VZV, EBV, and HHV-6-8

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Common Features of Herpesviruses

- Morphology
- Basic mode of replication
- Primary infection followed by latency
- Ubiquitous
- Ability to cause **recurrent** infections (reactivation of latent virus), **reinfections** (with a new virus), **persistent** infections (chronic low grade virus multiplication) **immortalizing infections** (EBV only)

8 Human Herpesviruses, 3 categories

- **Alpha**: short reproductive cycle, variable host range, latent in sensory neurons
  - Herpes simplex virus (HSV 1, 2)
  - Varicella-zoster virus (VZV)
- **Beta**: long reproductive cycle, narrow host range, latent in lymphoid cells & others (salivary glands, kidney)
  - Cytomegalovirus (CMV)
  - HHV6, HHV 7
- **Gamma**: narrow host range; latent in lymphoid cells, associated with tumors
  - Epstein Barr Virus (EBV)
  - Kaposi Sarcoma Virus (KSH, HHV8)

**Human Herpesviruses**

- Replication (lytic infection) occurs in a cascade
  - Latency occurs when the cascade is interrupted
- Transcription of viral genome and protein synthesis (cascade of gene expression), essential and luxury
  - 1. immediate early (IE): regulation of gene expression, DNA binding
  - 2. early (E): more transcription factors, enzymes, DNA polymerase
  - 3. late (L): structural proteins
- Encode targets for antiviral therapy
  - TK, DNA polymerase

**The rash of VZV is vesicular.**

- Vesicular fluid is highly infectious.
  - Well-formed virions are suspended in it.

**Human Herpesvirus (VZV)**
phospholipid envelope, tegument, icosahedral capsid, DNA core
**Varicella-zoster virus**

- The smallest of the herpesviruses
  - 125,000 base pairs
  - 70 Open reading frames (ORFs)
- Receptors: heparan sulfate, mannose-6 phosphate receptor (MPR), insulin degrading enzyme (IDE)

**Hypothesis:** VZV latency is established by free virions that infect sensory nerve endings

**VZV**

- Receives Its Final Envelope in the TGN

**Steps in the assembly and intracellular transport of VZV**

**MPRs sort lysosomal enzymes and target them to endosomes**

**VZV spreads in two ways**
In the body VZV spreads from cell-to-cell

- In varicella, VZV is transported from the respiratory mucosa to the blood (viremia) in T cells, where virus is not accessible to antibodies.
  - Because cell-to-cell spread is slow, the incubation period of varicella is long (2 weeks).
  - Slow spread prevents host from being overwhelmed before the immune response develops
- T helper (Th1) and cytotoxic T cells are required for host control of virus

Zoster is initially localized.

- Limited to 1-3 dermatomes.
- May disseminate in immunocompromised hosts.

Natural History of VZV

- **Primary infection: varicella**
  - Highly contagious (airborne)
  - Complications: bacterial superinfection, encephalitis, pneumonia, congenital syndrome
- **Secondary infection: zoster**
- Zoster is due to reactivation of latent VZV
  - DNA, RNA, proteins in ganglia at autopsy
  - Zoster in a few vaccinees caused by Oka vaccine
  - From low cell-mediated immunity (CMI) to VZV
- No asymptomatic shedding of VZV as with HSV

Varicella is a generalized illness. Infectious virions are produced in the skin vesicles.

Congenital varicella syndrome
**Fatal neonatal varicella**

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**Latent Infection with VZV**
- Latent infection in dorsal root ganglia (DRG)
- 6 of 68 genes (also RNA and proteins) expressed during latency
- Proteins of regulatory genes are expressed in cell cytoplasm, not nucleus
- Suggests regulatory proteins are blocked from normal action, leading to inhibition of cascade of gene expression preventing lytic infection from occurring (latency)
- Latency is established when cell-free VZV in skin vesicles invades neurons

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**Varicella Vaccine**
- Only herpesvirus for which there is a vaccine
- Live, attenuated, infectious virus (Oka strain)
- Licensed for routine use in healthy susceptible individuals in US, in 1995
- Recently there has been a marked decrease in varicella, in all age groups
  - Indicates herd immunity
- Contraindications: pregnancy, immunocompromised, allergy to vaccine components

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**VZV In the Immunocompromised**
- Varicella is likely to be severe
  - Prevent or modify with pre-formed antibodies just after exposure
  - Virus spreads from cell-cell in body
    - Requires CMI (cellular immunity) for host defense
  - Treat most immunocompromised patients immediately with acyclovir
- The frequency of zoster is increased
  - Probably related to low CMI response
  - Likely to suffer post-herpetic neuralgia (PHN) (also elderly)

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**Varicella Vaccine**
- Live attenuated; stimulates primary immunity
- Major complaint afterwards: mild rash in 5%
  - 1 month after vaccination; transmission is rare
  - Vaccine is extremely safe
- 85% completely protected; 15% partial immunity
- There is little evidence for waning immunity
- Subsequent zoster is rare
- Same vaccine (much higher dose) also used successfully to prevent zoster in the elderly (different mechanism of action… stimulates CMI to VZV)
The rash of VZV is vesicular.

- Vesicular fluid is highly infectious.
  - Well-formed virions are suspended in it.

Acyclovir (ACV) is useful to treat HSV, VZV

- Antiviral activity only in infected cells (TK)
- Sensitivity: HSV1, >HSV2, >VZV (EBV, CMV)
- Toxicity is unusual: gastrointestinal, neurologic (headache, seizures, delirium); anemia, thrombocytopenia, bone marrow suppression
- Resistance is a concern, especially in HIV-infected patients
- Newer drugs: famciclovir, valacyclovir
  - Administered orally and less frequently than ACV because better gastrointestinal absorption

Epstein-Barr Infections (EBV)

- Infectious mononucleosis, nasopharyngeal carcinoma, lymphomas (including Burkitt’s), oral hairy leukoplakia (lytic infection), X-linked proliferative disease (males only)
- B cells are latently infected in mononucleosis; T cells (atypical lymphocytes) are the host response
- Latency develops in memory B cells
- EBV is not related to chronic fatigue syndrome, but rarely severe chronic illness follows mononucleosis
- In mononucleosis, give steroids if airway obstruction, hemolytic anemia, severe cardiac, neurologic disease (no specific antiviral therapy)

Laboratory Methods for Diagnosis

- Culture (difficult), DFA, PCR, cytology on skin rash (Tzanck)
  - Can distinguish the Oka virus from wild type virus (PCR)
- Antibody titers, IgG (ELISA)
  - Acute serum, early in illness
  - Convalescent serum, 10-14 days after onset
- Antibody titers, IgM
  - False positives and false negatives can be a problem
Diagnosis of Mononucleosis

- Usually occurs in young adults
- Symptoms, signs: fever, adenopathy, exudative pharyngitis, rash (ampicillin) hepatosplenomegaly, fatigue
- Positive heterophile antibody (monospot)
- EBV specific antibodies
  - Anti VCA (develops early, persists)
  - Anti EBNA (develops late, persists)
  - Positive aby VCA, neg aby EBNA = acute mononucleosis

Herpesviruses 6, 7

- Herpesvirus 6 (beta, like CMV)
  - Roseola in infants (rash, fever, seizures)
  - Outcome of latency in CNS not understood
  - Fevers in immunosuppressed
  - Rare mononucleosis syndrome in adults
- Herpesvirus 7 (beta, like CMV)
  - Fevers in immunocompromised (HIV)
- Diagnosis, treatment are not fully developed
  - Most infections are self-limited

Herpesvirus 8 (KHSV)

- Closely related to EBV
- Encodes for human proteins (piracy)
  - IL-6, Bcl-2 (anti-apoptosis), chemokines
  - Infections are rare in children
  - Can cause non-specific fever and rash illness
- Causes Kaposi’s Sarcoma
  - Elderly
  - HIV-infected
- Causes primary-effusion lymphoma
- Castleman’s disease (lymphoma-like)

Summary: Herpesvirus Infections

- Particularly affect newborns, elderly, immunocompromised
  - Congenital (CMV, VZV) vs neonatal (HSV, VZV); primary maternal infections high risk
- Primary, latent, recurrent, reinfections
- Best diagnostic tool: PCR
- Antiviral therapy: HSV, VZV, CMV
- EBV and HHV8 cause tumors
- Vaccine now available against to prevent chickenpox (varicella) and zoster (shingles)