Histopathology2

Lecture 4

Diseases Caused by Viruses

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Viruses:

OVERVIEW

Obligate intracellular agent which ,depend on host in their replication ,composed of nucleic acid core (DNA or RNA) surrounded by a protein coat.

The viruses are:

1- The smallest infectious agents ranging from about 20-300nm in diameter.
2- They are all potentially infectious.
3- The viruses are presence of a single nucleic acid, absence of enzymes for energy, metabolism and absence of ribosomes.
4- They are obligate parasites; also they can be reproduce, living, growth inside living cells by using cellular synthesis machinery.
5- Most of viruses infect specific host cells that are due to specific attachment sites on the **host cells** called receptors.

Structure of virus:(Figure 1)

1-Nucleic acid (DNA or RNA): The DNA or RNA could be single or double stranded, linear or circular, exist as a single piece or multi – segmented pieces.

2- A capsid or a protein coat:

- Which is made up of protein subunits called capsomers surrounding the nucleic acid.
- It's function encases and stabilizes the viral nucleic acid against the extracellular environment
- Facilities the attachment and penetration by the virus upon contact with new susceptible cells.

3-Envelope:

- In some viruses, there is an outer envelope that encloses the coat.
- It is consist of lipids, proteins, and carbohydrate, derived from host cell membrane and may contain some proteins synthesized from virus genes.

4-Spikes: Spikes were enclosed of the envelope and can be attachment the membranes of the host cells.

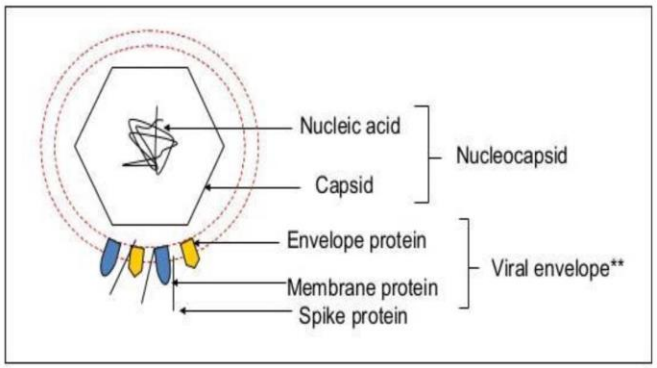

Figure 1. schematic overview of the structure of animal viruses.

Classification of viruses:

They are depends on the:

1. Site of infection: animal virus, plant virus, insect virus, bacterial virus (bacteriophage).
2. Type of nucleic acid
3. Shape of capsid.
4. Present or absence of envelope.

Viral genetic and Viral replication

Viral Nucleic Acids

- The viral nucleic acid (genome) is located internally and can be either single- or double-stranded DNA or single- or double-stranded RNA.
- Only viruses have genetic material composed of single-stranded DNA or of single stranded or double-stranded RNA.
- The nucleic acid can be either linear or circular.
- The DNA is always a single molecule; the RNA can exist either as a single molecule or in several pieces. For example, both influenza virus and rotavirus have a segmented RNA

genome.
- Almost all viruses contain only a single copy of their genome (i.e., they are haploid).
- The exception is the retrovirus family, whose members have two copies of their RNA genome (i.e., they are diploid).

Viral genetics

Viruses grow rapidly, there are usually a large number of progeny virions per cell. There is, therefore, more chance of mutations occurring over a short time period. The nature of the viral genome (RNA or DNA; segmented or non-segmented) plays an important role in the genetics of the virus. however , Viruses may change genetically due to mutation or recombination. DNA viruses tend to more genetically stable than RNA viruses. There are error correction mechanisms in the host cell for DNA repair, but probably not for RNA.

Mutation in viruses

1-Spontaneous mutations
2-Mutations that are induced by physical or chemical means.

Types of mutation

1. Point mutation.
2. Insertion mutation.
3. Deletion mutation.

Recombination:

Exchange of genetic information occurs when viruses of two different parent strains coinfect the same host cell and interact during replication to generate virus progeny that have some genes from both parents.

Replication of viruses:

is the formation of viruses during the infection process in the target host cells. Viruses must first get into the cell before viral replication can occur.

∇ Most DNA viruses assemble in the nucleus while most RNA viruses develop solely in cytoplasm.

Steps of viral replication (Figure 2)

A. Attachment & adsorption :

This is the first step in viral replication. Surface proteins of the virus interact with specific receptors on the target cell surface.

B. Penetration (Uptake):

After binding of virus, virus is taken up inside the cell which is referred as penetration or engulfment,

C. Uncoating:

This process include release of the viral genome from its protective capsid to enable the viral nucleic acid to replicate. The period of the replication cycle between the end of the uncoating stage and maturation of new viral particles is termed the Eclipse period . No virus is found inside the cell during this period .

D- Gene expression and genome replication

E- Assembly:

New virus genomes and proteins are assembled to form new virus particles. The assembly occurs in nucleus or cytoplasm of host cell depending upon types of virus. DNA virus assembled in nucleus except Poxvirus and RNA viruses assembled in cytoplasm except Influenza virus and Reo virus.

F- Release:

Release of mature virus from host cell is the final event in virus replication. enveloped viruses are released by budding from the infected cells. Unenveloped viruses are released by rupture or lysis of the infected cells.

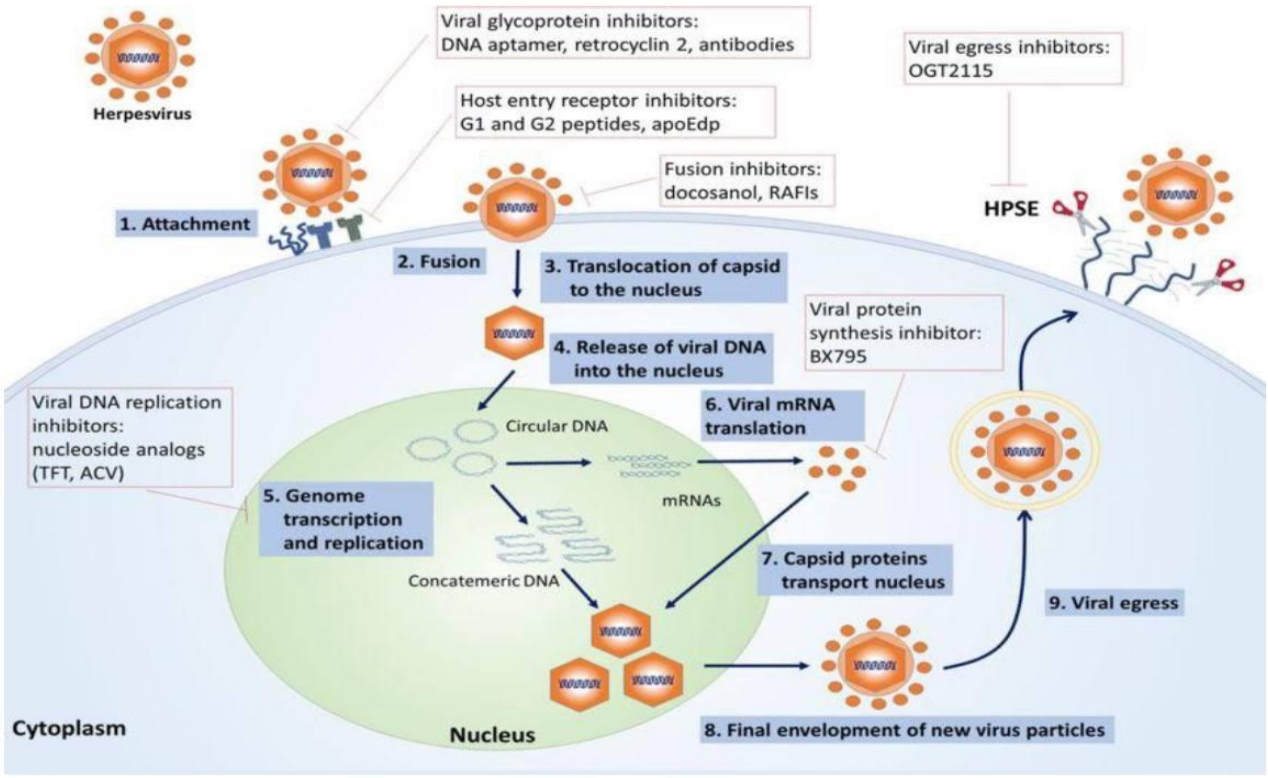

Figure 2. Replication steps of viruses (Herpes virus)

Some viruses cause diseases:

Viruses are important agents of many human diseases which ranging from the trivial (e.g.common cold) to the lethal (e.g. rabies) and viruses play role in the development of some types of cancer.

Viral infection:

- HIV (human immune deficiency virus)
- Viral hemorrhagic fever
- COVID 19

HIV (human immune deficiency virus):

Cause: it is caused by a Retrovirus called human immune deficiency virus, which is of two types:

- HIV I common in USA, Europe, central Africa.
- HIV II common in western Africa.

Structure of the virus:
The virus is composed of:

1. Two RNA strands.
2. Reverse transcriptase enzyme.
3. An outer envelope from the host cell membrane.

Transmission:

Sexually transmitted (homosexual males &heterosexual contacts of high risk groups). Parenteral route (I.V drug abusers, hemophiliacs, blood transfusion) From mother to baby (through the placenta, intrapartum during delivery or ingestion of infected breast milk.

HIV cannot be passed on by:

- kissing
- hugging
- shaking hands
- sharing space with someone
- sharing a toilet
- sharing household items such as cups, plates, cutlery, or bed linen
- any other general social contact.

Pathogenesis:

At the contact surface, which is usually a mucosal surface, the macrophages will get the virus, then they will secrete certain mediators result in accumulation of CD4 +ve T- lymphocytes , then the virus will get inside the CD4+ cells and start to use its reverse transcriptase enzyme to form proviral DNA & get incorporated into the host DNA result in formation of complete viral particles that bud from the cell membrane & will direct the cell for producing more HIV particles.

Outcome:

- Decrease CD4+ helper T lymphocytes.
- Increase CD8+ cytotoxic T lymphocytes.
- Impaired cell mediated immunity.
- Impaired humoral immunity.
- Abnormal macrophage function, decrease in chemotactic substances.

• If the virus remains inside the cell then this is called LATENT infection.
• If the virus replicate and release a new viruses◊ cell rupture and death i.e loss of the CD4 + cells , this is called PRODUCTIVE infection.

Natural history of HIV infection:

Three phases:

1. Early acute phase: it is the initial response of immunocompetent adults to HIV infection &it is a self limited illness develops 3-6 weeks after infection & characterized by nonspecific symptoms like sore throat,myalgia and fever . **High level of virus production &viremia**.
-CD4+ T cells count is more than 500 cells/microlit.

2. Middle chronic phase (a stage of relative containment of the virus (decrease viremia). The immune system is intact, but there is continued viral replication that may lasts for several years.
- Patients are either asymptomatic or develop persistent lymphadenopathy or minor opportunistic infections e.g thrush or herpes zoster.
- CD4+ T cells count is 200-500 cells/micolit.

3. Final crisis phase: Characterized by catastrophic breakdown of host defenses, marked increase in viremia &clinical course.
- Patients presented with fever of more than 1 month, fatique, weight loss &diarrhea.
- CD4+ cells count is less than 200 cells/micolit.
- Patients develop serious opportunistic infections, secondary neoplasms &/or neurological manifestations (AIDs defining conditions).

AIDS: (acquired immune deficiency syndrome)

It consists of groups of clinical signs and symptoms which will appear when the lymphocyte count drops to < 200 / microlit. In which the characteristic opportunistic infections and neoplasms of AIDS will appear.

Opportunistic infections:

- **Protozoal infection** (Pneumocystis carinii, toxoplasmosis &cryptosporidiosis).
- **Viral infection** (*cytomegalovirus, herpes simplex, varicella zoster*.
- **Bacterial infection** (mycobacterium T.B, nocardiosis &salmonella).

- **Fungal infection** (Candida, Histoplasma, Cryptococcus).
- **GIT protozoal infections**.

Malignant neoplasms:

Patients with AIDs have increased risk of malignancy because of:
- Profound defects in T cell immunity.
- Dysregulated B cell &monocyte functions.
- Multiple infections with known (e.g herpesvirus type 8, EBV, human papillomavirus) & unknown viruses.

These neoplasms include:

- **Kaposi sarcoma** Figure 3: it is a vascular tumor appears as purple nodule over the skin.
- **Malignant lymphoma**, mainly of the non Hodgkin type (diffuse large cell type of B cell origin).
- **Primary lymphoma of the brain**.
- **Invasive cancer of uterine cervix** due to increase prevalence of human papilloma virus.

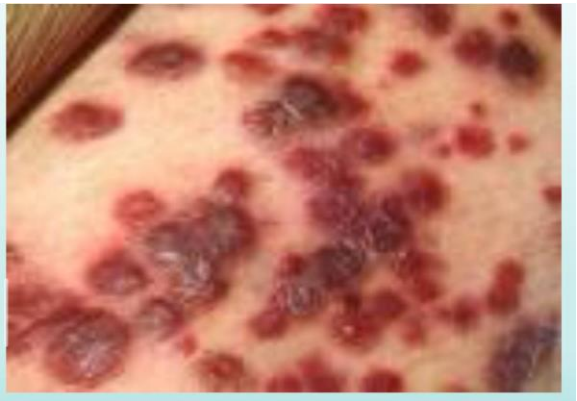

Figure 3. Kaposi sarcoma in patient with HIV infection.

Treatment of HIV

HIV is treated with antiretroviral medicines, which work by stopping the virus replicating in the body. This allows the immune system to repair itself and prevent further damage.

One of the main goals of HIV treatment is to reduce a person's viral load to an undetectable level. People with HIV who maintain an undetectable viral load have effectively no risk of transmitting HIV through sex, and a significantly lower risk of transmission through other means (such as shared needles).

Reducing viral load to **undetectable levels** in HIV treatment is a key goal, as it has several implications:

Immune system recovery: The reduction in viral replication allows the immune system to repair and restore CD4+ T lymphocyte counts, improving immune function.

Prevention of transmission: With an undetectable viral load, the risk of sexual transmission is **effectively zero**. This concept is known as **undetectable = untransmittable (U=U)**. The risk of transmission through other routes, such as needle-sharing, is also significantly reduced.

Note (People with HIV who are on effective treatment and have an **undetectable viral load** cannot pass on HIV through any of their body fluids.)

Viral Hemorrhagic Fever

- It is a severe life-threatening multisystem syndrome, in which there is vascular damage, leading to widespread hemorrhage and shock.
- The disease is transmitted to humans by bites of infected ticks, and by direct contact with blood or tissues from infected humans and livestock.
- Iraq is one of the eastern Mediterranean countries where is endemic with Crimean-Congo HF.

- **Viral hemorrhagic fever is caused by viruses of four distinct families:** Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae.

- **Each of these families share a number of features:**

1. They are all RNA viruses, and all are enveloped, in a fatty (lipid) coating.
2. Their survival is dependent on an animal or insect host, called the natural reservoir, (typically rodents) or insect vectors (mosquitoes and ticks).
3. The viruses are geographically restricted to areas where their host species live.
4. Some viruses that cause hemorrhagic fever (Ebola, Marburg, Lassa) also can spread from person to person.

Pathogenesis

- The pathogenesis of the infection and its complications vary among the different viruses, but there are some common features.
- Damage to blood vessels is often prominent, it may caused by direct infection of and damage to endothelial cells, or infection of macrophages and dendritic cells leading to production of inflammatory cytokines.
- Ebola carries a very high mortality rate, about 40% during the 2019 outbreak.
- With a few noteworthy exceptions, there is no cure or established drug treatment for Viral hemorrhagic fever.
- Effective vaccines for Ebola have been developed, and use of these will reduce the burden of disease.

Coronavirus SARS-CoV-2 (COVID-19)

- A novel coronavirus SARS-CoV-2-mediated disease called COVID-19 was first detected in Wuhan, China, and was reported to the WHO in December 2019.
- By the end of March 2020, the infection had become a worldwide pandemic.
- Epidemiologic studies suggest that the origin was a seafood and animal market in Wuhan, consistent with initial animal to-human transmission followed by person-to-person spread soon thereafter.
- The clinical manifestations ranged from mild to severe respiratory illness.
- The vastmajority of individuals who contract the virus recover after a flu-like disease.
- Severe and fatal illness with respiratory compromise, often associated with bilateral ground-glass opacities on chest imaging, occurs mainly in older individuals and those with comorbidities such as diabetes, COPD, and heart failure.
- The genomic sequence shows COVID-19 is related to bat coronaviruses and the SARS coronavirus.
- Histologic analysis of lung tissue done in patients revealed diffuse alveolar damage and inflammation with mainly mononuclear cells.

Questions

1. Explain the zoonotic origin of SARS-CoV-2, including the role of the Huanan Seafood Market, its genetic link to bat coronaviruses and SARS-CoV, and evidence of animal-to-human and human-to-human transmission.
2. What histological findings are commonly seen in the lungs of COVID-19 patients?
3. Describe the detailed structural components of the HIV virus, including the roles of its two RNA strands, reverse transcriptase enzyme, viral envelope, and other key proteins, and explain how these structures facilitate the virus's replication and integration into the host genome.
4. Discuss the implications of viral load reduction to undetectable levels in HIV treatment and its impact on transmission.
5. What is the main pathophysiological feature of Ebola infection?

6. Difference between latent and productive infection in viral hemorrhagic fever?
7. Discuss the role of natural reservoirs in the transmission dynamics of viral hemorrhagic fevers, and their impact on epidemic control.
8. How do viral hemorrhagic fever viruses evade host immune responses, and what makes treatment particularly challenging?
9. Explain the role of antiretroviral therapy in reducing viral replication and its subsequent effects on the immune system, particularly in terms of CD4+ T lymphocyte recovery, and how this contributes to the concept of "undetectable = untransmittable" (U=U) in HIV transmission.
10. How do mutations in RNA viruses contribute to **antigenic drift** and the development of viral resistance?
11. How do the replication rates of viruses contribute to genetic variation, and why is this particularly significant for RNA viruses?
12. Explain the role of recombination in viral evolution and how it differs from mutation.
13. What is the primary method of preventing HIV transmission in people with an undetectable viral load?
    a) Complete avoidance of sexual contact
    b) Use of highly effective antiretroviral treatment.
    c) Taking antibiotics.
    d) Regular vaccinations.
    e) Drinking large amounts of water.
    f) Using a condom only during menstruation.
14. Which of the following is NOT a characteristic of the HIV virus?
    a) It contains two RNA strands .
    b) It uses reverse transcriptase to convert its RNA into DNA.
    c) It has a protein shell called the capsid.
    d) It has an outer envelope derived from the host cell membrane.
    e) It replicates in the nucleus of the host cell.
    f) It infects CD4+ T lymphocytes.

Good Luck