LECTURE-6
Herpes virus and Pox virus

Introduction

Nearly everyone will be affected by some type of herpes virus at some time in his or her life. Herpes simplex virus belongs to the family of herpesviridae which consists of more than 80. distinct types of viruses that are found in nearly every kind of animals such as fishes, frogs, birds ,cats, dogs, mice, snakes, lizards, monkeys, cows, horses, humans, and more

Classification

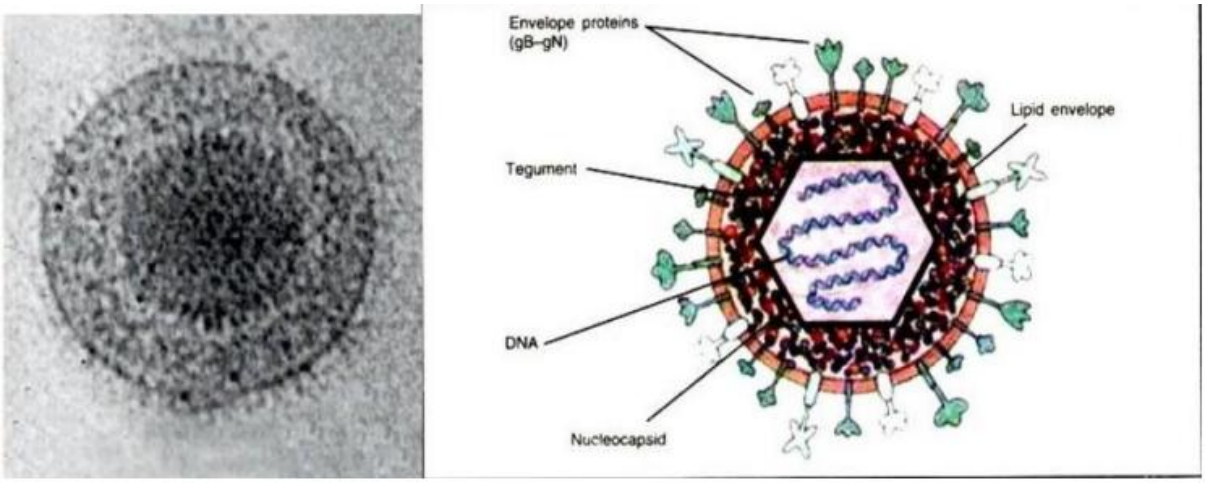
The classification of herpes viruses is complex! All herpes viruses share a common morphology and have **genomes of linear**, **doublestranded DNA** (dsDNA) but The family Herpesviridae is further subdivided into three **subfamilies:** Alphaherpesvirinae, Betaherpesvirinae and Gammaherpesvirinae, and the subfamilies are subdivided into genera.

TABLE 57-1 Classification of human herpesviruses

Subfamily	Scientific name	Common name	Site of latency
Alphaherpesvirinae	Human herpesvirus 1	Herpes simplex virus type 1	Neurons
	Human herpesvirus 2	Herpes simplex virus type 2	Neurons
	Human herpesvirus 3	Varicella zoster virus	Neurons
Gammaherpesvirinae	Human herpesvirus 4	Epstein–Barr virus	Lymphoid tissues
	Human herpesvirus 8	Kaposi's sarcoma-related virus	–
Betaherpesvirinae	Human herpesvirus 5	Cytomegalovirus	Monocytes and lymphocytes in secretory glands
	Human herpesvirus 6	Human B cell lymphotrophic virus	Lymphoid tissue
	Human herpesvirus 7	RK virus	Lymphoid tissue

Virion Properties

Herpes virus virions are **enveloped** and include a core, capsid, and tegument (a layer of globular material surrounding the capsid which is enclosed by a typical lipoprotein envelope with numerous small glycoprotein spikes). The nucleocapsid is spherical **icosahedral** . The core consists of the viral genome packaged as a single, linear dsDNA molecule within the protein capsid. **Because** of the variable size of the envelope, virions can range in diameter from 120 to 250 nm.



Types of human herpes viruses and their Characteristics

1- Herpes simplex virus type 1 (HSV-1)/

Human herpes virus-1 Herpes simplex virus type 1 causes mainly **oral** and **ocular manifestations**. **Fever blister** or **cold sores** of **the face**, **mouth**, and **lips** are the most common symptoms of **HSV-1** outbreaks.

Besides causing cold sores and possibly spreading to the genital region, **HSV-1** has now been linked with the development of serious neurological diseases such as **Alzheimer's disease**. One can contract HSV-1 through **direct contact with sites of viral shedding** or **mucocutaneous fluids** . Some of the infections caused by HSV-1 are **pharyngitis**, **tonsillitis**, **gingivostomatitis**, **stromal keratitis**, **retinitis**, **encephalitis**, **pneumonitis**, **esophagitis**, and **hepatitis**. The recurrences of HSV-1 can be triggered either by **internal factors** (fever, illness, menstruation, gastrointestinal and respiratory infections, diabetes, hyperthyroidism, fatigue and factors that depress the immune system); or **external factors** such as exposure to wind, burn, ultraviolet radiation and emotional stress .

2- Herpes simplex virus type 2 (HSV-2)/

Human herpes virus-2 Human herpes virus-2 is the typical cause of **genital herpes** and classified as a sexually transmitted disease. The **adolescents** and **adults** are mainly affected by HSV-2. Excretion of the virus from herpetic lesions mainly lips and genitals of asymptomatic people are regarded as the most important source of the virus. The genital herpes is characterized by painful ulcerated lesions and sores on the genitalia, which increases the risk of contracting HIV by two or three times, as it is believed **that 40-60%** of HIV patients showed prior infection with HSV-2. **Recurrent genital herpes** is mainly caused by HSV- 2 through direct contact with **sites** of viral shedding after reactivation of the virus from its latency in **sacral ganglia** during **sexual**

intercourse; transferred from mother to child through contact with an infected birth canal, infected caregiver or through ingestion of infected maternal secretions, known as intrauterine infections during child birth. **The neonatal infections by HSV-2 pose serious threats** in the **skin**, **eye**, **mouth**, **herpes encephalitis,** and **meningitis** and **dispersed multi-organ** infections as they often lead **to fatal diseases**

3- Herpes zoster virus (HZV)/ Varicella zoster virus (VZV)/

Human herpes virus-3 Chickenpox is the results of first-time infection by **HZV** and the virus causes **shingles** when it reappears in a person's life. Rarely, HZV may cause a life threatening due to the infection on central nervous system.

4- Epstein-Barr virus (EBV)/ Human herpes virus-4

Epstein-Barr virus is the major cause of infectious **mononucleosis** (**kissing disease**), chronic fatigue syndrome, and disorders of the immune system and linked with **lupus**, **lymphomas**, and **other cancers**. EBV is now considered to be quite damaging and causing genetic mutations in the body

5- Cytomegalovirus (CMV)/ Human herpes virus-5

Cytomegalovirus can cause **mononucleosis**, **hepatitis** and can be transmitted through sexual contact . The occurrence of CMV is strongly correlated with **asymptomatic vascular diseases** such as **heart**, **coronary artery** and **atherosclerosis**. CMV infects about 60% of adults, among homosexual men and is associated with HIV. CMV infection during pregnancy carries a high risk of intrauterine transmission which may result in **growth retardation**, **jaundice**, and **central nervous system** abnormalities. Those who are asymptomatic at birth may develop hearing defects or learning disabilities later in life.

6- Human herpes viruses - Types 6, 7 and 8 (HHV- 6, HHV-7 and HHV-8)

All human herpes viruses are associated with disorders of the immune system.

Viral replication

Herpes simplex virus (HSV) grows very rapidly in infected cells, requiring only 8–16 hours for completion. The virus infects most types of cells in human hosts and usually **causes lytic infections** of the fibroblasts and epithelial cells. After entry into the cell, the virion is uncoated, genome is released, and the genome DNA enters into the nucleus. The mRNA is transcribed by host cell RNA polymerase and then translated into early nonstructural proteins. Subsequently, the viral DNA polymerase replicates the genome DNA, during which synthesis of early proteins is stopped **but** synthesis of late structural proteins begins. These

late proteins are transported to the nucleus where **assembly** of virion occurs. The virion acquires its envelope by budding through the nuclear membrane. It also causes latent infections of neurons by the presence of multiple copies of HSV-1 DNA in the cytoplasm of infected neurons.

Diagnosis

Clinical examination of persons with no previous history of lesions and contact with an individual with known HSV-1 infection. The appearance and distribution of sores in these individuals typically presents as multiple, round, superficial oral ulcers accompanied by acute gingivitis, Also the diagnostic methods for detection of herpesvirus:-

- Virus-Specific Polymerase Chain Reaction (PCR).
- Electron Microscopy Of Vesicular Fluid Or Scrapings.
- Immunofluorescence Staining Of Smears Or Tissue Sections.
- Virus Isolation And Characterization Provide A Definitive Diagnosis.
- Specific enzyme immunoassays for antibody detection (serology).

Immunity, Prevention and Control

Control strategies are directed at management practices and vaccination. Bovine herpes virus 1 vaccines are used extensively, alone or in combination as multiple virus formulations, Inactivated and live-attenuated vaccines are available and recombinant DNA vaccines Although they do not prevent infection, vaccines significantly reduce the incidence and severity of disease. Prevention of the HSV 1 infection can be achieved by avoiding the physical contact, kissing when the lesions are present, touching or using the patient's eating or drinking utensils. Even though antiviral treatments can reduce the frequency, and severity of outbreaks, there is no treatment that can eradicate herpes simplex virus-1. However, asymptomatic carriers of the HSV-2 are still contagious. Some asymptomatic individuals are unaware of their infection, they are considered at high risk for spreading HSV.

POXVIRUSES

General features and diseases caused by Poxviruses: -

-Poxviruses are Very large, brick-shaped viruses about 300 x 200 nm (the size of small bacteria).

-They have a complex internal structure - a large double-stranded DNA genome is enclosed within a "core" that is flanked by 2 "lateral bodies".
-The surface of the virus particle is covered with filamentous protein components, so that the particles have the appearance of a "**ball of knitting wool**".
-The entire particle is enclosed in an envelope derived from the host cell membranes.
-Most poxviruses are host-species specific, but vaccinia is a remarkable exception.
- True pox viruses are antigenically rather similar, so that infection by one elicits immune protection against the others.

Four orthopoxviruses cause infection in humans: **variola, vaccinia, cowpox, and monkeypox.**

Variola virus infects only humans in nature, although primates and other animals have been infected in an experimental setting.

Vaccinia, cowpox, and monkeypox viruses can infect both humans and other animals in nature.

- **Chickenpox** is **not** a true poxvirus and is caused by the herpesvirus varicella zoster.
-**The life cycle** of poxviruses is complicated by having multiple infectious forms, with differing mechanisms of cell entry. Poxviruses are unique among human DNA viruses in that they replicate in the cytoplasm of the cell rather than in the nucleus. To replicate, poxviruses produce a variety of specialized proteins not produced by other DNA viruses, the most important of which is a viral- associated DNA-dependent RNA polymerase. Both enveloped and unenveloped virions are infectious. The viral envelope is made of modified Golgi membranes containing viral-specific polypeptides, including hemagglutinin. Infection with either variola **major** virus or variola **minor** virus confers immunity against the other.

Laboratory Diagnosis of Poxviruses: -

- **Microscopically**, poxviruses produce characteristic cytoplasmic inclusion bodies, the most important of which are known as **Guarnieri bodies**, and are the sites of viral replication. Guarnieri bodies are readily identified in skin biopsies stained with hematoxylin and eosin, and appear as pink blobs. They are found in virtually all poxvirus infections but the absence of Guarnieri bodies could not be used to rule out smallpox.

-The diagnosis of an orthopoxvirus infection can also be made rapidly by **electron microscopic** examination of pustular fluid or scabs. All orthopoxviruses exhibit identical brick-shaped virions by electron microscopy.

If particles with the characteristic morphology of herpesviruses are seen this will eliminate smallpox and other orthopoxvirus infections.

-Definitive laboratory identification of variola virus involved growing the virus on chorioallantoic membrane (part of a chicken embryo) and examining the resulting pock lesions under defined temperature conditions.

- Strains were characterized by polymerase chain reaction (PCR). -Serologic tests and enzyme linked immunosorbent assays (ELISA), which measured variola virus-specific immunoglobulin and antigen were also developed to assist in the diagnosis of infection.

Chickenpox was commonly confused with smallpox in the immediate post eradication era. A variety of laboratory methods were available for detecting chickenpox in the evaluation of suspected smallpox cases.

-Some pox viruses can be isolated by cell-culture.

Smallpox virus

-belongs to the genus **Orthopoxvirus**. The last naturally occurring case was diagnosed in October 1977, and the World Health Organization (WHO) certified the global eradication of the disease in 1980, making it the only human disease to be eradicated.

-There are two forms of the smallpox, **variola major** is the severe and most common form, with a more extensive rash and higher fever. **Variola minor** is a less common presentation, causing less severe disease, typically discrete smallpox, with historical death rates of 1% or less.

- **Subclinical (asymptomatic)** infections with variola virus were noted but were not common. In addition, a form called variola sine eruption (smallpox without rash) was seen generally in vaccinated persons. This form was marked by a

fever that occurred after the usual incubation period and could be confirmed only by antibody studies or, rarely, by viral culture.

- Moreover, there were two very rare and **fulminating types** of smallpox, the **malignant** (flat) and **hemorrhagic forms**, which were usually fatal. **Transmission:** -

1.Transmission occurred through inhalation of airborne variola virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person.

2.It was transmitted from one person to another primarily through prolonged face-to-face contact with an infected person, usually, within a distance of 1.8 m (6 feet),

3.It could also be spread through direct contact with infected bodily fluids or contaminated objects (fomites) such as bedding or clothing.

4.Rarely, smallpox was spread by virus carried in the air in enclosed settings such as buildings, buses, and trains.

5.The virus can cross the placenta, but the incidence of congenital smallpox was relatively low.

6.Smallpox was not notably infectious in the prodromal period and viral shedding was usually delayed until the appearance of the rash, which was often accompanied by lesions in the mouth and pharynx.

7.The virus can be transmitted most frequently during the first week of the rash when most of the skin lesions were intact.

8.Infectivity waned in 7 to 10 days when scabs formed over the lesions, but the infected person was contagious until the last smallpox scab fell off.

9.Smallpox was highly contagious, but generally spread more slowly and less widely than some other viral diseases, perhaps because transmission required close contact and occurred after the onset of the rash.

10. The overall rate of infection was also affected by the short duration of the infectious stage.

11. In temperate areas, the number of smallpox infections was highest during the winter and spring. In tropical areas, seasonal variation was less evident and the disease was present throughout the year.

12. Age distribution of smallpox infections depended on acquired immunity.

13. Vaccination immunity declined over time and was probably lost within thirty years.

14. Smallpox was not known to be transmitted by insects or animals and there was no asymptomatic carrier state.

VACCINIA VIRUS

- A large, complex, enveloped virus belonging to the poxvirus family.
- It has a linear, double-stranded DNA genome.

-The vaccinia virus is the source of the modern smallpox vaccine, which the World Health Organization used to eradicate smallpox in a global vaccination campaign in 1958–1977.

-Although smallpox no longer exists in the wild, vaccinia virus is still studied widely by scientists as a tool for gene therapy and genetic engineering.
-Vaccinia virus is able to undergo multiplicity reactivation (MR), the process by which two, or more, virus genomes containing otherwise lethal damage interact within an infected cell to form a viable virus genome, MR provides the advantage of recombinational repair of genome damages.

- Whole-genome sequencing has revealed that vaccinia is most closely related to horsepox, and the cowpox strains found in Great Britain are the least closely related to vaccinia.

- Vaccinia contains within its genome genes for several proteins that give the virus resistance to interferons.

- Vaccinia virus infection is typically very mild and often does not cause symptoms in healthy individuals, although it may cause rash and fever.

- Immune responses generated from a vaccinia virus infection protects the person against a lethal smallpox infection. For this reason, vaccinia virus was, and still is, being used as a live-virus vaccine against smallpox.

Questions

1- Compare between HSV type 1 and 2 ?

2- what are the Steps of HSV viral replication?

3- Enumerate the types of human herpes viruses?