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Overview of Herpesviruses

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INTRODUCTION TO HERPESVIRUSES

What is a Herpesvirus?

Identification of a virus in the family *Herpesviridae* is based on the morphology of the virus particle. Viewed through an electron microscope, the virions of different members of the *Herpesviridae* family are indistinguishable and consist of four distinct components: the core, capsid, tegument, and envelope (Fig. 1) *(1)*. The core contains a double-stranded DNA genome arranged in an unusual torus shape that is located inside an icosadeltahedral capsid that is approx 100 nm in size and contains 162 capsomeres *(2)*. Located between the capsid and the viral envelope is an amorphous structure termed the tegument that contains numerous proteins. The tegument structure is generally asymmetrical, although some virus members (such as human herpesvirus 6 [HHV-6] and human herpesvirus 7 [HHV-7]) have been shown to have well-defined tegument structures *(3,4)*. Presumably, the tegument is responsible for connecting the capsid to the envelope and acting as a reservoir for viral proteins that are required during the initial stages of viral infection *(5,6)*. The outermost structure of the herpes virion is the envelope, which is derived from cell nuclear membranes and contains several viral glycoproteins. The size of mature herpesviruses ranges from 120 to 300 nm owing to differences in the size of the individual viral teguments *(1)*.

The life cycle of all herpesviruses in their natural host can be divided into lytic (resulting in the production of infectious progeny) and latent (dormant) infections. During a lytic infection the virus is replicated and newly synthesized particles are released into the surrounding medium. During a latent infection viral replication is suppressed, resulting in the formation of a quiescent state. The establishment of viral latency is a hallmark of all known herpesviruses. As described below, the sites of lytic and latent infections differ among the various members of the human herpesvirus family.

Herpesvirus Subfamilies

The Herpesvirus Study Group of the International Committee on the Taxonomy of Viruses *(7)* has divided the herpesviruses into three subfamilies, termed alphaherpesvirinae, betaherpesvirinae, and gammaherpesvirinae (Table 1). Membership into a

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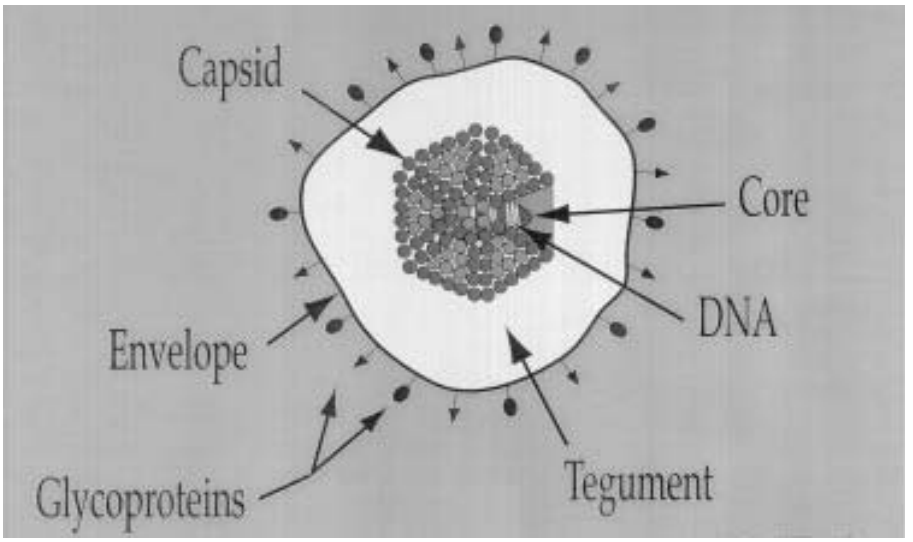

Fig. 1. Schematic drawing of a typical herpesvirus particle.

Table 1
Subfamily Membership of the Human Herpesviruses

Alphaherpesvirinae	Betaherpesvirinae	Gammaherpesvirinae
HSV-1	CMV	EBV
HSV-2	HHV-6	HHV-8
VZV	HHV-7	

particular subfamily is based on biologic and genetic properties (demonstrated in Fig. 2) and has been useful in predicting the properties of newly discovered isolates (such as HHV-6, HHV-7, and human herpesvirus 8 [HHV-8]). The alphaherpesvirinae are characterized by a variable host range, a short replicative cycle in the host, rapid growth and spread in cell culture, and the establishment of latent infections in sensory ganglia *(7).* Members of this subfamily are often referred to as neurotropic herpesviruses. Among the human herpesviruses, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), and varicella-zoster virus (VZV) belong to the alphaherpesvirinae. The betaherpesvirinae are characterized by a fairly restricted host range with a long reproductive cycle in cell culture and in the infected host, which often results in the development of a carrier state. Latency is established in lymphocytes, secretory glands, and cells of the kidney as well as other cell types *(8).* The human herpesviruses cytomegalovirus (CMV), HHV-6, and HHV-7 are members of this subfamily. The gammaherpesvirinae are characterized by a restricted host range with replication and latency occurring in lymphoid tissues, although some members have

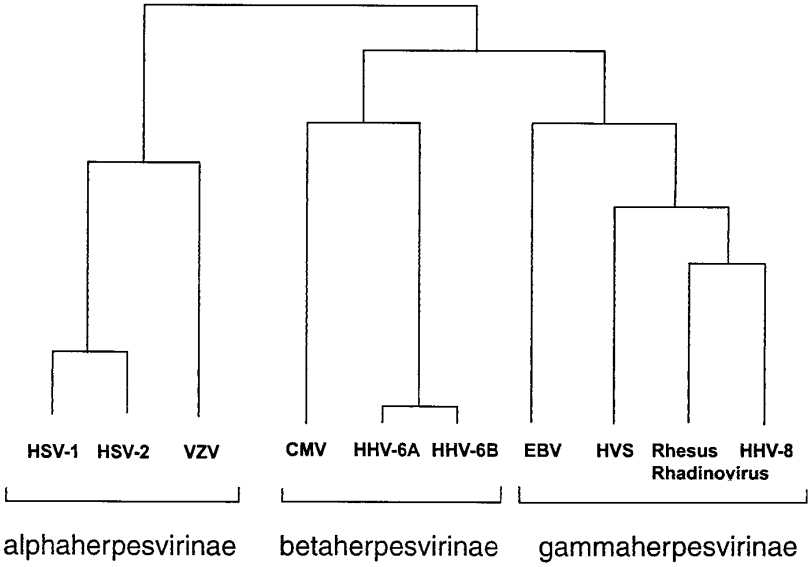

Fig. 2. Genetic relatedness of different herpesviruses. The genetic relationship between different herpesviruses was determined by analysis of the predicted amino acid sequence of the glycoprotein B homolog from each virus. Analysis was performed using the program Pileup from the GCG Sequence Analysis Program.

demonstrated lytic growth in epithelial, endothelial and fibroblastic cells *(7,9)*. Among the lymphoblastic cells, viral replication is generally restricted to either T or B cells. The gammaherpesvirinae subfamily is further divided into two genera, *Lymphocryptovirus* and *Rhadinovirus*. Among the human herpesviruses, Epstein–Barr virus (EBV) is a member of the *Lymphocryptovirus* genus while the newly discovered HHV-8 is a member of the *Rhadinovirus* genus *(10,11)*.

Animal Herpesviruses

Herpesviruses have been found in almost all animal species. Besides the human herpesviruses mentioned previously, herpesviruses have also been identified in nonhuman primates, cattle, horses, pigs, sheep, goats, wildebeests, deer, reindeer, dogs, guinea pigs, hamsters, elephants, cats, mice, harbor seals, shrews, birds, amphibians, reptiles and fish. There are well over 100 different herpesviruses identified to date (reviewed by Roizman and Sears *[1]*). These herpesviruses cause a variety of diseases ranging from inapparent infections to death. In addition, a number of them such as pseudorabies virus in pigs and Marek's disease virus in chickens represent serious threats to agriculture.

Most of the nonhuman herpesviruses can be classified into one of the three subfamilies described earlier. A notable exception is a recently described herpesvirus of elephants *(12)*. Richman and co-workers *(12)* recently described the detection of a novel herpesvirus of elephants that appears to be responsible for a highly fatal disease among perinatal Asian and African elephants. Separate but highly related strains were isolated from African and Asian elephants that had died from this disease, which was characterized by a

sudden onset, edema in the skin of the head and proboscis, cyanosis of the tongue, decreased levels of white blood cells and platelets, and internal hemorrhages. Histologically, basophilic intranuclear inclusion bodies were detected in vascular cells of the heart, liver, and tongue. Death was found to be due to myocardial failure from capillary injury and leakage. Identification of the causative agent as a herpesvirus was based on electron micrographs of viral capsids from infected organs. Sequence analysis of two viral genes and comparison of the DNA sequences of these genes with those of known herpesviruses (representing the three herpesvirus subfamilies), revealed that the two elephant-derived strains may represent a new subfamily. Interestingly, the strain isolated from Asian elephants was present in benign papilloma lesions of African elephants. The authors have suggested that the two strains have crossed species (from African to Asian and from Asian to African elephants). As a result, in their natural host, the viruses cause a benign infection, while in the other elephant species, viral infection results in a fatal disease.

ALPHAHERPESVIRUSES

Human Alphaherpesvirus Members and Associated Diseases

Three human herpesviruses belong to the alphaherpesvirus subfamily: HSV-1, HSV-2, and VZV. HSV-1 and HSV-2 belong to the genus simplexvirus, are very closely related at genetic and nucleic acid levels, and produce similar diseases (reviewed by Whitley and Gnann *(13)*). Clinically, both HSV-1 and HSV-2 cause a variety of syndromes ranging from inapparent infections and self-limiting cutaneous lesions to fatal encephalitis. In addition, both viruses establish and maintain a latent state in nerve cells from which recurrent HSV infections arise.

In a primary infection, HSV enters the body through a mucosal membrane or abraded skin and establishes infection locally in epithelial cells. Viral replication in the epithelial cells results in the amplification of virus, the formation of a virus-filled blister, and the elicitation of both cellular and humoral immune responses. The virus then spreads from the site of primary infection by retrograde transport to the nuclei of sensory neurons that innervate the site of the local infection *(14)*. Studies using animal models have indicated that a limited viral replication occurs within these neurons followed by the establishment of latency. A latent HSV infection is characterized by the presence of viral genomes in the nuclei of sensory ganglia neurons and the absence of viral replication or protein production (reviewed by Hill *[15]*).

A latent HSV infection is maintained for the life of the host, but the virus (in some individuals) can be reactivated periodically to produce infectious virus resulting in asymptomatic shedding or recurrent disease. During reactivation, viral replication occurs within the reactivated neuron, and the virus is transported back down the axon, where it can establish an infection in the epithelia of the skin. Studies using both animal models and human subjects have shown that viral reactivation can be triggered by a variety of stressful or stress-related stimuli including heat, ultraviolet light, fever, hormonal changes, menses and surgical trauma to the neuron *(16–19)*. Although the virus appears to be latent most of the time, HSV infection probably is best characterized as reoccurring reactivations divided by periods of latency.

VZV belongs to the genus varicellavirus and is related genetically at the amino acid sequence level to both HSV-1 and HSV-2 *(20)*. VZV gets its name from the two dis-

eases it causes: the childhood disease varicella (more commonly known as chickenpox) and the adult disease herpes zoster (commonly known as shingles). Varicella is the clinical outcome of a primary VZV infection, while herpes zoster is the result of the reactivation of latent VZV. Although HSV can reactivate frequently, VZV generally reactivates only once during the host's lifetime *(21)*.

VZV is considered to be endemic among most populations *(22)*. The majority of varicella cases occur in children younger than 10 of age and can be epidemic among cloistered children, such as schools, nurseries, etc. A VZV infection begins as a result of direct contact with viral lesions or inhalation of airborne droplets. A primary viremia develops that results in the spread of virus to multiple organs, including the spleen and liver *(23)*. A secondary viremia, mediated by lymphocytes, results in the spread of virus to cutaneous epithelial cells and the development of characteristic "chicken pox" lesions. VZV is communicable at least 1–2 d prior to the onset of a rash and during the presence of the virus-infected lesions.

Epidemiology of Alphaherpesvirus Infections

Epidemiologic studies of HSV-1 and HSV-2 based on clinical symptoms alone are inadequate due to the fact that many primary infections are asymptomatic *(13)*. Primary HSV-1 infections occur most often in young children and present clinically as gingivostomatitis. Primary infection is associated with socioeconomic factors such that individuals in lower socioeconomic classes seroconvert at an earlier age when compared to members of higher socioeconimic classes (reviewed by Whitley and Gnann *[13]*). In the United States, the seroprevalence for HSV-1 increases from 20% to 40% in children under the age of 4 to approx 80% among individuals over the age of 60 *(24)*.

The seroprevalence of HSV-2 is lower than that of HSV-1 primarily because its mode of transmission is most often through sexual encounters. Fleming and colleagues *(25)* recently reported that the age-adjusted seroprevalence of HSV-2 in the United States has risen 30% during the last 13 yr to 20.8% or one in five individuals. These rather disturbing results indicate that sexual transmission of HSV-2 has not abated, but has continued to increase to alarming levels.

Varicella zoster virus is fairly ubiquitous in the general population with the majority of individuals seroconverting during childhood *(26)*. With the advent and use of the live attenuated varicella vaccine (LAVV), which is recommended to be given to pre-school-age children, the incidence of VZV infections should diminish. The LAVV vaccine has been shown to be quite effective (85–95%) in preventing development of chickenpox *(27,28)*.

Overview of Replication

Our current understanding of the replication cycle of herpesviruses is due to the extensive amount of research performed on HSV-1 replication. For the purposes of this chapter, we use the replication cycle of HSV-1 as our model for herpesvirus replication. HSV replication begins with the enveloped virus particle binding to the outside of a susceptible cell resulting in a fusion between the viral envelope and cellular membrane (Fig. 3). As a result of membrane fusion, the nucleocapsid enters the cell cytoplasm and migrates to the nuclear membrane. The viral genome is released from the

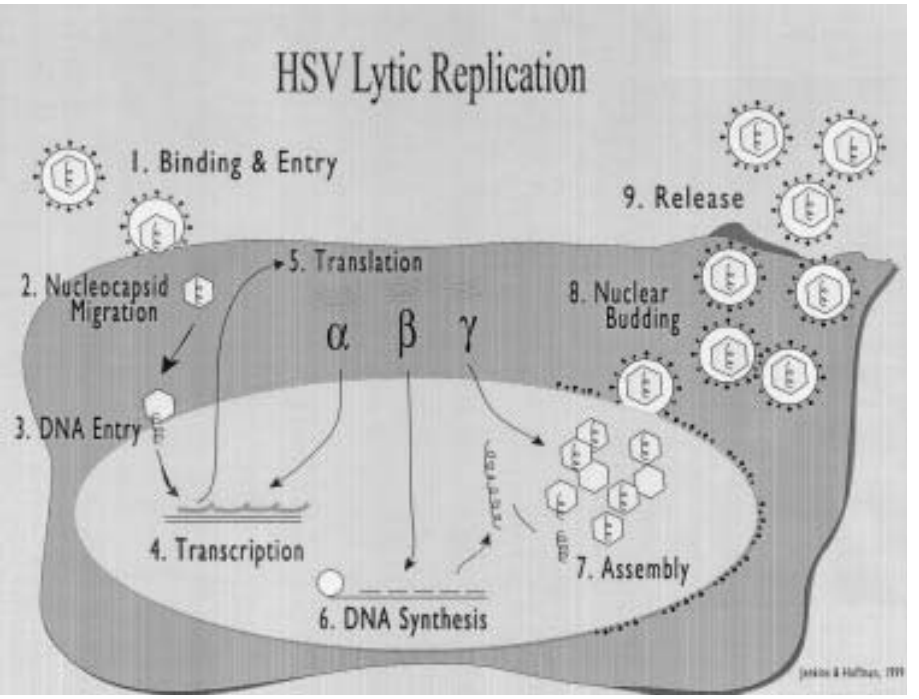

Fig. 3. Schematic of herpes simplex virus replication cycle. **1.** Virus particles bind to specific receptors on cell surface. Fusion occurs between the viral envelope and cell membrane, resulting in the release of the nucleocapsid into the cytoplasm. **2.** Viral nucleocapsid migrates to the nuclear membrane. **3.** Viral DNA is released from the nucleocapsid and enters the nucleus through a nuclear pore. **4.** HSV transcription is initiated in a coordinated, cascade fashion producing the three classes of mRNA, α, β, and γ. Viral mRNA is transported to the cytoplasm where translation occurs. **5.** The different viral proteins are produced and transported to their appropriate cellular location. Alpha (α) proteins are involved in regulation of viral transcription; β proteins are involved primarily in DNA synthesis; γ proteins represent primarily structural proteins. **6.** Synthesis of viral DNA occurs through a rolling circle mechanism in the nucleus producing DNA concatamers. **7.** Empty capsid structures are assembled in the nucleus and unit length viral DNA is packaged into the capsid producing a nucleocapsid. **8.** The nucleocapsid buds through the nuclear membrane and is released from the cell **(9).**

capsid structure and enters the nucleus through nuclear pores. Once inside the nucleus, viral-specific transcription and translation, and replication of the DNA genome occur.

HSV genes are divided into three major temporal classes (α, β, and γ) that are regulated in a coordinated, cascade fashion (for review see Roizman and Sears *[1]*). The α or immediate-early (IE) genes contain the major transcriptional regulatory proteins, and their production is required for the transcription of the β and γ gene classes. β proteins are not produced in the absence of α proteins, and their synthesis is required for viral DNA replication. The β proteins consist primarily of proteins involved in viral nucleic acid metabolism. The γ proteins reach peak rates of synthesis after the onset of DNA replication and consist primarily of viral structural proteins.

Once synthesized, the viral DNA is packaged into preformed capsid structures and the resulting nucleocapsid buds through the nuclear membrane, obtaining its envelope. The replication of HSV is fairly rapid, occurring within 15 h after infection, and it is extremely lethal to the cell resulting in cell lysis and death.

Latency

A hallmark of all herpesviruses is the ability to establish and maintain a latent infection. Latency is defined as a state of infection in which the viral genome persists in the infected cell in the absence of any viral replication, although depending on the specific herpesvirus, there may be a limited amount of viral transcription. Latency results in the long-term survival of the virus in its host and is why herpesvirus infections are described as once infected, always infected. Indeed, herpesvirus infections are for life.

Latent herpesvirus infections can be reactivated resulting in the production of a lytic cycle of replication and recrudescent disease. The frequency of reactivation and the type of recrudescent disease varies among the different human herpesviruses.

Members of the alphaherpesvirinae subfamily establish latent infections in sensory ganglia. Evidence from both human and animal models have demonstrated that the site for HSV latency is the neuron *(29–31).* Identification of the site of VZV latency is less clear with some laboratories advocating the neuron while others point to ganglionic cells surrounding the neuron *(32,33).*

Neurons latently infected with HSV do not produce virus or detectable virus-specific proteins. While the absence of virus production suggests that viral gene transcription is absent, a small subset of viral transcripts, termed the latency associated transcripts (LATs), are transcribed during active and latent infections *(34–38).* The function of the LAT transcripts is unclear. Viral deletion mutants indicate that the LATs are not required to establish latent infection *(39,40),* although a decreased frequency of reactivation in LAT mutants has been reported *(41–44).*

Reactivation of HSV begins within the latently infected neuron. Following reactivation, the virus is transported down the axon of the neuron and establishes a peripheral infection in the skin. Recurrent HSV infections are generally less severe compared to primary infections both in terms of number of lesions formed and length of appearance *(45).*

In immunocompetent hosts, active herpes simplex virus infections rapidly stimulate immune responses that function to restrict viral replication and the spread of virus. In addition, the host's immune response is most likely involved in the establishment of latent infections. In fact, the establishment of latency could be viewed as a double-edged sword. It provides the host with a mechanism to limit viral spread and cellular damage while, at the same time, ensuring the persistence and survival of the virus. In HSV-infected neonates and immunocompromised hosts, virus replicates to high titers, often with wide dissemination and generally extensive viral pathology. While the mechanisms involved in controlling HSV replication and establishment of latency are not completely understood, it has become increasingly evident that they involve interactions among nervous, immune and endocrine systems (reviewed in Turner and Jenkins *[46]*).

VZV latency appears to be quite different from HSV. There are no LAT homologs in VZV, and therefore there is no equivalent LAT gene expression during latency. Several laboratories have reported, however, the detection of gene expression from several

VZV genes in latently infected ganglia *(47–49).* Because these genes also are expressed during a lytic replication, what role, if any, they play in VZV latency is unclear (reviewed by Kinchington *[50]*). Reactivation of latent VZV causes the disease herpes zoster, or shingles. This reactivated disease is quite different from recurrent HSV lesions in that the resulting rash and blisters occur throughout an entire dermatome (an area of the skin that is innervated by a single spinal nerve *[21]*). The appearance of VZV vesicles in a dermatome is evidence that following viral reactivation, the infection spreads throughout the ganglia and is transported to the skin via the numerous axons associated with that ganglia. Fortunately, zoster rarely occurs more than once in a lifetime.

BETAHERPESVIRUSES

Human Betaherpesvirus Members and Associated Diseases

There are three human herpesviruses belonging to the subfamily betaherpesvirinae: CMV, HHV-6, and HHV-7. CMV was originally given the name "salivary gland virus" when it was cultivated in 1956 from several salivary gland tissues *(51–53).* The more descriptive name of cytomegalovirus was given by Weller in 1960 *(54).* CMV infects epithelial cells, polymorphonuclear leucocytes, and T cells in the infected host *(55).*

CMV is a frequent cause of asymptomatic infections in humans. As a result, clinical CMV disease is fairly uncommon except among neonates and immunocompromised individuals *(56).* Congenital CMV infection is estimated to occur among 1% of all newborns in the United States *(57),* making it the most common congenital infection. Among the newborns infected with CMV, approx 10% will exhibit clinical symptoms. Congenital CMV infection results in cytomegalic inclusion disease (CID) which presents as a widely disseminated infection with multiorgan involvement. CID is the leading cause of mental retardation, deafness, and other neurologic deficits among neonates *(56).* In immunocompromised individuals with a cell-mediated deficiency (such as bone marrow and solid organ transplant patients and individuals with AIDS), primary or reactivated CMV infections can result in several life-threatening diseases including interstitial pneumonia, gastroenteritis, hepatitis, and leukopenia *(56).* In addition, CMV infection can result in graft versus host disease in bone marrow transplant patients and is the leading cause of retinitis among AIDS patients. In apparently healthy adults, a primary CMV infection can result in a heterophile-negative mononucleosis-like disease *(56).*

CMV is the prototype of the betaherpesvirinae, and until 1986 it was the sole human member of this subfamily. In 1986, a novel virus was isolated from the lymphocytes of individuals with lymphoproliferative disorders *(58).* This subsequently was found to be a newly discovered herpesvirus and is now termed human herpesvirus 6 (HHV-6). Four years later, in 1990, another novel herpesvirus was isolated from cultured lymphocytes of a healthy adult *(59).* This virus was found to be highly related, yet distinct from HHV-6 and was given the name human herpesvirus 7 (HHV-7). HHV-6 and HHV-7 are closely related at the genetic level and share homology, to a lesser extent, with CMV. HHV-6 has been shown to have two major variants (A and B) that can be distinguished at the DNA level *(60,61).* Both HHV-6 and HHV-7 exhibit a T-cell tropism. In addition, HHV-6 has been found to also infect epithelial cells, natural killer (NK) cells, and monocytes *(62).*

HHV-6 infection is most often asymptomatic, occurring in young children *(8)*. It has been definitively shown to be the causative agent of the childhood disease exanthem subitum (also called roseola infantum), which is characterized by a high fever for 3–5 d followed by a small red rash on the neck and trunk that lasts for 1–2 d *(63)*. HHV-6 variant B is responsible for almost all cases of exanthem subitum, and in a recent study was implicated as the primary cause of emergency room visits, febrile seizures, and hospitalizations among children under the age of 3 yr *(64)*. HHV-6 infections in young children also have been associated with hepatitis, encephalitis, and seizures. Primary infections in healthy adults are rare (due to the high seroprevalence rate among adults) and are associated with heterophile-negative mononucleosis, hepatitis, and lymphadenopathy *(8)*. Among adults, the greatest risk of HHV-6-associated disease is in transplant patients. Solid-organ and bone marrow transplant recipients who reactivate HHV-6 following transplant are at risk for several disorders including a fever and rash, pneumonitis, hepatitis, and neurologic disorders *(8)*. HHV-6 reactivation also has been associated with graft rejection among some renal transplant patients *(65)*. More recently, HHV-6 has been linked to multiple sclerosis (MS) by the detection of viral DNA in MS plaques *(66)* and more than 70% of MS patients have been shown to have evidence of an active HHV-6 infection *(67)*. Definitive proof for a causal role of HHV-6 in MS, however, is still lacking. HHV-7 infection is not associated with any definitive disease although there have been some reports of roseola infantum linked to HHV-7 infection *(68–70)*.

Epidemiology of Betaherpesvirus Infections

Horizontal CMV transmission can occur (1) during birth by direct contact with virus-containing cervical or vaginal secretions, (2) by ingestion of breast milk, (3) by direct contact with saliva, (4) by contact with blood products or upon receiving transplanted tissues, and (5) by sexual transmission *(56)*. Interestingly, the incidence of CMV infections in the United States is not uniform over time, but instead shows peak increases within distinct age groups *(57)*. These increases are seen during the first few months of life (from maternal secretions or breast milk), during the toddler years (from saliva of family members and other children), during the teenage years (from intimate kissing), and during young adulthood (from sexual transmission). Worldwide, CMV infection and seroprevalence is associated with age, geographic location, and socioeconomic status (SES) *(57)*. In developed countries, 40–60% of adults in middle to upper level SES are CMV seropositive compared to more than 80% among those in a lower SES. In contrast, in developing countries more than 80% of all children have seroconverted by the age of 3.

HHV-6 and HHV-7 infections are highly ubiquitous. Seroconversion to HHV-6 occurs predominantly (> 90%) between 1 and 2 yr of age *(71,72)*. HHV-7 infection occurs slightly later, with more than 85% of children seroconverting by age 3 *(73)*.

C. BETAHERPESVIRUS LATENCY

The targets for CMV latency in seropositive individuals are peripheral blood and bone marrow derived monocytes *(74)*. Latently infected cells have been shown to express two classes of latency associated transcripts that map to the region of the CMV genome that encodes for the major immediate-early protein. The sites for HHV-6

latency have been reported to include monocytes, macrophages and the salivary glands *(33),* while the sites for HHV-7 latency have not been clearly defined.

GAMMAHERPESVIRUSES

Human Gammaherpesvirus Members and Associated Diseases

There are currently two human herpesviruses belonging to the gammaherpesvirinae subfamily: EBV and HHV-8. EBV is the prototype for the *Lymphocryptovirus* genus while HHV-8 belongs to the genus *Rhadinovirus.* Members of both genera are characterized by a tropism for lymphoid cells and the ability to induce cell proliferation in vivo resulting in lymphoproliferative disorders.

EBV is well established in the majority of the world's human population. Its prevalence rate stands at > 90%. The majority of primary EBV infections are believed to be asymptomatic *(75).* While no disease or illness has been associated with a primary EBV infection in healthy infants, in other individuals (particularly in adolescents and young teens), primary EBV can result in infectious mononucleosis. An EBV infection begins with the virus infecting the epithelial layer of the nasopharynx and spreading to nearby B cells. As a result of viral replication, fever, pharyngitis, lymphadenopathy, splenomegaly, hepatocellular dysfunction, and oftentimes skin rashes develop *(76,77).*

Normally, the immune response to EBV is aggressive, resulting in a rapid elimination of virus-infected cells. The immune response includes the activation of NK cells, antibody-dependent cellular cytotoxicity (ADCC), and EBV-specific cytotoxic T cells (CTL) *(77).* The immune response controls viral replication, marking the end of the primary infection and forcing the virus into establishing latency in B cells *(78).*

In 1994, using representational difference analysis Chang and colleagues *(79),* described the detection of DNA sequences in AIDS-associated Kaposi's sarcoma (KS) lesions belonging to a new human herpesvirus termed Kaposi's sarcoma-associated herpesvirus (KSHV) or HHV-8. The predicted amino acids encoded by these DNA sequences were found to share homology to proteins encoded by herpesvirus saimiri (HVS) and EBV.

HHV-8 DNA has been found in > 95% of all KS tissues *(79–84),* and in two unusual types of lymphoma termed primary effusion lymphoma (PEL, previously called body-cavity based lymphoma) and multicentric Castleman's disease (MCD) *(85–87).* The precise role of HHV-8 in the development of these cancers is not known, but is the focus of intensive laboratory efforts (*see* Chapter 11). Currently, there has not been a disease associated with a primary HHV-8 infection.

Epidemiology of Gammaherpesvirus Infections

EBV infection is ubiquitous throughout the world such that by the age of 30, 80–100% of all individuals have seroconverted *(9).* Seroprevalence among younger individuals varies according to SES, similar to HSV-2 and CMV *(88).* In developing countries, primary EBV infection occurs during the first few years of life, while in developed countries it occurs more often during adolescence. The primary route of EBV transmission is oral, although limited transmission following transplantation has been reported *(76).* Approximately 50% of the primary infections occurring during adolescence result in clinical infectious mononucleosis *(88).*

Seroepidemiology studies of HHV-8, as well as the epidemiology of KS, have indicated that transmission of HHV-8 appears to be primarily through sexual contact. For example, HHV-8 seroprevalence among homosexual men has been significantly linked to multiple sexual partners *(89–91).* While HHV-8 infection is increased among homosexual men, it is not increased among intravenous drug users, indicating that transmission does not occur significantly through blood inoculation *(92)* (Bernstein, Jacobson, and Jenkins, *unpublished results*). The seroprevalence of HHV-8 among individuals above the age of 15 ranges from 0% to 20% depending on the serologic assay *(93–96).* HHV-8 infection in children under the age of 15 is rare in the United States and the United Kingdom (Jenkins, unpublished results) *(97),* but it does occur in KS-endemic regions of Mediterranean and African countries. HHV-8 DNA was been found in saliva, peripheral blood mononuclear cells (PBMCs), and semen of infected individuals *(98–103),* although not consistently. The exact nature of an HHV-8 infection including location, spread into various tissues, timing of viral shedding, and location of infectious virus remains undetermined at present. Further, the potential for viral transmission by routes other than sexual contact must be investigated, given that there has been some documentation of horizontal transmission from mother to child *(97).*

Latency

Epithelial cells and B cells are important targets in the life cycle of EBV. Differentiating epithelial cells have been shown to be permissive for lytic replication while B lymphocytes are the primary target for latency and represent a virus reservoir in humans *(77).* The ability of EBV to establish latent infections in B cells is believed to be directly responsible for the development of several different neoplasms, including endemic Burkitt's lymphoma, undifferentiated nasopharyngeal carcinoma, Hodgkin's disease, and polyclonal B-cell lymphocytosis *(104,105).* The association of EBV with some of these neoplasms has demonstrated important geographic variations. Both Hodgkin's disease and sporadic Burkitt's lymphoma from Latin America have higher rates of EBV-association than cases from Western countries. Furthermore, the EBV-association in all African Burkitt's lymphoma is unique and exhibits distinctive clinical and pathologic features. A recent investigation of primary intestinal lymphomas of Mexican origin demonstrated the presence of EBV in all examined cases of T-cell non-Hodgkin's lymphomas, Burkitt's lymphoma, and in a proportion of other B-cell non-Hodgkin's lymphomas *(106).*

In immunologically compromised individuals, EBV can cause a malignant B-lymphocyte proliferation directly linking it to lymphoproliferative disorders, as well as virus-associated hemophagocytic syndrome, certain forms of T-cell lymphoma, and some gastric carcinomas *(107).* Serologic studies have been largely used to correlate virus presence to the pathogenesis of many these diseases.

Latency of the gammaherpesvirinae is quite unique distinct from that of the alphaherpesvirinae and betaherpesvirinae. EBV infection of B cells triggers the expression of several latent-specific proteins whose functions (among others) are to maintain the EBV genome as an episome in the latently infected B cell and to transform the B cell to ensure long-term survival (reviewed by Kieff and Leibowitz *[9].*). To accomplish this, EBV latency consists of a complex pattern of viral gene expression. Given that EBV must establish and maintain a latent infection in a relatively short-lived B cell, while

HSV and VZV latency occurs in differentiated and nondividing neuronal cells, perhaps it is not surprising that the pattern of latent viral gene expression is quite different between these virus subfamilies.

The cancers associated with HHV-8 (KS, PEL, MCD) appear to represent a predominantly latent infection, as the majority of the cells express latent proteins and do not produce significant amounts of virus *(108,109).* Several HHV-8 latent proteins have been identified, but their function is not known. If similar to EBV, these proteins would serve to establish and maintain viral latency. These answers will depend on the development of HHV-8 mutants that can be studied in vitro or in suitable animal models.

SUMMARY

The human herpesviruses induce a variety of illnesses ranging from asymptomatic to life-threatening infections and cancer. The majority of these viruses are acquired during childhood and persist for life. The ability of the herpesviruses to establish and maintain a latent infection adds an additional layer of complexity to the viruses' life cycle and complicates all attempts to eradicate the virus from infected individuals. While much has been learned about the human herpesviruses over the last 30 yr, there is still much more to be learned before they are no longer a serious health threat.

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