DNA enveloped viruses

HERPESVIRUSES

- The herpesvirus family contains six important human pathogens: herpes simplex virus types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein–Barr virus, and human herpesvirus 8 (the cause of Kaposi's sarcoma).

- All herpesviruses are structurally similar. Each has an **icosahedral** core surrounded by a lipoprotein **envelope**.

- The genome is linear double-stranded DNA. The virion does not contain a polymerase. They are large (120–200 nm in diameter), second in size only to poxviruses.

- They replicate in the nucleus, form intranuclear inclusions, and are the only viruses that obtain their envelope by budding from the nuclear membrane.

- The virions of herpesviruses possess a **tegument** located between the nucleocapsid and the envelope. This structure contains regulatory proteins, such as transcription and translation factors, which play a role in viral replication.

- Herpesviruses are noted for their ability to cause **latent infections.** In these infections, the acute disease is followed by an asymptomatic period during which the virus remains in a quiescent (latent) state. When the patient is exposed to an inciting agent or immunosuppression occurs, reactivation of virus replication and disease can occur.

- With some herpesviruses (e.g., herpes simplex virus), the symptoms of the subsequent episodes are similar to those of the initial one; however, with others (e.g., varicella-zoster virus), they are different. Some information is available regarding the mechanism by which herpes simplex virus (HSV) and cytomegalovirus (CMV) initiate and maintain the latent state. Shortly after HSV infects neurons, a set of "**latency-associated transcripts**" (LATS) are synthesized. These noncoding, regulatory RNAs suppress viral replication. The precise mechanism by which they do so is unknown. The process by which latency is terminated and reactivation of viral replication occurs is unclear, but various triggers such as sunlight, fever, and stress are known. CMV establishes latency by producing microRNAs that inhibit the translation of mRNAs required for viral replication. Also, the CMV genome encodes a protein and an

RNA that have the ability to inhibit apoptosis in infected cells. Inhibition of apoptosis allows the infected cell to survive.

- Three of the herpesviruses, HSV types 1 and 2 and varicella-zoster virus (VZV), cause a **vesicular rash,** both in primary infections and in reactivations. Primary infections are usually more severe than reactivations. The other two herpesviruses, CMV and Epstein–Barr virus (EBV), do not cause a vesicular rash.

- Four herpesviruses, namely HSV types 1 and 2, VZV, and CMV, induce the formation of **multinucleated giant cells,** which can be seen microscopically in the lesions. The importance of giant cells is best illustrated by the Tzanck smear, which reveals multinucleated giant cells in a smear taken from the painful vesicles of the genitals caused by HSV type 2.

- The herpesvirus family can be subdivided into three categories based on the type of cell most often infected and the site of latency. The **alpha herpesviruses**, consisting of HSV types 1 and 2 and VZV, infect epithelial cells primarily and cause latent infection in neurons. The **beta herpesviruses**, consisting of CMVs and human herpesvirus 6, infect and become latent in a variety of tissues. The **gamma herpesviruses**, consisting of EBV and human herpesvirus 8 (HHV-8, Kaposi's sarcoma–associated virus), infect and become latent primarily in lymphoid cells.

- Certain herpesviruses are associated with or cause cancer in humans (e.g., Epstein–Barr virus is associated with Burkitt's Kaposi's sarcoma itself also can result from a primary infection. lymphoma and nasopharyngeal carcinoma, and human herpesvirus 8 causes Kaposi's sarcoma). Several herpesviruses cause cancer in animals (e.g., leukemia in monkeys and lymphomatosis in chickens).

POXVIRUSES

The poxvirus family includes three viruses of medical importance: smallpox virus, vaccinia virus, and molluscum contagiosum virus. Poxviruses are the largest and most complex viruses.

SMALLPOX VIRUS

Disease: Smallpox virus, also called variola virus, is the agent of smallpox, the only disease that has been eradicated from the face of the Earth. **Eradication** is due to the vaccine. There is concern regarding the use of smallpox virus as an agent of bioterrorism. Poxviruses of animal origin, such as cowpox and monkey pox.

Important Properties: Poxviruses are brick-shaped particles containing linear double-stranded DNA, a disk-shaped core within a double membrane, and a lipoprotein envelope. The virion contains a DNA-dependent RNA polymerase. This enzyme is required because the virus replicates in the cytoplasm and does not have access to the cellular RNA polymerase, which is located in the nucleus. Smallpox virus has a single, stable serotype, which is the key to the success of the vaccine. If the antigenicity varied as it does in influenza virus, eradication would not have succeeded. Smallpox virus infects only humans; there is no animal reservoir.

Transmission & Epidemiology: Smallpox virus is transmitted via respiratory aerosol or by direct contact with virus either in the skin lesions or on fomites such as bedding. Prior to the 1960s, smallpox was widespread throughout large areas of Africa, Asia, and South America, and millions of people were affected. In 1967, the World Health Organization embarked on a vaccination campaign that led to the eradication of smallpox. The last naturally occurring case was in Somalia in 1977.

Prevention: The disease was eradicated by global use of the **vaccine,** which contains live, attenuated **vaccinia virus.** The success of the vaccine is dependent on five critical factors:

(1) smallpox virus has a single, stable serotype.

(2) there is no animal reservoir, and humans are the only hosts.

(3) the antibody response is prompt, and therefore exposed persons can be

Protected.

(4) the disease is easily recognized clinically, and therefore exposed persons can be immunized promptly.

(5) there is no carrier state or subclinical infection.

MOLLUSCUM CONTAGIOSUM VIRUS

- Molluscum contagiosum virus (MCV) is a member of the poxvirus family but is quite distinct from smallpox and vaccinia viruses. The lesion of molluscum contagiosum is a small (2–5 mm), flesh-colored papule on the skin or mucous membrane that is painless, nonpruritic, and not inflamed. The lesions have a characteristic cup-shaped (umbilicated) crater with a white core. The lesion is composed of hyperplastic epithelial cells within which a cytoplasmic inclusion body can be seen. The inclusion body contains progeny MCV. Note that these lesions are different from warts, which are caused by papillomavirus, a member of the papovavirus family.

- MCV is transmitted by close personal contact, including sexually. The disease is quite common in children, in whom lesions often occur around the eyes and on the trunk. Adults often have lesions in the genital area. The lesions can be large and numerous in patients with reduced cellular immunity, such as AIDS patients. In immunocompetent patients, the lesions are self-limited but may last for months.

- The diagnosis is typically made clinically; the virus is not isolated in the clinical laboratory, and antibody titers are not helpful. Removal of the lesions by curettage or with liquid nitrogen is often effective. There is no established antiviral therapy, but cidofovir may be useful in the treatment of the extensive lesions that occur in immunocompromised patients.

HEPADNAVIRUSES

HEPATITIS B VIRUS (HBV)

Disease: HBV causes hepatitis B.

Important Properties:

- HBV is a member of the hepadnavirus family. It is a 42-nm **enveloped** virion, with an icosahedral nucleocapsid core containing a **partially double-stranded circular** DNA genome. The envelope contains a protein called the **surface antigen** (HBs Ag), which is important for laboratory diagnosis and immunization. Within the core is a **DNA-dependent DNA polymerase.**

- The genome contains four genes (four open reading frames) that encode five proteins; namely, the S gene encodes the surface antigen, the C gene encodes the core antigen and the e antigen, the P gene encodes the polymerase, and the X gene encodes the X protein (HBx). The DNA polymerase has both RNA-dependent (reverse transcriptase) and DNA-dependent activity.

- Electron microscopy of a patient's serum reveals three different types of particles: a few 42-nm virions and many 22-nm **spheres** and long **filaments** 22 nm wide, which are composed of surface antigen.

- HBV is the only human virus that produces these spheres and filaments in such large numbers in the patient's blood. The ratio of filaments and small spheres to virions is 1000:1.

-In addition to HBsAg, there are two other important antigens both located in the core of the virus: the **core antigen** (HBc Ag) and the **e antigen** (HBe Ag). The core antigen, as the name implies, is located on the nucleocapsid protein that forms the core of the virion, whereas the e antigen is soluble and is released from infected cells into the blood. The e antigen is an important indicator of **transmissibility.** For vaccine purposes, HBV has one serotype based on HBs Ag. However, for epidemiologic purposes, there are four serologic subtypes of HBs Ag based on a group-specific or y and w or r. This leads to four serotypes—adw, adr, ayw, and ayr—which are useful in epidemiologic studies because they are concentrated in certain geographic areas.

- The specificity of HBV for liver cells is based on two properties: virus-specific receptors located on the hepatocyte cell membrane (facilitate entry) and transcription factors found only in the hepatocyte that enhance viral mRNA synthesis (act postentry).

- Humans are the only natural hosts of HBV. There is no animal reservoir.

Transmission & Epidemiology:

- The three main modes of transmission are via blood, during sexual intercourse, and perinatally from mother to newborn. The observation that needle-stick injuries can transmit the virus indicates that only very small amounts of blood are necessary. HBV infection is especially prevalent in addicts who use intravenous drugs.

- Hepatitis B is found worldwide but is particularly prevalent in Asia. Globally, more than 300 million people are chronically infected with HBV, and about 75% of them are Asian. There is a high incidence of **hepatocellular carcinoma (hepatoma)** in many Asian countries—a finding that indicates that HBV is a human tumor virus.

- Immunization against HBV has significantly reduced the incidence of hepatoma in children. It appears that the HBV vaccine is the **first vaccine to prevent a human cancer.**

- Prevention involves the use of either the **vaccine** or **hyperimmune**

globulin or both.