

Common Characteristics and Distinct Features of Human Pathogenic Herpesviruses

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1.1 Hallmarks of Herpesvirus Infections

The members of the family of the *herpesviridae* are phylogenetically very old viruses that co-evolved over millions of years with their hosts. Depending on the type of the target cell that is entered by the virion, herpesviruses can take two different paths of infection. Virus progeny is generated only in productively infected cells. This type of infection is associated with host cell lysis. In contrast, other cells repress lytic viral gene expression and preserve the herpesviral genome for a very long time, a state that is called latency. However, herpesvirus latency can be reversed to a productive infection mode, i. e., the herpesviral genome replicates and produces an infectious virus. These basic principles of herpesvirus biology imply that: 1) herpesvirus *disease* manifestations must be distinguished from herpesvirus *infection*, 2) diseases can occur already during primary replication, but also a long time after primary infection as a result of virus reactivation, and 3) recurrent disease manifestations can occur due to the lifelong infection.

This chapter very briefly introduces the nature of herpesviruses and their life-style. It concentrates on those family members of the human herpesviruses (HHV) that cause severe herpetic eye diseases.

1.2 Virus Taxonomy and Herpesviral Subfamilies

The membership in the family is based on the common architecture of the virion (comprising an icosahedral capsid surrounding the core, a largely unstructured tegument, and an outer lipid bilayer envelope) and a double-stranded DNA genome ranging from 124 to 235 kbp. To date, nine distinct members of the *herpesviridae* have been known to cause infection in humans as their natural hosts (see Table 1.1), which are subdivided into three subfamilies, *alpha*, *beta*, and *gamma*. Based on these criteria, remarkably divergent viruses have been included in the herpesvirus family. While the *alpha herpesviridae* are

Table 1.1 Human pathogenic herpesviruses

Designation	Synonym	Abbreviation	Genome size (Kbp)	Subfamily	Site of latency
Human HV1	Herpes simplex virus 1	HSV-1	152	α	Sensory neurons in ganglia (e.g. ganglion trigeminale Gasseri)
Human HV2	Herpes simplex virus 2	HSV-2	155	α	Sensory neurons in ganglia (e.g. sacral and vagal ganglia)
Human HV3	Varicella zoster virus	VZV	125	α	Dorsal root ganglia neurons, trigeminal ganglia neurons, ganglia of the autonomic nervous system
Human HV4	Epstein-Barr virus	EBV	172	$\gamma 1$	Memory B lymphocyte
Human HV5	Cytomegalovirus	CMV	235	β	CD34 + hematopoietic stem cell
Human HV6A	HHV-6 variant A	HHV-6A	170	β	CD34 + hematopoietic stem cell, monocytes?
Human HV6B	HHV-6 variant B	HHV-6B	168	β	CD34 + hematopoietic stem cell, monocytes?
Human HV7		HHV-7	145	β	CD4 + T lymphocytes ?
Human HV8	Kaposi's sarcoma associated HV	HHV-8	210	$\gamma 2$	B lymphocyte

usually neuroinvasive, the beta subfamily members display a broader cell tropism that includes myelomonocytic cells, while the gamma herpesviruses are typically lymphotropic.

1.3 General Themes of Human Herpesvirus Infections

Besides the virion structure and the length of the dsDNA genomes, human herpesviruses share further biological characteristics, which are important for the understanding of their infection and disease.

Latency and recurrent infection: Upon primary infection, herpesviruses invariably establish a lifelong latent state of infection in a specific type of target cell. Latent viral genomes persist as closed circular episomal DNA in the nucleus as long as lytic gene expression is repressed, i.e., no infectious virus can be recovered from latently infected tissue. Latent genomes are transcriptionally active by expressing a limited set of genes, but they become periodically reactivated for transcribing lytic genes and producing infectious progeny which then spreads from cell to cell. Recurrences occur in the presence of both cell-mediated and humoral immune responses (i.e., antibodies). Depending on the particular herpesvirus, conditions of the host and the site of virus shedding reactivation events can occur without clinical symptoms but also lead to disease. The herpesvirus produced during the reactivation episode can be transmitted to a new host which becomes primary or super-infected.

Gene expression: During productive (lytic) infection, herpesviral genes are transcribed in a temporal order and assigned to three distinct classes, i.e., *immediate early*, *early*, and *late*. Depending on the particular virus, one herpesviral replication cycle takes between 20 and 100 hours. The transcriptional program of the host cell becomes completely altered or even shut off during productive herpesvirus infection.

Cell lysis: In most tissues, virus replication is lytic, i.e., it is accompanied by the destruction of the infected cell.

Immune control: The latent state and replication of the herpesviruses are controlled by cellular immunity. Of particular importance are cytotoxic CD8⁺ T lymphocytes, cytokine-producing CD4⁺ T lymphocytes, as well as natural killer (NK) cells. Accordingly, immunocompromised patients lacking effective cell-mediated immune defence are prone to frequent and extensive phases of reactivation that often lead to overt disease.

Immune evasion: The herpesviruses are equipped with many genes that subvert immunity. Generally, T cell recognition, NK cell recognition, interferon responses, and apoptosis of infected cells are avoided by all herpesviruses. Moreover, the β - and γ -viruses have acquired former host genes ("molecular piracy"), which modify the immune response. Among these are cytokines like CMV-encoded and EBV-encoded IL-10 that down-regulate antiviral immune responses and inflammation. Moreover, the β -herpes subfamily expresses chemokines as well as chemokine receptors that exploit the host immune response: virus-encoded chemokine-receptors mediate chemotaxis and promote the spread of infected cells.

Characteristics of Human Pathogenic Herpesviruses

Enzymes involved in nucleic acid metabolism: To achieve a high yield of genome replication, the herpesviruses express virus-specific arrays of enzymes that support DNA synthesis, such as thymidine kinases, ribonucleotide reductases, and DNA polymerases. Such enzymes allow for the therapeutic inhibition of viral replication by antiviral drugs.

1.4 Distinct Features of Human Herpesviruses

Human pathogenic herpesviruses also differ in many regards, and some of these private features account for the virus-specific pathogenesis and disease pattern. These properties include the attachment of HHV virions to target cell receptors and the host cell tropism of infection. In addition, the site of latency, the pattern of reactivation, and the spread of recurrent infection critically determine the clinical picture of herpesvirus diseases. The alpha-herpesviruses HSV and VZV target neuronal ganglion cells as a site of latency and are competent for trans-neuronal spread during the primary and recurrent phase of infection. Despite sharing neuroinvasiveness as a unique property, the frequency of reactivation events between both viruses differs considerably (see Fig. 1.1). The unequal reactivation events of HSV and VZV have direct consequences for boosting of antiviral immunity. The higher frequency of reactivation events by HSV results in efficient *endogenous* boosting that maintains immune memory. In contrast, efficient boosting of VZV-specific memory responses relies to a larger extent on exposure with *exogenous* VZV (i.e., household contacts of children undergoing varicella). Waning of VZV-immunity over a life-time leads to increased risk of herpes zoster.

Detailed analysis of Fig. 1.1

In some children, primary HSV-1 infection presents itself as herpetic gingivostomatitis, but does not cause clinical symptoms in the majority of infected individuals (semicircle with checker board pattern). Primary replication is followed by intermittent phases of latent and reactivated HSV infection. Reactivation events are frequent and can occur without clinical manifestations (white semicircles) or cause disease, e.g., herpetic keratitis (blue semicircles). Primary VZV replication results in chickenpox in almost all patients (blue semicircles), followed by usually only one episode of recurrent VZV infection. In most cases, recurrent VZV replication involves the skin (e.g., as zoster ophthalmicus), but can also present as disease without skin manifestation (zoster sine herpette). *x-axis: time; y-axis: amount of infectious virus progeny produced.*

Finally, there is still preliminary but growing evidence supporting the notion that genetic variabilities within most or even all of the members of the HHV substantially contribute to the development and manifestation of specific herpesviral diseases.

Some of the virus-specific features of those HHV which are implicated in herpetic eye diseases are described below, i.e., HSV-1/2, VZV, CMV, and EBV.

Cell tropism and virus spreading

HSV-1/2: Virion attachment and virus entry are mediated by a number of viral glycoproteins, specifically the cell surface

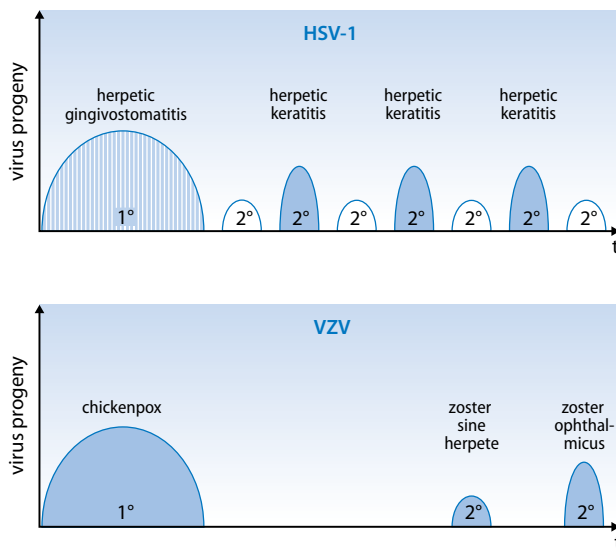


Fig. 1.1 Typical pattern of latent and productive infection of Herpes simplex virus 1 (HSV-1, *top panel*) and varicella zoster virus (VZV, *lower panel*) in the immunocompetent host

molecules nectin-1, the herpes virus entry mediator (HVEM, a member of the tumor necrosis factor receptor family), and 3-O-sulfated heparan sulfates. HSV shows a strong tropism to neuronal cells, but also lymphocytes, endothelial cells, fibroblasts, and epithelial cells of the skin and mucosa. Following local spread in the tissue at the primary site of infection, HSV enters sensory neurons by fusion at the axonal termini. The nucleocapsid of the virus is carried by retrograde axonal transport along microtubules to the nucleus in the cell body of the neuron.

VZV: Insulin degrading enzyme (IDE) was identified as a cellular receptor of cell-free as well as cell-associated VZV binding to the glycoprotein, gE, of the virion. VZV has a similar tropism to HSV, which includes neurons, lymphocytes, fibroblasts, and epithelial cells of the skin and mucosa. Unlike other herpesvirus infections, primary infection with VZV, varicella, is contracted by inhalation of infectious aerosol. Based on its particular tropism for T lymphocytes, the virus has established a cell-associated viremia. Thus, VZV can access neurons either hematogenously or by centripetal neural transport after entry at axonal termini in mucocutaneous lesions.

CMV: CMV usually enters the body via mucosal sites. Virion entry involves $\beta 1$ integrin expression on target cells. Upon local replication in epithelial cells, fibroblasts, and smooth muscle cells, the virus spreads to endothelial cells. Detached endothelial cells establish cell-associated viremia to visceral organs and the bone marrow. There, infection of stroma cells and cells of the myelomonocytic lineage occurs, including megacaryocytes and CD34+ CD38-hematopoietic progenitor cells, where CMV establishes a latent state of infection. Remarkably, CMV displays a pronounced tropism to retinal pigment epithelial cells in vitro.

EBV: The virus binds via its outer envelope glycoprotein gp350/220 to CD21, which is also the receptor for the C3d

component of complement. Major histocompatibility class II molecules represent a further entry receptor used by the virus. EBV entry to B lymphocytes is thought to differ from entry to polarized epithelial cells. The EBV integral membrane protein, BMRF2, which binds to $5\beta 1$ integrin, is implicated in this process. Oral and lingual epithelium is likely to be the primary target of orally transmitted virus. In parallel, EBV colonization of the B lymphocyte pool takes place, where latent EBV genomes are found in the CD27+ B cell memory subset at a low frequency of approx. 10^{-5} infected cells. Colonization of the B cell pool is necessary and sufficient for EBV persistence. EBV genome carrying B cells have the capacity to seed throughout the lymphoid system and to migrate back to oropharyngeal sites. Primary (i.e., infectious mononucleosis) and latent EBV infection is under strict control of antiviral T cells recognizing latent and lytic antigens, respectively.

Latency and reactivation patterns

HSV-1/2: In a fraction of infected neurons of a ganglion which harbor 10 to 30 copies of latent HSV genomes per cell, productive infection becomes periodically reactivated. Nucleocapsids are carried by anterograde axonal transport along microtubules to axon terminals where the egress of enveloped infectious particles takes place, allowing for trans-synaptic and further intercellular spread (e.g., to cells of the conjunctiva and cornea). Virus gene expression and replication in neurons is controlled by T cells and interferon- γ . The latent virus is frequently reactivated after local stimuli, such as injury to tissues innervated by neurons harboring latent HSV, by corneal scarification, or by systemic factors (e.g., exposure to UV light, physical or emotional stress, hormonal imbalance, and hyperthermia).

VZV: Latent VZV genomes are readily detected in trigeminal ganglia and dorsal root ganglia. In some cases, latent VZV is also found in geniculate ganglia, olfactory bulbs, and ganglia of the autonomic nervous system. In trigeminal ganglia, VZV and HSV genomes can be detected in the same neuron. Reactivation and shedding of VZV from neurons along cutaneous nerve pathways typically presents itself as herpes zoster, although reactivation can also lack a vesicular rash and cause neuritis (zoster sine herpette, e.g., Bell's palsy).

CMV: Latent CMV genomes can be reactivated from CD34+ hematopoietic stem cells, identifying this cell type as the principal site of latency. The viral load produced during primary CMV replication correlates with the copy number of latent genomes present in organs and the relative risk of recurrent disease. Moreover, CMV latency and reactivation is controlled by T lymphocytes, NK cells, and IFN γ , but also endocrine factors, as reflected by the increasing probability to shed virus during pregnancy and lactation. Depending on the extent of reactivated infection, the virus can be found in almost all organs including white blood cells. The reactivated virus is disseminated via infected myelomonocytic and endothelial cells to peripheral sites where the virus spreads locally from cell to cell. Shedding of cell free virus occurs from the salivary glands into saliva and mammary glands and into breast milk. Further sites of extensive virus shedding are the genital and urethral tracts.

EBV: EBV is spread by the oral route. Shedding of EBV detectable in saliva as a result of reactivation and replication at oropharyngeal sites occurs frequently in immunocompetent

carriers. In immunologically compromised patients, EBV induces various tumors and oral hairy leukoplakia, a replicative lesion of the immunocompromised host on the lateral borders of the tongue.

Epidemiology

Human herpesviruses are ubiquitous agents distributed worldwide but restricted to humans as their natural host. Seroepidemiological studies have determined the prevalence of virus-specific IgG in many countries, indicating the frequency of infection within a defined population. Geographic location, socioeconomic status, and age are the primary factors that influence the acquisition of infection. HSV-1, VZV, and EBV are found in 80–99% of the adult population in all countries, while the seroprevalence of CMV infection ranges from 50% (Western Europe) to 99% (African and Asian countries). HSV-2 is found less frequently than HSV-1, in 20% to 70% of adults depending on socioeconomic status, race, and geographic location.

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