

Human Herpesvirus Infections

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There are eight known human herpesviruses, of which seven cause defined disease syndromes. Six of these, herpes simplex virus (HSV-1, HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8), will be covered in this lecture. Human herpesviruses have co-evolved with humans over a very long period of time. Although all the viruses discussed here can cause serious and even fatal disease, the majority of infected humans never develop serious disease or have recurrent benign disease. This may be attributed to the ability of the viruses to maintain a persistent infection that does not, in general, adversely affect the host to a great degree.

Characteristics of herpesviruses

- 1) Persistence
- 2) Latency
- 3) Reactivation
- 4) Tissue tropism

However, the very characteristics that allow successful persistent infection and spread among the population also allow these viruses to cause disease when something goes wrong. This can be a genetic defect, a weakening of the immune system, a secondary oncogenic event, such as a chromosomal translocation, or other environmental factors.

There are several characteristic differences between the various types of herpesviruses. In general, the alphaherpesviruses cause disease during the lytic phase of their replication, during which they cause damage to the infected cell. The betaherpes viruses also cause disease during lytic replication. EBV and KSHV are transforming viruses and may cause disease via abnormal proliferation of the infected cells.

Classification of herpesviruses

- **Alphaherpesviruses**
 - HSV-1 and HSV-2
 - Varicella-zoster virus (VZV)
- **Betaherpesviruses**
 - Cytomegalovirus (CMV)
 - HHV-6 and HHV-7
- **Gammaherpesviruses**
 - Epstein-Barr Virus
 - Kaposi's sarcoma-associated herpesvirus (KSHV,HHV-8)

The sites of latency and tissue tropism of the different herpesviruses is also distinctive and is related to the types of disease which they cause. For example, EBV infects B lymphocytes and is associated with several types of lymphoma and lymphoproliferative syndromes.

Cell types infected by different herpesviruses

- **VZV and HSV**
 - Epithelial cells and neurons
- **CMV**
 - Ductal epithelium, leukocytes
- **EBV**
 - Oropharyngeal epithelium, B lymphocytes
- **KSHV**
 - Endothelium, B cells

Other Characteristics of Herpesvirus Subfamilies

Alphaherpesvirinae

- Variable host range (cross species)
- Short reproductive cycle
- Destruction of infected cells (e.g. skin)
- Latency in neural sensory ganglia
- Rapid spread in culture

Betaherpesvirinae

- Restricted host range
- Long reproductive cycle
- Slow progression in culture
- Cytomegalic changes
- Infect many tissues (neutrophils, liver , colonic epithelium, kidney)
- Latency in many tissues

Gammaherpesvirinae

- Restricted host range
- Infect lymphocytes
 - EBV - B cells
 - KSHV- B cells, endothelial cells
- Some replication in epithelial cells
- Latency in lymphocytes
- Little infectious virus produced

Herpes simplex virus is a ubiquitous virus that infects greater than 95% of the adult population (HSV-1) and to varying degrees in the case of HSV-2, depending on the population studied. There are many manifestations of HSV infection in addition to the common cold sore or fever blister. The more common are listed below.

Infections caused by HSV-1 and HSV-2

Herpes labialis
Genital herpes
Herpes gladiatorum
Herpetic whitlow
Eczema herpeticum
Congenital HSV infection
Herpetic gingivostomatitis
Disseminated infections
 Pneumonia
 Esophagitis
 Hepatitis
Chronic and resistant infections
"B" virus (Herpesvirus simiae) HSV of primates

Infections caused by CMV

Mononucleosis
Congenital infection
Immunocompromised
 Pneumonitis
 Retinitis
 Colitis
 Esophagitis
 Oral ulcers
 Hepatitis
 Systemic syndromes

Epstein Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus are gammaherpesviruses of humans that play an etiologic role in the development of a variety of hematologic disorders. Infection with both viruses occurs worldwide. EBV infection is ubiquitous and its prevalence approaches a hundred percent in most adult populations. Both viruses establish persistent latent infection in lymphocytes that is usually benign. However, in the presence of other environmental, genetic and iatrogenic cofactors, EBV or KSHV infection is associated with the development of a variety of lymphoproliferative diseases and lymphoma. In addition, EBV is associated with nasopharyngeal carcinoma and a proliferative disease of the oral epithelium known as oral hairy leukoplakia in immunosuppressed patients, as well as some cases of gastric carcinoma, all epithelial malignancies or disorders. Similarly, KSHV is associated with a malignancy of endothelial origin, Kaposi's sarcoma.

The characteristics of these viruses that enable them to cause malignancies are closely related to the same properties that enable them to carry out their strategy of lifelong persistence.

Properties of transforming herpesviruses

- **Encode genes that enable them to:**
 - Drive infected cell proliferation
 - Prevent apoptosis of infected cells
 - Avoid immune attack
 - Infect new cells

EBV-associated diseases

- Burkitt's lymphoma
- Post-transplant lymphomas
- Hodgkin's disease
- Nasopharyngeal carcinoma
- Oral hairy leukoplakia
- Gastric carcinoma
- AIDS-associated lymphomas

The diseases caused by KSHV, particularly Multicentric Castleman's disease (MCD) and KS, may not be classic virally transformed malignancies. That is, these diseases may be, at least initially, an oligoclonal proliferation of infected and uninfected cells which are driven not just by virus-encoded oncogenes but also by secreted viral products. Some KSHV-infected cells secrete homologs of cellular cytokines such as viral interleukin 6, which act as growth signals for nearby cells. This is a different paradigm for viral oncogenesis.

KSHV- associated diseases

Kaposi's sarcoma

Multicentric Castleman's disease

Primary effusion lymphoma