LECTURE 3 & 4 *lect. Dr. Ahmed Yaseen Abed*
-Viral Genetic &Viral Replication
-Viral Pathogenesis and Transmission

Viral Genetic

Each virus carries within the protective capsid a nucleic acid-based blueprint for replication of infectious virus particles (virion). Once a virus has invaded a cell, it is able to direct the host cell machinery to synthesize new progeny. The viral genome may be composed of RNA or DNA, single or double stranded. Encoded proteins may be **nonstructural**, such as nucleic acid polymerases required for replication of genetic material **or structural**, those proteins necessary for assembly of new infectious virions.

However, **all viruses lack the** genetic information encoding proteins necessary to generate metabolic energy or protein synthesis. The viral genome RNA or DNA rarely codes for more than few proteins necessary for replication or physical structure. Viruses as a group are the only class of organisms with subspecies **that keep RNA as their sole genetic material**. Likewise, they are the only group of self-replicating organisms with subspecies that **use single-stranded DNA genomic content**. Multiple forms of virus genomes are found in virions infecting human cells.

Host cell RNA such **as ribosomal RNA** can be found in virions, but there is **no** evidence for a functional role in virus replication. For enveloped viruses, glycoproteins are the major type of protein present on the exterior of the membrane. The existence/presence of a lipid envelope provides an operational method with which to separate viruses into two distinct classes—those that are inactivated by organic solvents.

Multiplication of DNA viruses

As DNA viruses, carry a neutral charge, the DNA is duplicated to mRNA by the action of transcriptase enzyme. mRNA is transferred to the ribosomes for synthesis of (early and late) proteins by translation which are responsible for the formation of a new strand of DNA.

Multiplication of RNA viruses

RNA viruses either carry **a –ve or as +ve** charge. In positively charged nucleic acid viruses, the nucleic acid itself acts as mRNA and the multiplication goes as

mentioned above. While negatively charged viruses, the strand need a transcription for **another +ve charge strand** by the action of transcriptase enzyme

Replication of viruses

All of the dynamic events associated with the virus (transcription & replication of genomes) occurs within **the living host cell**. All DNA viruses multiply inside the host cell nucleus (**except poxvirus**) and all RNA viruses multiply in the **cytoplasm.**

Stages of viral replication:

1- Attachment
2- Penetration
3- Uncoating
4- Gene expression and biosynthesis
5- Assembly
6- Release

1- Attachement to host cell

The first stage in viral infection is attachment of virus to specific receptor on the surface of host cell:

A. Receptor molecules differ for different viruses. For example, **HIV** attaches to **CD4 receptor** on **helper T-cell** and **Rabies virus** binds to **acetylcholine receptor.**
B. The attachment of virus determines the organ specificity such as hepatitis virus infect liver, influenza virus infect respiratory tract, and so on.
C. The specificity of attachment determines the host rang of viruses. Some viruses have the narrow range, whereas others have abroad ranged.

2- Penetration

Following attachment, virions can enter cells by one of the following ways:

A- Translocation of virion across plasma membrane.
B- Endocytosis: in which the virus is accumulated inside cell.
C- Fusion with Plasma Membrane : The virus fuses directly with the plasma membrane of the cell, and enter into host cell.

3- Uncoating

Uncoating occurs concomitantly with or shortly after penetration, Uncoating is removing the capsid proteins. Uncoating may be occurring in cytoplasm or in nucleus. A **low pH** within the **vesicle** and presence of **cellular enzymes** which lead to dissolve the proteins of capsid , then result in uncoating and release of viral **nucleic acid** into infected host cell. The viral nucleic acid may remain in cytoplasm or migrate to nucleus.

4- Gene expression and biosynthesis:

Virus cannot replicate by binary fission or mitosis, but they replicate by **complex process**. When the viral genome released inside living host cell, the virus is control on host cell biosynthesis, inhibition of macromolecules synthesis and use the energy of host cell in synthesis of viral macromolecules.

The gene expression involves

A- Replication of viral genome (**synthesis of viral nucleic acids**): The DNA viruses replicate in nucleus (except **pox viruses** in cytoplasm), whereas the RNA viruses are replicate in the cytoplasm (except **retro viruses** and **influenza virus** in nucleus).

B- Transcription of viral mRNA: **synthesis of mRNA in viruses** in various pathways, transfer of genetic information from parental genome to mRNA is called **transcription.**

C- Translation of mRNA (**synthesis of viral proteins**): Once the mRNA of either DNA viruses or RNA viruses is synthesized, and it translated by ribosome of host cell into viral protein.

5-Assembly of Viruses

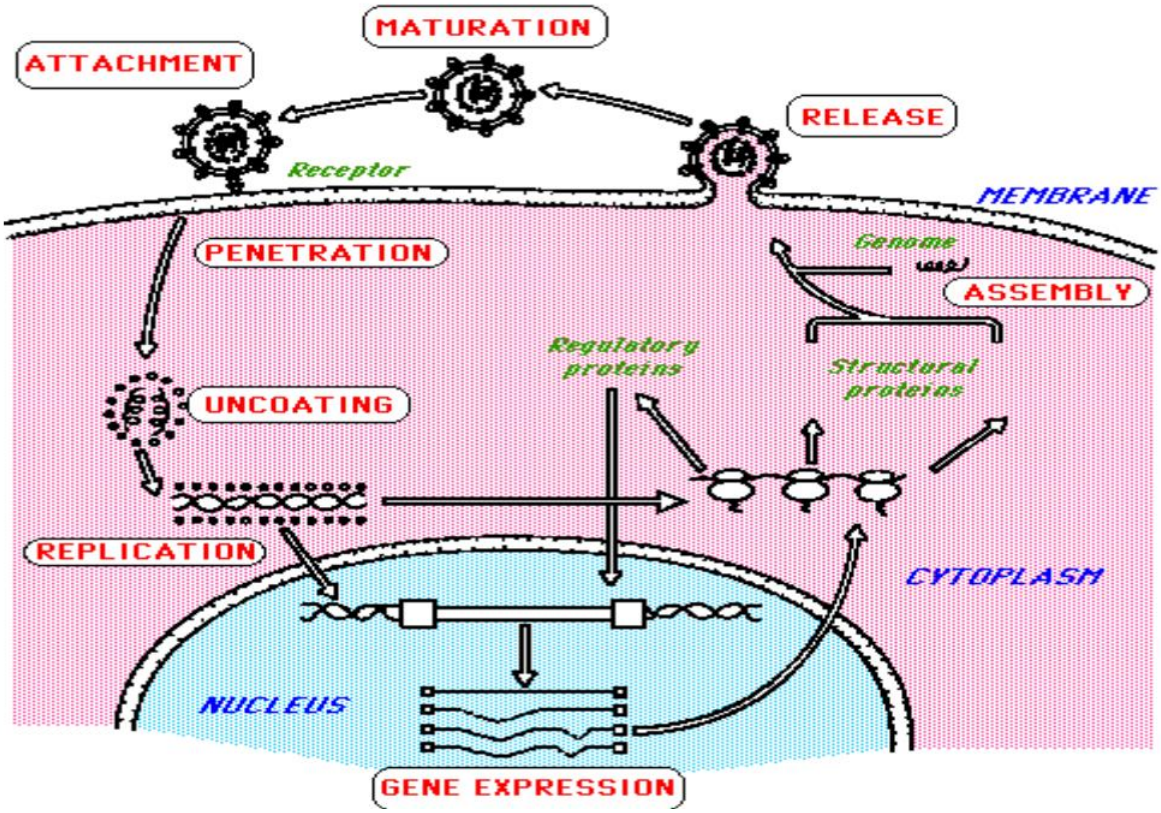
The virus produces many copies of their nucleic acid and proteins. The newly synthesized viral genome and structural proteins are assembling to form many **progeny viruses**. The packaging of viral nucleic acid into capsid is accruing either in **cytoplasm** or **in nucleus of infected cell**.

6-Release of virus

The virus mature particles are released from the infected cell by one of two processes:

A- **Lysis** of infected cell.

B- **Budding** (without lysis) through the outer cell membrane. Some viruses are enveloped; they acquired their envelopes from cell membrane during releasing, while other enveloped viruses acquire their envelope from nuclear membrane of infected cell.



Viral Pathogenesis and Transmission

Viral Pathogenesi

Viral pathogenesis: is the process by which a viral infection leads to disease in the host.

- **Pathogenic mechanisms:**
  1- Implantation of virus at the portal of entry.
  2- Local replication.
  3- Spread to target organs (disease sites).
  4- Spread to sites of shedding of virus into the environment.

➢**Many factors affect pathogenic mechanisms:**

1- Accessibility of virus to tissue

2- Cell susceptibility to virus multiplication

3- Virus susceptibility to host defenses

4- The virulence characteristics of the infecting virus.

➢ **Outcome of Viral Infection**

❖ **Acute Infection**

✓ Recovery with no residue effects

✓ Recovery with residue effects e.g. acute viral encephalitis leading to neurological sequelae.

✓ Death

✓ Proceed to chronic infection

❖ **Chronic Infection**

1- Silent subclinical infection for life e.g. **CMV**
2- A long silent period before disease e.g. **HIV**
3- Reactivation to cause acute disease e.g. **herpes**.
4- Chronic disease with relapses and exacerbations e.g. **HBV, HCV**.
5- Cancers e.g. (Human herpes-8) **HHV-8**

➢ **Factors included in Viral Pathogenesis**

For pathogenic virus, there are a number of critical stages in replication which determines the nature of disease they produce which included;

1-Entry into the Host

2-Course of Infection (Primary Replication ,Secondary Replication, Systemic Spread, spread throughout the host)

3-Cell/Tissue Tropism

4-Cell/Tissue Damage

5-Host Immune Response

6-Virus Clearance or Persistence

1- **Entry into the host**

The first stage in any virus infection. In the case of pathogenic infections, the site of entry can influence the disease symptoms produced. Infection can occur via:

A- Skin

B- Respiratory tract

C- Gastrointestinal tract

D- Genitourinary tract

E- Conjunctiva and other mucous membranes

2-Course of Viral Infection

❖ **Primary Replication**

After entry to potential host, the virus must initiate an infection by entering a susceptible cell. This frequently determines whether the infection **will remain localized at the site of entry** or spread to become systemic infection.

Localized infections

Virus primary replication	
Rhinoviruses Papillomaviruses Rotaviruses	upper respiratory tract Epidermis Intestinal epithelium

❖ **Secondary replication**

Occurs in systemic infections **when a virus reaches other tissues in which it is capable of replication,** e.g. **poliovirus** (gut epithelium- nervous in brain &spinal cord). If the virus can be prevented from reaching tissues where secondary replication can occur, generally no disease results.

Systemic Infections

Virus	**primary replication**	**secondary replication**
Enteroviruses Herpesviruses	Intestinal epithelium Oropharynx or G.U. tract	Lymphoid tissues, C.N.S Lymphoid cells, C.N.S

❖ **Spread throughout the host**

Apart from direct cell-cell contact, there are 2 main mechanisms for spread throughout the host:

- **Via the bloodstream**
- **Via nervous system**

The virus may get into the bloodstream by **direct inoculation**- e.g. Arthropod vectors, blood transfusion, or I.V drug abuse.

The virus may travel **free in the plasma** (Togaviruses, Enteroviruses) or in **association with** red cells (Orbiviruses) platelets (Herpes simplex virus). Spread to the nervous system is preceded by primary viremiaa.

3- Cell/ Tissue tropism

Tropism- is the ability of a virus to replicate in **particular cells or tissues**- is controlled partly by **the route of infection** but largely by **the interaction of a virus attachment protein (V.A.P)** with a specific receptor molecule on the surface of a cell and has a considerable effect on pathogenesis.

4-Host immune response

Has a major impact on the outcome of an infection. In the most cases the virus is cleared completely from the body and results in complete recovery. In other infections, the immune response is unable to clear the virus completely and the virus persists. In general, cellular immunity plays the major role in clearing virus infection whereas humoral immunity protects against reinfection.

5- Cell /Tissue damage

Viruses may replicate widely throughout the body without any disease symptoms **if** they **do not** cause significant cell damage or death. **Retroviruses** do not generally cause cell death, being released from the cell by budding rather than by cell lysis and cause persistent infections, even being passed vertically to offspring if they infect the germline.

6- Viral Clearance or Persistence

The majority of viral infections are cleared but certain viruses may cause persistent infections. There are 2 types of chronic persistent infections : **1-True Latency** -the virus remains **completely latent** following primary infection e.g. **Herpes simplex virus** .

2- **Persistence** - the virus **replicates continuously** in the body at a **very low level e.g. (HIV)**

Virulence and cytopathogenicity

Viral strains that kill target cells and cause disease are called **virulent viruses**, but other strains that have mutated and lost their ability to cause cytopathic effect (CPE) and disease are termed as **nonvirulent** or **attenuated strains**. Some attenuated strains can be used as **live vaccines**. Examples are **MMR** (measles, mumps, rubella).

Virulence: is the relative ability of a virus to cause disease, virulence can be measured as the degree of pathogenicity between closely related viruses to cause disease.
Cytopathogenicity: is the ability of a virus to cause degenerative changes in cells or cell death.

Virulence and cytopathogenicity depend on the nature of viruses and the characteristics of cells such as permissive and non-permissive cells.
a- **A permissive cell**: **permits** production of **progeny virus particles** and \ or **viral transformation**.

b- **A non-permissive cell** does **not** allow **virus replication**, but it may permit **the transformation of the cell**.

- Replication of the virus results in alterations of cellular morphology and function, when a lytic virus infects a permissive cell, lots of daughter viruses are produced and this is followed by lysis of the infected cells, called **cytopathic effects (CPE)** of the virus and that changes of the cell followed by cell death.

The features of CPE are morphologic changes of the cell organelles including:
1- **Nucleus** (inclusion bodies, thickening of the nucleus, swelling, nucleolar changes, margination of chromatin)

2- **Cytoplasm** (inclusion bodies, vacuoles).
3- **Membranes** (cells round up, loss of adherence, cell fusion {syncytial})
4- **Cellular lysis** (disintegration).

Transmission of human viruses

Infection can be **direct**, for instance, **respiratory** spread of influenza virus, or **indirect**, for example, arboviruses (west nile virus, yellow fever virus, dengue virus) transmission involving a **mosquito vector**.

Viruses are transmitted via 3 ways:

1- **Horizontal** (common route of transmission : **person to person**)

2- **Vertical** (**mother –to-child** transmission) routes can occur in utero, during delivery (via birth canal), and through breast-feeding. Some viruses are transmitted through sexual routes.

3- **Zoonotic** (**animal-to-human**) transmission of viral infections can occur from the bite of animals (eg, rabies) or insects (eg, dengue, yellow fever, west Nile) or from inhalation of animal excreta (eg, hantavirus, arenavirus).

Routes of transmission

1- Direct Contact Transmission

Direct **contact transmission** occurs through direct body contact with the tissues or fluids of an infected individual. Physical transfer and entry of microorganisms occurs through mucous membranes (e.g., eyes, mouth), open wounds, or abraded skin. Direct **inoculation** can occur from bites or scratches.

2- Fomite Transmission

Fomite transmission involves inanimate objects contaminated by an **infected individual** that then come in contact with a susceptible animal or human. Fomites can include a wide variety of objects such as exam tables, cages, medical equipment, environmental surfaces, and clothing. Disease examples include **canine parvovirus** and **feline calicivirus** infections.

3- Aerosol (Airborne) Transmission

Aerosol transmission encompasses the transfer of pathogens via very small particles or droplet nuclei. **Aerosol particles** may be inhaled by a susceptible host or deposited onto mucous membranes or environmental surfaces. This can occur from breathing, coughing, sneezing, or vocalization of an infected individual, but also during certain medical procedures (e.g., bronchoscopy, dentistry, inhalation anesthesia). Very small particles may remain suspended in the air for extended periods and be disseminated by air currents in a room or through a facility. However, most pathogens pertinent to companion animal veterinary medicine do not survive in the environment for extended periods or do not travel great distances due to size and as a result require close proximity or contact for disease transmission. Examples of common aerosolized pathogens include **canine influenza**, and **canine distemper** virus.

4- Oral (Ingestion) Transmission

The ingestion of pathogenic organisms can occur from contaminated **food** or **water** as well as by licking or chewing on **contaminated objects** or surfaces. Environmental contamination is most commonly due to **exudates**, feces, urine,or saliva. Examples of diseases acquired via oral transmission include **feline panleukopenia**.

5- Vector-Borne Transmission

Vectors are living organisms that can transfer pathogenic microorganisms to other animals or locations and include **arthropod vectors** (e.g., mosquitoes, fleas, ticks) and **rodents** or **other vermin**. Vector-borne transmission can be

an important route of transmission in climates where these pests exist year-round and may be brought into the practice by an infested patient. Examples of vector borne disease is **plague**.

6- Sexually transmitted

Sexually transmitted of viruses are more common.

Important terms

Viral Disease: is the result of complex interactions between the virus and susceptible host.

Infectivity: is the frequency with which an infection is transmitted when there is contact between a virus and a susceptible host, and represents the ability of the virus to infect an individual. Measures of infectivity are generally expressed as attack rates (number of persons infected after exposure/ the number of susceptible persons).

Prevalence: is the total number of cases of disease in a population during a defined time period (number of new and old cases of disease \ population at risk), and represents the burden of disease in a population.

Incubation period: is the time between exposure to the organism and appearance of the first symptoms of the disease (after virus entry into the host, viruses have variable incubation periods).

Epidemiology: deals with distribution and determinants of disease in human populations.

- **Endemic** (disease present at fairly low, but constant level).
- **Epidemic** (infection greater than normally occurs in the population)
- **Pandemic** (infections that are spread worldwide involving a novel

virus and person-to-person spread).

Questions

1- ---------- is defined as the time from the onset of infection to the appearance of virus extracellularly.

2- Enumerate the replication steps of virus?

3- Mention the types of viral release ways from the host cell infection ?

What is the pathogenesis of virus ?

Write the important routs for transmission of viruses?

What are you know about the following?

- Incubation period
- vertical transmission
- horizontal transmission
- Animal-to-human transmission

Q/ give definition to:

Virulence, pathogenicity, Cytopathogenicity, Tropism, infectivity, epidemiology, Pandemic.