The Human Herpesviruses

- 8 Human Herpesviruses are currently known

- Herpes simplex virus-1 (HSV1) $\alpha$ (herpes, mostly facial)
- Herpes simplex virus-2 (HSV2) $\alpha$ (herpes, mostly genital)
- Varicella Zoster virus (VZV) $\alpha$ (chicken pox/shingles)
- Epstein-Barr virus (EBV) $\gamma$ (mononucleosis, Burkitts lymphoma)
- Cytomegalovirus (CMV) $\beta$ (childhood fever, mono)
- Human herpesvirus-6 (HHV-6) $\beta$ (roseola, rash)
- Human herpesvirus-7 (HHV-7) $\beta$ (roseola, no disease)
- Kaposi’s Sarcoma herpesvirus (KSHV) $\gamma$ (KS, B-cell lymphomas)

- Also called HHV-8

All herpesviruses have both lytic and latent phases and can cause disease in either phase
Many herpesviruses are common in the population

- HSV-1 70% * Kissing/direct skin contact
- HSV-2 20% Sexual transmission
- VZV 95% Saliva or skin
- EBV 95% Saliva
- CMV 85% Saliva, urine, semen
- HHV-6 95% Saliva
- HHV-7 95% Saliva
- KSHV 1-5% Blood, Saliva

*all of these %s are estimates or based on specific United States test populations

Because latency is always for the lifetime of the host-
You probably have 3-6 herpesviruses in you right now

Animal herpesviruses

- There are 100’s of known animal herpesviruses
  - They have been isolated from: Oyster, Catfish, Elephant, Pig, Snake, Penguin, Turkey, bald Eagle, frog, Salmon, goldfish, eel, Chicken, etc......

- Herpesvirus infections are important to the farm industry and zoos
  - Marek’s disease virus causes tumors in chickens and most chickens are vaccinated in this country
  - The Woodland park zoo lost a baby elephant to a herpesvirus infection and no longer keeps elephants

- Given the breadth of herpesvirus infection in the animal kingdom, did Herpesviruses speciate with animals?
Herpes Characteristics: Virion

- Icosahedral capsid
  - 120-260 nm
  - 150 hexons, 11 pentons and portal complex

- Enveloped
  - Multiple viral glycoproteins in the envelope

- There is a structure called tegument between capsid and envelope (matrix?) that contains approximately 20 different viral proteins

Herpesvirus Characteristics: Genome

- Large double stranded DNA genome 125-240 kbp

- Linear in virion but circularizes in the nucleus of infected cell

- Genome has long unique region(s) of genome flanked by repeats
  - KSHV has a single unique region with 20-40 terminal repeats
  - HSV1 and 2 has a unique long and unique short region both flanked by the two distinct repeats

- Genomes encode between 80 and 250 proteins
Herpesvirus Genes

• There are 41 genes conserved between alpha, beta and gamma herpesviruses in six conserved gene blocks
  • Structural proteins
    • Capsid proteins, tegument proteins, envelope glycoproteins
    • Assembly and nuclear egress proteins
  • Viral DNA replication
    • Pol, Helicase/primase, SSB, pol processivity
  • Nucleotide metabolism
    • Ribonucleotide reductase, Uracil-DNA glycosylase, dUTPase

• Other genes include immune evasion, regulatory and many other function specific to each family or each virus

• Gene expression is very compact
  • Many nested genes, many antisense genes, alternatively spliced genes
  • However, spliced genes are relatively rare in most herpesviruses

• Gene nomenclature is a hot mess!

HSV Gene Expression

• Immediate early genes—regulatory genes
  • VP16 activates I.E. genes
  • I.E. proteins are required for early and late gene synthesis

• Early genes—replication genes
  • Polymerase, helicase, ssb, etc….
  • Replication is required for true late gene synthesis

• Late genes—structural genes
  • Capsid proteins, glycoproteins, assembly proteins,
Viral Entry and I.E. expression

1. Extracellular space
2. Early transcription
3. Early mRNAs
4. I.E. Proteins
5. Late mRNA
6. Rolling Circle Replication
7. Late mRNA

Translate I.E. Proteins

VP16

Translate late proteins

Lytic Replication
Virion Production and Egress

- There are assembly sites in the nucleus
- Capsids bud into the intranuclear membrane
- Virus double envelopes and de-envelops through the golgi
- Virus buds from the cell
  - By fusion?

Three Genus of mammalian herpesviruses

- Alpha: (HSV-1, HSV-2, VZV)
  - rapid replication (6 hours)
  - neuronal latency
  - can cross species

- Beta: (CMV, HHV-6, HHV-7)
  - Slow replication (48+ hours)
  - latency in immune lineage cells
  - very tight species specificity even in cell culture

- Gamma: (EBV, KSHV)
  - rapid replication (6-12 hours),
  - latency in B and T cells as well as epithelial or endothelial cells,
  - species specificity
  - Gamma herpesviruses can be oncogenic

- These delineations have held up in the genomic era
Herpes Simplex Virus 1 and 2

- Facial or Genital sores
- Keratitis (eye disease)
- Encephalitis
- Herpetic whitlow
  - Needle sticks
- Disseminated sores in immunocompromised people and neonates

Spread of Herpes Simplex

- Kissing - direct contact not saliva (Generally HSV-1)
  - HSV infects the sub-cutaneous epithelial cells in the lip area (hence direct contact)
  - Wrestling (called herpes gladitorium)
- Sexual transmission - Genital herpes (Generally HSV-2)
  - Penile, vaginal and anal sores
- Finger cuts (herpetic whitlow)
- Vertical transmission
  - HSV-1 can be transmitted to newborn in the birth canal
  - Newborn will often be covered in sores and encephalitis is likely leading to permanent brain damage or death
  - Most common with primary infection, less so for reactivation since fetus with have maternal antibodies
  - Between 1 in 5000 and 1 in 20000 births in the U.S. have severe neonatal herpes infections
Herpes Simplex Pathogenesis

- HSV infects mucoepithelial cells and spreads cell to cell causing inflammation and cell death
- Single or multiple lesions form small ulcers (and can be painful)
- Virus is cleared from initial site of infection by adaptive immune response
- HSV infects the neurons around the epithelial cells and travels up the neuron
- HSV-1 and 2 establish latency in trigeminal or dorsal root ganglia
  - Trigeminal ganglia is bundle of sensory neurons that innervate the face, while dorsal root ganglia innervates the genitals
- Viral genome remains as an episome
  - (it does not integrate)
- Recurrent infection begins with tingling in the lip area and can lead to a similar disease in the similar region as the initial infection

Herpes Simplex Latency: LAT (Latency associated transcript)

- During latent infection HSV-1 and 2 express only a single long non-coding RNA (no protein)
  - LAT encodes microRNAs (small regulatory RNA)
  - microRNAs target expression of genes involved in apoptosis and other processes (goal: keep latently infected cell alive)
- Because no protein is made there are limited targets for T-cell responses to latently infected cells
  - However, T-cells respond during reactivation and likely shut down most virus reactivations
- Other herpesviruses that are latent in dividing cells make proteins to maintain the viral genome as an episome when cells divide
  - KSHV and EBV encode proteins during latency that tether the viral genome to the host genome
- There is epigenetic control of latent and lytic genes to maintain latency
Reactivation

- Stress, UV light, fever, hormonal changes, menstruation, can all induce HSV reactivation
  - The molecular signals that induce reactivation are poorly understood
- Virus initiates lytic replication in neurons
- Virions travel back down the neuron to the site of initial infection and spreads to other cells to cause a lesion
- Immune system then controls the lytic infection limiting the size of the sore
  - In immunocompromised patients sores can become very large and cover more of the skin
- Only a very small percentage of latently infected cells reactivate at any given time leaving many latently infected neurons for future reactivations
- "Unlike Love, Herpes is forever"

Encephalitis

- Rarely the virus reactivates and travels to the brain where it initiates lytic infection
- Since the brain is also an immunoprivileged site and the virus can replicate
- This can lead to herpes encephalitis
- Herpes encephalitis is deadly if untreated
  - It is treated with herpes simplex antivirals
Reactivation and Spread of Herpes Simplex Virus

• Most infections are asymptomatic
  • Of the 50-70% of the population that has HSV-1 a much lower percentage actually have clinically recognizable sores

• From studies at the Hutch and UW it was found regular sub-clinical shedding of HSV-2 even between clinical events

• Discordant couples study:
  • Long term study where one partner has genital herpes and the other does not
  • Taking valtrex (valacyclovir) every day decreases chance of passing herpes to partner
    • 14/743 versus 27/741 over 8 months
    • New England Journal of Medicine 2004 (L. Corey et. al)

• Therefore, earlier views on latency are somewhat incorrect as the virus reactivates much more often then once thought based on clinically overt disease

Treatment

• Antiviral chemotherapy
  • Primarily Acyclovir (Zovirax) a nucleoside analog
    Valtrex (valacyclovir) a pro-drug of acyclovir is now commonly used because it increases bio-availability of acyclovir
  • Acyclovir is phosphorylated by viral thymidine Kinase
  • It is then incorporated into DNA chains by viral polymerase
  • Incorporated Acyclovir terminates the ongoing DNA chain
  • Acyclovir has few or no side effects
  • Acyclovir works only on lytic virus

• There are other drugs that work in a similar fashion
  • HSV Valacyclovir, Penciclovir, Famciclovir, etc.
  • CMV Ganciclovir, Valganciclovir, Foscarnet, Cidofovir, etc.
There is only a vaccine for one human herpesviruses

• There is no vaccine for HSV-1 or 2
• There is a live attenuated vaccine “Oka” for VZV (the chicken pox vaccine)
  • given to infants (and seronegative adults)
  • The vaccine can cause very mild pox
  • A potential danger is creating a population of adults that in the long term future could be susceptible to chicken pox
    • However, boosters should handle this problem
  • Similar vaccine (called Zostavax) is used to prevent shingles (about 50% effective for people over 60), this acts as an immune boost to infected patients
    • This vaccine is actually just a higher dose vaccine as the actual chicken pox vaccine
    • A new sub-unit vaccine was recently approved to prevent shingles that appears to be more effective

Herpes B

• Herpes B is an alpha herpesvirus of Macaque monkeys
  • Closely related to HSV-1 and 2
• Zoonotic infections from Macaque monkeys in primate center where the bite of monkey can pass on virus
• Lethal consequences for humans: Virus often causes encephalitis in humans
  • Without aggressive antiviral therapy infected person will likely die
  • Approx. 2 dozen people have died from herpes B
• One documented case of human to human transmission (wife of animal care worker)
• Causes no major disease in monkeys! Example of evolving with natural host species
• The reverse is true for HSV-1
  • The LD$_{50}$ for HSV-1 in Aotus monkeys is approximately 10 pfu
Key points for herpesviruses

• Large enveloped double stranded DNA viruses that are ubiquitous in the human and animal population
• 8 human herpesviruses cause a variety of diseases
  • HSV-1 and 2 cause facial and genital sores and more rarely encephalitis
• Herpesviruses replicate in the nucleus by rolling circle replication using viral proteins
• All herpesviruses establish latency with minimal gene expression
• There are drugs that limit herpesvirus replication but no treatments for latent infection
• Herpesviruses have evolved with their hosts to limit disease and allow spread
  • However long term latency with some of the herpesviruses can lead to cancer (a lecture for another day)