

Herpesviruses

Reading: Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapters 41 & 42.

I. **Overview/Classification.** The members of the herpesvirus family are large, DNA-containing, enveloped viruses. Nearly 80 known Herpesviruses infect a wide range of species from oysters to humans. A hallmark of herpesviruses is that they cause a lifelong latent infection in their natural hosts. The dynamics of latency, and the ability to subsequently reactivate, depends on multiple factors dictated by the genetics of the individual subfamily of virus and the physiology of the host. There are 8 herpesviruses that infect humans, and these are divided into three subfamilies (alpha, beta and gamma herpesviruses) based largely on the type of cells they infect, and whether they are able to induce cell proliferation. This family is comprised of members that cause chicken pox, fever blisters, genital herpes, infectious mononucleosis, shingles, and a number of ocular infections.

A. *Alphaherpesvirinae*. Fast growing, cytolytic viruses. Characterized by ability to establish latency in neurons. Subdivided into two genera:

1. *Simplexvirus*
 - a) Herpes simplex virus 1 (oral herpes)
 - b) Herpes simplex virus 2 (genital herpes)
2. *Varicellovirus*
 - a) Varicella-zoster virus (chickenpox, shingles)

B. *Betaherpesvirinae*. Slow growing, cytomegalic. Characterized by latency in lymphocytes. This family is subdivided into two genera:

1. *Cytomegalovirus*
 - a) Cytomegalovirus (microcephaly, infectious mono)
2. *Roseolovirus*
 - a) Human Herpesvirus 6 (Roseola Infantum)
 - b) Human Herpesvirus 7 (Roseola Infantum)

C. *Gammaherpesvirinae*. Characterized by latency in B and T lymphocytes and the ability to induce lymphoproliferation. This family is subdivided into two genera:

1. *Lymphocryptovirus*
 - a) Epstein-Barr virus (Infectious mononucleosis*)
2. *Rhadinovirus*
 - a) Human Herpesvirus 8 (Kaposi's Sarcoma Associated Virus)

II. Biologic properties/virion structure/genome

A. Biologic properties

1. Virion stability

- a. sensitive to dessication (do not survive long on hard surfaces)
- b. easily inactivated by detergents and lipid solvents

B. Virion structure

1. enveloped spherical virion;
2. icosahedral capsid, 120 - 200 nm in diameter
3. envelope is studded with 10 - 14 virally encoded glycoproteins.
4. Space between envelope and capsid is filled with amorphous combination of proteins termed "tegument". These proteins are important for initiation of the viral infection,

C. Genome structure

1. linear double-stranded DNA, 120 – 230 kb in length. This large genome implies genetic complexity and ability to encode multiple functions, greater independence from host processes, and more viral targets for antiviral therapy.
2. genomes comprised of one or more repeated regions. In genomes with more than one repeat, multiple isomers are present.

D. Replication

1. Penetration by fusion with the plasma membrane
2. Replication occurs in the nucleus
3. The 80 or so viral genes are expressed in a regulated cascade:
 - a) Immediate early (IE) genes are transcribed by the host polymerase
 - b) The IE genes activate Early (E) genes which facilitate viral replication.
 - c) The Late (L) genes are comprised of mainly structural proteins.
4. Capsids assemble in the nucleus and bud through the nuclear membrane.
5. The capsid is enveloped via the golgi after which the mature virion exits the cell via exocytosis.

E. Latent Infection

1. Viral DNA maintained in latently infected cells as an extrachromosomal episome (circle).
2. Latently infected cells do not contain virions, just viral DNA, and viral gene transcription is extremely limited.
3. Mechanism of establishment and maintenance of latency poorly understood, but seems to be controlled in a cell-type specific manner.
4. Various "stressors" can stimulate some latently infected cells to reactivate. Stressors include emotional stress, trauma, cold, sunlight, fever, menstrual cycle, immunosuppression.

III. Diseases and Clinical Syndromes

A. HHV-1 (HSV-1)

1. Transmission by direct contact
2. Primary infection of oral mucosa
3. Infection extremely widespread: >80% of adults seropositive; mostly inapparent.
4. Acute symptomatic primary infection (herpetic gingivostomatitis) in 10 – 15% of primary infections.
5. Life-long latency established in trigeminal ganglia.
6. Recurrent infections generally appear near site of primary infection.
7. Immunosuppression can cause disseminated disease.
8. Rare complications include encephalitis, and keratitis and stromal disease of the eye (and occur in otherwise healthy individuals).

B. HHV-2 (HSV-2)

1. Transmission by sexual contact
2. Primary infection of genital mucosa
3. Estimated infection rate of 20% in U.S.
4. Lifelong latency established in sacral ganglia
5. Recurrent infection near site of primary infection.
 - a) often more painful and more frequent than HSV-1 reactivations
6. Neonatal infections (infection of eyes acquired during birth) are often lethal (75% mortality).

C. HHV-3 (varicella-zoster)

1. Extremely widespread
2. Respiratory infection, replication locally and in lymph nodes, viremia, dissemination to skin and internal organs
3. Lifelong latency established in ganglionic nerve cells.
4. Infrequent reactivation (herpes zoster).

D. HHV-4 (Epstein-Barr Virus; EBV)

1. Extremely widespread (90% of population), usually inapparent
2. Transmission by direct contact with saliva.
3. Replication in local epithelium.
4. Life-long latency in B lymphocytes.
5. Can cause infectious mononucleosis.
6. Associated with Burkitt's lymphoma and nasopharyngeal carcinoma

E. HHV-5 (Cytomegalovirus; CMV)

1. Infection widespread (80% of adults), largely inapparent
2. Transmission by transplacental passage, infection at birth, nursing, blood transfusion, sexual contact.
3. Clinical neonatal disease in 0.1% of births.
 - a) high mortality (30%)
 - b) congenital abnormalities and neurological damage

4. Mononucleosis
5. Immunosuppression can cause disseminated disease; problem in organ transplant recipients.
6. CMV retinitis is a leading cause of blindness in patients with AIDS

F. HHV-6 & 7

1. Roseola infantum (also known as exanthem subitum or sixth disease)
2. Infection widespread, largely inapparent
3. Generally occurs during first year of life

G. HHV-8 (Kaposi's sarcoma associated virus)

1. The etiologic agent of Kaposi's sarcoma
2. Infections primarily associated with high-risk sexual practices.
3. Virus encodes a number of growth factors and anti-apoptotic proteins

IV. Treatment/Vaccines

A. Antivirals

1. Acycloguanosine and its derivatives are effective in restricting herpesvirus replication
 - a) palliative, not curative
 - b) high therapeutic index results from specificity for viral thymidine kinase (TK) and viral DNA polymerase in concert.
 - i. acyclovir must be phosphorylated by the viral TK in order to interact with the viral DNA polymerase
 - ii. phosphorylated acyclovir is a chain terminator
 - c) resistant mutants do occur
2. Foscarnet is active against CMV

B. Vaccines

1. an effective live, attenuated vaccine is available for VZV
 - a) does not provide lifelong immunity
 - b) must be used with care in immunocompromised
2. no vaccines for other herpesviruses have yet been approved.
3. Impossible to prevent latent infections?