Medical Virology

Lecture 2 **Asst. Prof. Dr. Dalya Basil**

Herpesviruses, Orthomyxoviruses, and Retro virus

- Herpesviruses Structure & Composition: Herpesviruses Enveloped DNA viruses. All herpesviruses have a core of double-stranded DNA, protein coat that exhibits icosahedral symmetry and has 162 capsomeres.

- The nucleocapsid is surrounded by an envelope that is derived from the nuclear membrane of the infected cell and contains viral glycoprotein spikes.

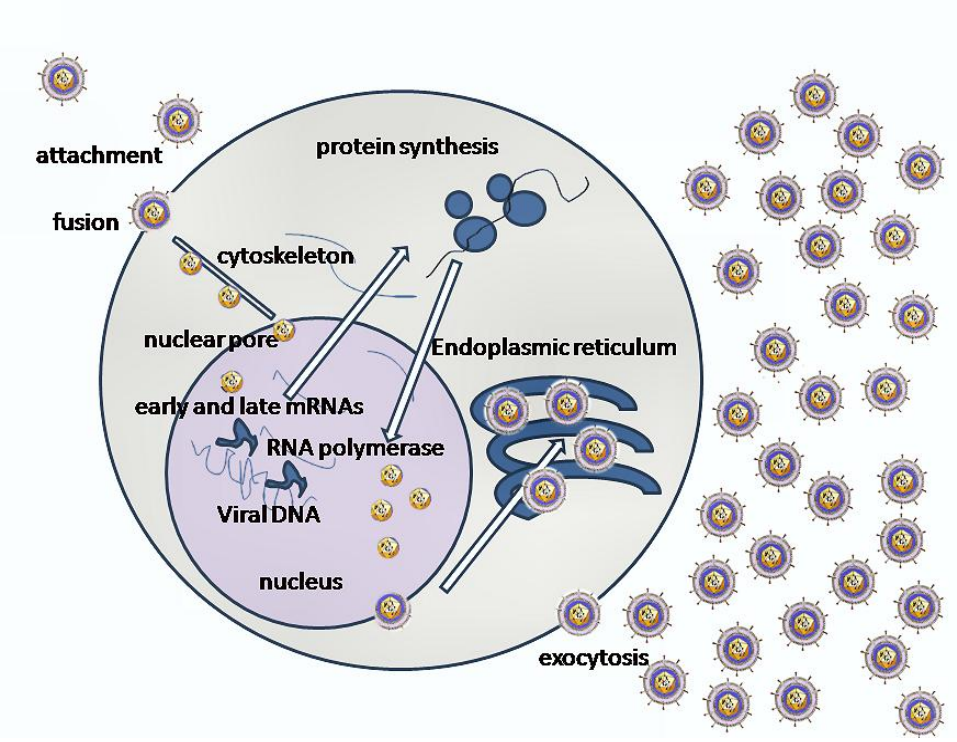
Classification of Herpes viruses

Classification of Human Herpesviruses					
	Biologic Properties			Examples	
Subfamily ("-herpesvirinae')	Growth Cycle and Cytopathology	Latent Infections	Genus ("-*virus*")	Official Name ("Human - Herpesvirus")	Common Name
Alpha	Short, cytolytic	Neurons	*Simplex*	1	Herpes simplex virus type 1
				2	Herpes simplex virus type 2
			Varicello	3	Varicella-zoster virus
Beta	Long, cytomegalic	Glands, kidneys	*Cytomegalo*	5	Cytomegalovirus
	Long, lymphoproliferative	Lymphoid tissue	*Roseolo*	6	Human herpesvirus 6
				7	Human herpesvirus 7
Gamma	Variable, lymphoproliferative	Lymphoid tissue	*Lymphocrypto*	4	Epstein-Barr virus
			Rhadino	8	Kaposi sarcoma-associated herpesvirus

Life Cycle of Herpes viruses

All herpesviruses are nuclear-replicating the viral DNA is transcribed to mRNA within the infected cell's nucleus.

Infection is initiated when a viral particle contacts a cell with specific types of receptor molecules on the cell surface. Following binding of viral envelope glycoproteins to cell membrane receptors, the virion is internalized, allowing viral DNA to migrate to the cell nucleus. Within the nucleus, replication of viral DNA and transcription of viral genes occurs. Herpes virus particle assembles in the nucleus before it buds off, enveloping itself in nuclear membrane material. The viral particle then releases from the cell.



Herpesvirus Diseases:

- HSV-1 and HSV-2 infect epithelial cells and establish latent infections in neurons. Type 1 is classically associated with oropharyngeal lesions and

causes recurrent attacks of "fever blisters." Type 2 primarily infects the genital mucosa and is mainly responsible for genital herpes. Both viruses also cause neurologic disease. HSV-1 is the leading cause of sporadic encephalitis in the United States. Both type 1 and type 2 can cause neonatal infections which are often severe.

- **Varicella-zoster virus** causes chickenpox (varicella) on primary infection and establishes latent infection in neurons. Upon reactivation, the virus causes zoster (shingles). Adults who are infected for the first time with varicella-zoster virus are apt to develop serious viral pneumonia.

- **Cytomegalovirus** replicates in epithelial cells of the respiratory tract, salivary glands, and kidneys and persists in lymphocytes. It causes an infectious mononucleosis. In newborns, cytomegalic inclusion disease may occur. It is an important cause of congenital defects and mental retardation.

- **Human herpesvirus 6** infects T lymphocytes. It is typically acquired in early infancy and causes exanthem subitum (roseola infantum). **Human herpesvirus 7**, also a T-lymphotropic virus, has not yet been linked to any specific disease.

- **EBV** replicates in epithelial cells of the oropharynx and parotid gland and establishes latent infections in lymphocytes. It causes infectious mononucleosis and is the cause of human lymphoproliferative disorders, especially in immunocompromised patients.

- **Human herpesvirus 8** appears to be associated with the development of Kaposi sarcoma, a vascular tumor that is common in patients with AIDS.

- Human herpesviruses are frequently reactivated in immunosuppressed patients (eg, transplant recipients, cancer patients) and may cause severe disease, such as pneumonia or lymphomas.

- Herpesviruses have been linked with malignant diseases in humans and lower animals: like EBV with Burkitt lymphoma, with nasopharyngeal carcinoma, and with other lymphomas, and like KSHV with Kaposi sarcoma.

Orthomyxoviruses:

- Linear, 8 segmentedRNA (7 in influenza C), helical enveloped viruses.

- Replication takes place in cytoplasm.

- **Influenza viruses** are the only members of this family.

- These are important human pathogens as they cause both outbreaks and pandemics (infrequently) that kill thousands of people.

Three kinds of Influenza viruses known:

- Influenza A virus causes worldwide epidemics.

- Influenza B virus causes major outbreaks of Influenza.

- Influenza C virus cause mild respiratory tract infections and no outbreaks.

- Influenza virus genome is a segmented, SS, negative polarity RNA with a helical nucleocapsid and an outer lipoprotein envelope.

- The envelope has 2 different spikes, a hemagglutinin (HA) and a neuraminidase (NA).

- The function of the HA is to bind to the cell surface receptor usually a neuraminic acid or sialic acid; to infect the cell. The HA is highly antigenic and a target of the neutralising antibody.

- The hemagglutinin functions at the beginning of infection.

- The hemagglutinin agglutinates red blood cells, and this is the basis of diagnostic Hemagglutination inhibition test.

- The neuraminidase cleaves neuraminic acid to release the progeny virus from the infected cell.

- Neuraminidase functions at the end.

- Neuraminidase also degrades the protective mucosal layer in the respiratory tract and enables the viruses to gain entry to the respiratory epithelial cells.

Antigenic Changes of Orthomyxoviruses:

Changes in the antigenicity of hemagglutinin and neuraminidase confers on the Influenza A virus the ability to cause pandemics.

- Two types of antigenic changes are known:
- 1) Antigenic shift that involves a major change based on the reassortment of segments of the genome RNA.

- 2) Antigenic drift signifies a minor change based on mutations in the genome RNA. Thus, Influenza viruses have many serotypes.

Influenza A virus have 2 matrix proteins M1 and M2.

M1 is located between the internal nucleoprotein and the envelope and provides structural integrity.

M2 protein forms an ion channel between the interior and the exterior of the virus. It transports protons into the virion causing the disruption of the envelope. This leads to the uncoating of the virus and frees the nucleocapsid containing the RNA genome and allows it to migrate to the nucleus.

A non structural protein called NS-1, by its ability to inhibit the production of interferon mRNA reduces the host innate defence and is an important determinant of virulence of the virus.

Influenza Virus Replication Cycle:

- After viral hemagglutinins interact with the surface receptors, the virus enters the cell in vesicles and uncoats mediated by the M2 proteins and is facilitated by the low pH within the endosome/vesicle.
- The viral nucleocapsid enters the cytoplasm and migrates to the nucleus where the genome RNA (8 segments) gets transcribed into mRNA by the viral RNA polymerase (transcriptase).
- Most RNA's move to cytoplasm, some remain in the nucleus to serve as a template for the synthesis of negative polarity strand RNA genomes for the progeny, by a different subunit of viral RNA polymerase (replicase).

Clinical findings

- Uncomplicated Influenza : Abrupt symptoms include chills, headache, dry cough, muscular aches. These may be induced by influenza A or B. In contrast, influenza C causes a common cold illness, Coryza.
- Pneumonia : complications occur only in the elderly and debilitated. Influenza infection enhances the susceptibility of patients to bacterial superinfection, due to loss of ciliary clearance, dysfunction of phagocytic cells.
- Reye's Syndrome : an acute encephalopathy of children and adolescents (2-16yrs).

Retroviruses

Taxonomy: Synonym(s): RNA tumor virus group (and related agents). Retroviruses are currently classified into 7 genera icluding Lentivirus (HIV).

Host: Virus infects vertebrates.

Morphology: Virions enveloped; slightly pleomorphic; spherical; 80-100 nm in diameter. Surface projections of envelope small (surface appears rough), or distinct (8 nm long glycoprotein); spikes; dispersed evenly over all the surface. Capsids isometric (to spherical), or rod-shaped (or a truncated cone eg HIV). Nucleoid of spherical nucleocapsid symmetric, or asymmetric.

Virion structure: Roughly spherical, 100nm in diameter Icosahedral or conical capsid, Packaging **2 identical copies** of (+)strand RNA and viral enzymes (RT, PR, and IN) in enveloped virion.

Retrovirus life cycle:

- Early phase & Late phase

Early phase: Retrovirus enters cell by the fusion pathways.

- Attachment and Entry

- Reverse transcription

  - Viral RNA is converted into a double-stranded DNA copy by reverse transcription. → proviral DNA
  - A copy of proviral DNA is integrated into the cellular genome at a random site.

- Late phase: Expression of viral RNA through transcription of proviral DNA

  - Synthesis of viral proteins through translation and post-translational modification
  - Assembly and budding of virions

Human Immunodeficiency Virus (HIV):

Family: Retroviridae

Genus: Lentivirus

Species: Human Immunodeficiency Virus (HIV)

Types of HIV:

- There are **two types** of HIV: **HIV-1 and HIV-2**. Both types are transmitted by sexual contact, through blood, and from mother to child, and they appear to cause clinically indistinguishable AIDS. However, it seems that HIV-2 is less easily transmitted, and the period between initial infection and illness is longer in the case of HIV-2.

- Worldwide, the predominant virus is HIV-1, and generally when people refer to HIV without specifying the type of virus they will be referring to HIV-1. The relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found elsewhere.

AIDS Signs and Symptoms:

- **Acute phase:**

- Last several weeks
- Mononucleosis or influenza-like syndromes

- **Latency period:**

- Two weeks to >20 years depends on several factors
- Few or no symptoms

- **During the disease (AIDS):**

- Low CD4+ T cell level
- Various opportunistic infections, cancers