1 Herpesviruses

Herpesviruses existed 250 million years ago (the age of pangaea)

Herpesviruses can be found in every mammal species, as well as some other host species

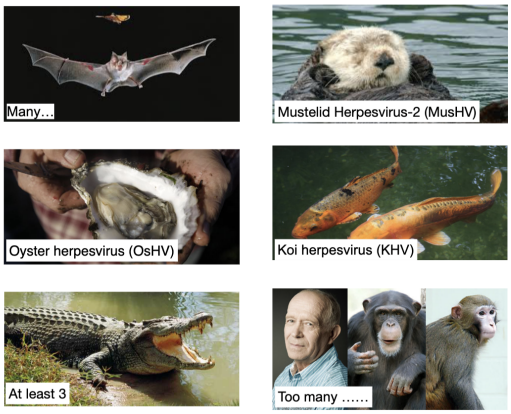

Figure 1: Herpesviruses are ubiquitous

1.1 Evolution

Herpesviruses are 'specialist' viruses

Most herpesviruses are extremely specialized to their specific host

Some herpesviruses have coevolved with their hosts

→ Ancient (50m years) HSV1 (Human Herpesvirus Simplex 1) still causes cold sores today

Some herpesviruses switch hosts

→ HSV2 (5m years) is specialized to humans and none of the other species in the same families

1.2 The Virion

1. Relatively large virus
2. Genome is made of DNA
3. Encode 70-200+ proteins

1.3 Generalities

Herpesviruses are successful pathogens and extremely well adapted to their hosts

Few or no clinical symptoms

High infection rates within their host population (generally 60-80%)

Infection is life-long

1.4 Modes of Life Cycle

Latency: Dormant (very little expression / no virions produced)

Lytic cycle: Reactivation (virions are made / cell death)

After primary infection, herpesviruses persist for life in a latent stage

1.4.1 Latent Stage

1. Upon infection, the viral DNA is transported to the nucleus where is circularizes

   Circular form is called an episome

2. The episome is maintained in the nucleus of the infected cell with minimal viral expression

1.4.2 Lytic Replication (Reactivation)

1. Maintenance of the viral reservoir in the host
2. Viral spread to new hosts
3. Not associated with disease, but may be accompanied by clinical symptoms
4. Stimuli leading to reactivation are not well understood

1.5 Evading Immune Response

Can evade both innate and adaptive immune response

Replication extremely quickly before cytotoxic T lymphocytes (CTLs) are activated

MHC-I molecules present viral peptides to CTLs

Viral protein 'hides' the MHC molecules in order to make the infected cell 'invisible'

A large fraction of their genome is dedicated to immune evasion

2 Human Herpesviruses

8 species from 3 subfamilies

Alpha Herpesviruses (Latency in neurons)

Herpes Simplex Virus 1 (HSV1) - 60%

Cold Sores

Herpes Simplex Virus 2 (HSV2) - 12%

Genital herpes

Varicella Zoster Virus (VSV) - 95% (Vaccine)

Chicken pox, Shingles

Beta Herpesviruses (Latency in CD34+ (Hematopoietic stem cells))

Cytomegalovirus (CMV) - >50%

Retinitis, Birth defect

Human Herpesvirus 6 (HHV6) - 90%

Roseola

Human Herpesvirus 7 (HHV7) 85%

Roseola

Gamma Herpesviruses (Latency in β cells (Antibody-secreting cells))

Epstein-Barr Virus (EBV) - 90%

Mono, Lymphoma, Carcinoma

Kaposi's Sarcoma Associated Herpesvirus (KSHV) - 10%

Sarcoma

Herpesviruses do not survive long outside a host (transmission usually requires intimate contact)

2.1 Human Cytomegalovirus (HCMV)

Seroprevalence is high worldwide

Virus is spread through bodily fluids, including blood, urine, saliva, breast milk, tears, semen, vaginal fluids

CMV infection is generally asymptomatic

Reactivation happens in episodes and is also generally asymptomatic

→ Individuals are unlikely to know that they have been infected or are shedding

2.1.1 Immunocompromised Patients

Includes people:

1. With acquired immune deficiency syndrome (AIDS)
2. Who have receinved chemotherapy, radiation therapy, or steroid therapy
3. Who have receinved an organ or bone marrow transplant

Serious symptoms affect the eyes, lungs, liver, esophagus, stomach, and intestines

In transplant patients, may cause graft disfunction or rejection

2.2 Congenital CMV

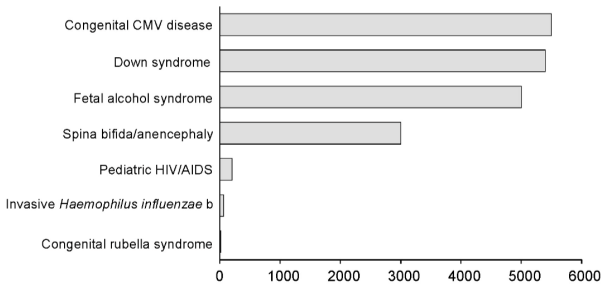

Figure 2: Relative burden of congenital CMV with relation to familiar congenital disorders

A pregnant woman can pass CMV to her fetus

1 in 150 babies are born with CMV

First children are less likely to have congenital CMV

10% are symptomatic and will develop long-lasting problems

90% are asymptomatic, some may still develop long-lasting problems

2.2.1 Outcomes of Symptomatic Congenital CMV Infection

1. Visual impairment
2. Brain abnormalities
3. Microcephaly
4. Hearing impairment
5. Premature birth / Low birth weight
6. Coordination disorders
7. Liver, lung, and spleen issues
8. Epilepsy

2.2.2 Ways to Help Prevent CMV

1. Do not share food, utensils, drinks, or straws
2. Do not put a pacifier in your mouth
3. Avoid contact with saliva
4. Do not share a toothbrush
5. Wash hands

2.3 Antiviral Drugs

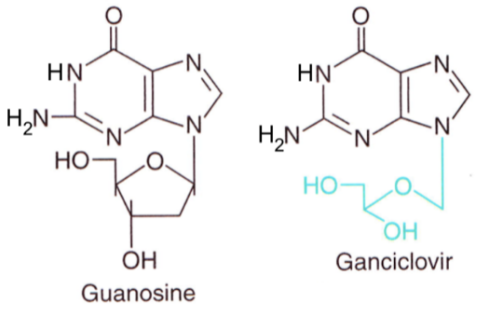

Figure 3: Antiviral drugs inhibit the viral polymerase (nucleoside analogs)

Drugs are given to immunosuppressed patients with active HCMV replication

May improve hearing and developmental outcomes for babies with signs of congenital CMV infection at birth

Can have serious side effects

2.4 Vaccine Development

CMV vaccine ranked as highest priority by the US Institute of Medicine

Primary population that could benefit are women of child-bearing age and transplant recipients (prior to transplantation)

Models suggest that vaccination of toddlers would offer strong indirect protection to women

3 Herpes Simplex Virus 1 and 2

HSV-1 causes sores around the mouth and lips (Can cause genetal herpes in 10-30% of cases)

HSV-2 causes sores around genitals and rectum (Can cause oral herpes in 5% of cases)

HSV also associated with recurrent eye infections and in rare cases encephalitis

3.1 Transmission

HSV is transmissible when areas of skin with the virus come into contact with mucous membranes (most common in mouth, vagina, and anus)

HSV-1 often spread through kissing or oral sex

HSV-2 often spread through vaginal, anal, or oral sex

3.2 Seroprevalence

3.7 billion people under age 50 has HSV-1

417 million people between ages 15 and 49 have HSV-2

3.3 Latency

Approximately 75% of patients with primary genital HSV infection are asymptomatic

Establishment:

1. Lytic replication in epithelial cells at the mucosal membrane
2. Viral capsid moves down the axon via retrograde transport
3. Latent HSV DNA in sensory neurons

Reactivation works in the opposite way as establishment and causes an recurrent infection at same site

Reactivation leads to shedding, transmission, and symptoms

Observed reactivation triggers:

1. Mestruation
2. Fatigue
3. Stress
4. Illness
5. Exposure to sunlight
6. Weakened immune system

Latency is established in the Trigeminal ganglia (TG)(HSV-1), and the lumbar and sacral dorsal root ganglia (DRG)(Primarily HSV-2)

Asymptomatic shedding is frequent

HSV-2 Shedding detected in $\sim$20% of days in symptomatic individuals and $\sim$10% of days in asymptomatic individuals

Most transmission events occur when individuals are asymptomatic

3.4 Drugs and Vaccine

Vaccine candidates are currently being evaluated:

1. For therapeutic purposes (reduction of viral shedding)
2. For preventive purposes (prevent infection)

Antiviral Drugs (Acyclovir, Valacyclovir, Famcyclovir) are nucleoside analogs

Only $\sim$50% reduction in transmission rate ($\sim$70-80% suppression of lesions)

3.5 Testing

Testing for genital herpes is recomended for people who have symptoms

1. Confirm infection
2. Learn about medications
3. Learn how to lower risk of spreading the infection

CDC recommends against screening asymptomatic people

1. Many false positives
2. Oral vs. genital herpes cannot be determined
3. No evidence that a blood test would change their sexual behavior
4. Risk of stigmatizing people outweighs health outcomes

4 Gamma Herpesviruses

4.1 Kaposi's Sarcoma

Before 1980s: Very rare disease found mainly in older men, patients who had organ transplants, or African men

More cases in the early 1980s in Africa and in gay men with AIDS

→ At the peak of the AIDS epidemic, 20% of men with AIDS developed KS

Discovery of HIV in 1983-1984 showed that AIDS is caused by a retroviral ablation of CD4+ T cells

4.1.1 Viral Spread

KS By 1990, scientists built a compelling case for KS being caused by a sexually transmitted infection in people with AIDS (but not by HIV)

More common if a person had contracted HIV through sexual contact (rather than another way, like blood transfusion)

Other groups of people with suppressed immune systems (such as transplant recipients) are also at risk

Very few agents are known to increase the risk of cancer by 100 times, let alone 20,000

Most well-known case is infection by hepatitis B virus causing liver cancer

→ Strengthened the case for KS being caused by infection

4.1.2 Discovery

Compared the DNA from healthy tissue against DNA from KS lesions

Led to discovery of KSHV or HHV8

4.2 EBV and KSHV

Eptein Barr virus and KSHV infections are usually asymptomatic but can sometimes cause cancers in infected cells

Epstein Barr virus:

1. Mononucleosis (kissing disease) (not a cancer)
2. Burkitt lymphoma (B-cells)
3. Nasopharynx Carcinoma (epithelial cells) (associated with smoked fish)

Kaposi's Sarcoma herpesvirus:

1. Primary effusion lymphoma (B-cells)
2. Kaposi's sarcoma (Endothelial cells)

4.3 Latency

Viruses need to tether their episomes to the DNA of the host, otherwise the episome would be lost during cell division

During latency, EBV encodes EBNA-1 and KSHV encodes LANA

Used to attatch viral episome to chromosomes

HSV-1 doesn't need this protein because neurons do not replicate

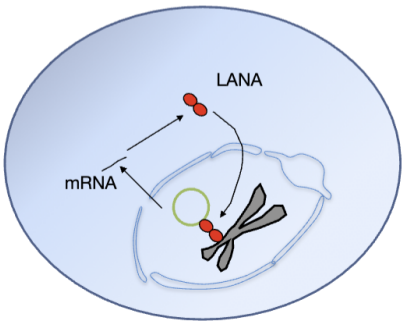

Figure 4: LANA protein

Required for:

1. Episome maintenance
2. Episome replication
3. 'Encouraging' cellular division (possibly the cause of cancers?)

    Allows for viral spread without reactivation