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room number: virus

Which are shared features of persistent infections with polyomavirus, HBV, and HCV?

A. Genomes are present but not expressed
B. Liver damage
C. Kidney damage
D. Virus particles are produced
E. All of the above
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 non-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
  - HHV6
Herpes simplex virus 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
Often infected in utero or during birth (80% of babies)

Incubation 2-12 days

Primary infection usually inapparent, but can result in combinations of fever, sore throat, ulcerative and vesicular lesions, gingivostomatitis, edema, swollen lymph nodes, anorexia, malaise
Post-infection events in neurons

- 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
Trigeminal ganglion
Reactivation

- Sunburn (UV), physical or emotional stress, nerve damage, hormonal imbalance, steroids
- Stimulate production of viral proteins needed to activate viral transcription program
Neuronal stress
Kinase activation
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room number: virus

Persistence of herpes simplex virus in nerve ganglia requires which of the following?

A. Continuous episomal DNA replication
B. Low level production of virions
C. Silencing of all gene expression except LAT and miRNA
D. UV light, stress, or steroids
E. All of the above
Epstein-Barr virus

- 95% of US adults are seropositive and carry EBV 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

B cells are essential for EBV latency

Infectious mononucleosis
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)
Varicella-zoster virus (VZV)

Infection via conjunctiva and upper respiratory tract
Reproduction in primary lymph nodes
Primary viremia
Reproduction in liver, spleen, and other organs
Secondary viremia
Infection of skin and appearance of rash
Reactivation
Infection of sensory ganglia and establishment of latent infection
To central nervous system

Varicella (chickenpox)
Herpes zoster (shingles)
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 (non-replicating)
- 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

- Primary infection in immunocompetent host usually asymptomatic or febrile, mono-like illness
- 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)
HCMV

- Major problem in organ transplantation
- Virus crosses placenta, can cause severe multi-organ congenital defects, death

http://www.cdc.gov/cmv/trends-stats.html
What do persistent infections with EBV, VZV, and CMV have in common?

A. B cells are essential for latent infection
B. May cause congenital birth defects
C. Viral DNA persists as an episome
D. The factors governing reactivation are well known
E. All of the above
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
- Infect lymphoid, endothelial, liver, CNS, salivary cells
- Latency: HHV-6 monocytes, macrophages, CD34+ progenitors; HHV-7 CD4+ lymphocytes
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
Everyone

We each harbor 8-12 chronic infections
Next time: Transformation and oncogenesis