

Virology

Lec (3)

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Teaching Objectives:

1. To list steps of pathogenesis.
2. To recognize the differences between local and systemic infection.
3. To explain viral pathogenesis at the cellular level.

Pathogenesis: The ability of viruses to cause disease, viruses must enter a host, come in contact with susceptible cells, replicate, and produce cell injury.

Steps in viral pathogenesis:

1-Viral entry and Primary viral replication:

- ✚ **Skin** [Bites like rabies and yellow fever virus, **Injection** like HBV, HCV, HIV, HSV and **Mild trauma** like HPV and pox virus.
- ✚ **Respiratory tract** [Influenza virus, Respiratory syncytial virus and Cytomegalovirus]
- ✚ **Gastrointestinal tract** [Rotavirus, Poliovirus and Hepatitis A virus (HAV)].
- ✚ **Urogenital tract** [Human papillomavirus (HPV), Herpes simplex virus-2 (HSV-2)].
- ✚ **Transplacental** [Rubella and Cytomegalovirus (CMV)].

Some viruses replicate at the primary site of entry like influenza viruses (respiratory infectious) and rotaviruses (gastrointestinal infectious), this viruses produce disease at the portal of entry and have no further systemic spread and usually name locally infection. They spread locally over the epithelial surfaces, but there is no invasion of underlying tissues or spread to distant sites.

2- Viral spread and cell tropism.

Many viruses produce disease at site distant from their portal of entry like poliovirus which enter through the gastrointestinal tract but may produce central nervous system disease, this virus's primary replication at the site of entry, then spread within the host via the blood stream or lymphatic's. The presence of virus in the blood is called **viremia**.

* The differences between local infection and systemic infection.

Important features	Local infection	Systemic infection
Site of pathology	Portal of entry	Distant site
Incubation period	Relatively short	Relatively long
Duration of immunity	May be short	Usually lifelong
Viremia	Absent	Present
Role of secretory antibody (IgA) in resistance	Important	Not important

Viruses tend to exhibit organ and cell specificities; tropism determines the pattern of systemic illness produced during a viral infection. As an example hepatitis B virus has a tropism for liver hepatocytes, and hepatitis is the primary disease caused by the virus.

Tissue and cell tropism by a given virus usually reflect the presence of specific cell surface receptors for that virus. Receptors are components of the cell surface with which a region of viral surface (capsid or envelope) can specifically interact and initiate infection. Factors affecting viral gene expression are important determinants of cell tropism also some viruses need proteolytic enzymes, certain paramyxoviruses are not infectious until an envelope glycoprotein undergoes proteolytic cleave.

3- Cell injury and clinical illness.

Destruction of virus infected cells in to the target tissues and physiologic alterations produced in the host by the tissue injury are partly responsible for the development of disease in some tissues such as intestinal epithelium can rapidly regenerate and withstand extensive damage better than others such as brain.

Clinical illness from viral infection is the result of a complex series of events the general symptoms is malaise and anorexia, can be result from host response function such as cytokine.

4- Recovery from infection.

Recovery mechanisms include both non-specific and specific immune response, interferon and other cytokines, humeral and cellular - mediated immunity and possibly other host defense factors are involved.

5- Viral shedding.

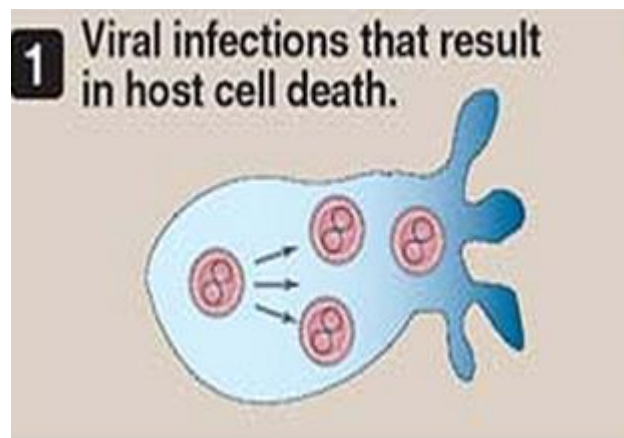
The last stage in pathogenesis is the shedding of infectious virus into the environment. This is a necessary step to maintain a viral infection in population of hosts. Shedding usually occurs from the body surfaces involved in viral entry. Shedding does not occur in some viruses like rabies virus.

Viral pathogenesis at the cellular level. Cells show a variety of different responses to viral infection, depending on the cell type and virus. Many viral infections cause no apparent morphologic or functional changes in the cell (This observation highlights the wide variations in the nature of the interaction between the virus and the cell). When

changes do occur, several (potentially overlapping) responses can be recognized, there are four main effects of virus infection on the cell.

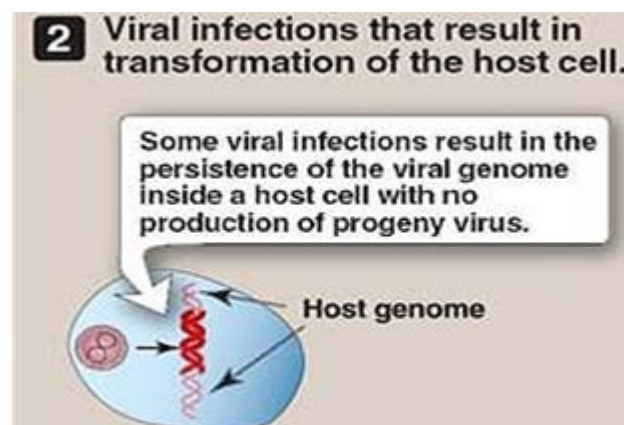
1- Death of the cell.

Due to inhibition of macromolecular synthesis like inhibition of host cell protein synthesis frequently occurs first and is probably the most important effect. Inhibition of DNA and RNA synthesis may be a secondary effect for example poliovirus inactivates an initiation factor (IF) required for cellular mRNA to be translated into cellular proteins. But poliovirus mRNA has a special ribosome initiating site that allows it to bypass the IF so that viral proteins can be synthesized.



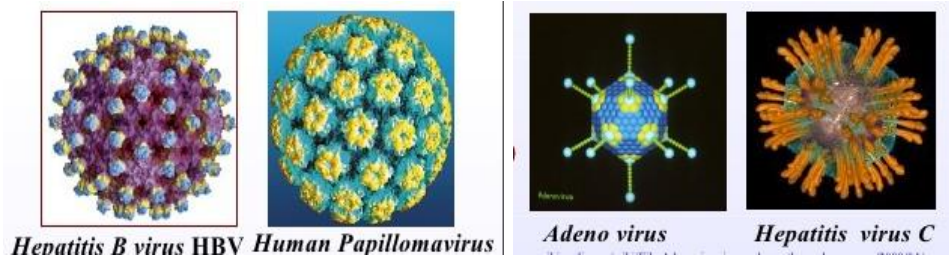
2- Malignant transformation.

Some viruses transform normal cells into malignant cells. In many ways, this is the opposite of cell death, because malignant cells have less fastidious growth requirements than do normal cells, and they have an indefinitely extended lifetime. Transformation is an irreversible genetic process caused by the integration of viral DNA into the host's DNA. Occurs when cells are infected with oncogenic viruses like EBV, HBV and HPV.



DNA viruses

- **Small DNA tumor viruses**, which include Human papilloma virus (HPV), SV40 and Adenovirus .
- **Large DNA tumor viruses**, herpesviruses such as Epstein Barr virus (EBV) and kaposi sarcoma herpesvirus (KSHV).
- **Other** hepatitis B virus (HBV)



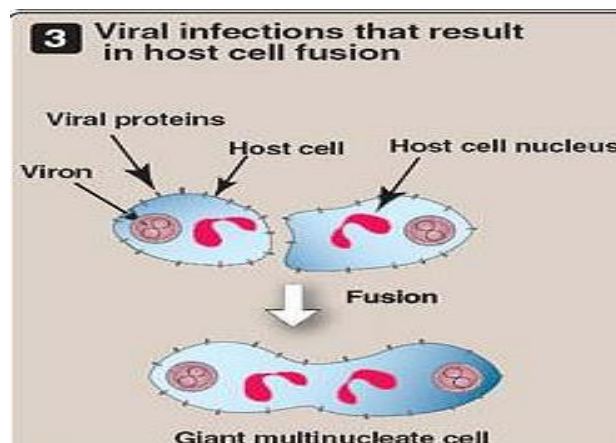
80% of viral associated cancers are cervical cancer (HPV) and liver cancer (HBV and HCV).

RNA viruses

Human T cell leukemia virus 1 (HTLV1)

3- Fusion of cells to form multinucleated cells.

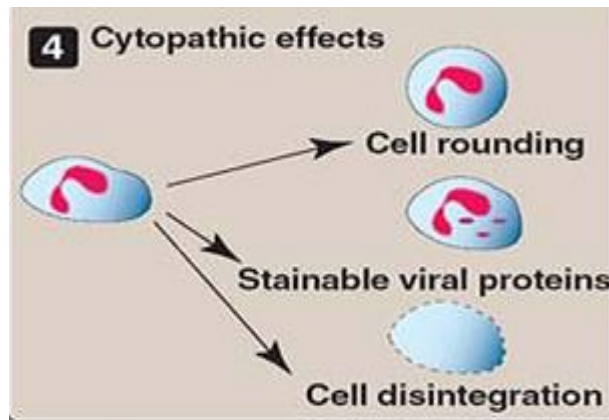
After infection with Herpes simplex virus and Respiratory syncytial virus. Fusion occurs as result of cell membrane changes which are probably causal by the insertion of viral proteins into the membrane.



4- Cytopathic effect (CPE).

cytopathic effect or cytopathogenic effect (abbreviated CPE) refers to structural changes in the host cells that are caused by viral invasion. The infecting virus causes lysis of the host cell or when the

cell dies without lysis due to an inability to reproduce. Both of these effects occur due to CPEs. If a virus causes these morphological changes in the host cell, it is said to be cytopathogenic. Common examples of CPE include rounding and darkening of the infected cell, fusion with adjacent cells to form syncytia or giant cell, and the appearance of nuclear or cytoplasmic inclusion bodies. Detection of virus in a clinical specimen frequently is based on the appearance of CPE in cell culture.



Infection of cells with certain viruses leading to formation of Inclusion bodies, are aggregates of virions in specific location in the cell that are useful for laboratory diagnosis, two important examples are Negribodies in the cytoplasm of rabies virus-infected cells and owl's eye inclusion in the nucleus of cytomegalovirus- infected cells.

Common types of CPEs

Total destruction

Total destruction of the host cell monolayer is the most severe type of CPE. To observe this process, cells are seeded on a glass surface and a confluent monolayer of host cell is formed. Then, the viral infection is introduced.

Subtotal destruction

Subtotal destruction of the host cell monolayer is less severe than total destruction. Similarly to total destruction, this CPE is observed by seeding a confluent monolayer of host cell on a glass surface then introducing a viral infection.

Focal degeneration

Focal degeneration causes a localized attack of the host cell monolayer. Although this type of CPE may eventually affect the entire tissue, the initial stages and spreading occur at localized viral centers known as foci. This type of CPE is characteristic of herpesviruses and poxviruses.

Swelling and clumping

Swelling and clumping is a CPE where host cells swell significantly. Once enlarged, the cells clump together in clusters. Eventually, the cells become so large that they detach. This type of CPE is characteristic of adenoviruses.

Foamy degeneration

Foamy degeneration is also known as vacuolization. It is due to the formation of large and/or numerous cytoplasmic vacuoles. This type of CPE can only be observed with fixation and staining of the host cells involved. Foamy degeneration is characteristic of certain retroviruses, paramyxoviruses, and flaviviruses.

Syncytium

Syncytium is also known as cell fusion and polykaryon formation. With this CPE, the plasma membranes of four or more host cells fuse and produce an enlarged well with at least four nuclei. Although large cell fusions are sometimes visible without staining, this type of CPE is typically detected after host cell fixation and staining. Herpesviruses characteristically produce cell fusion as well as other forms of CPE. Some paramyxoviruses may be identified through the formation of cell fusion as they exclusively produce this CPE.

Inclusion bodies

Inclusion bodies may only be seen with staining as they indicate areas of altered staining in the host cells. Typically, they indicate the areas of the host cell where viral protein or nucleic acid is being synthesized or where virions are being assembled. Also, in some cases, inclusion bodies are present without an active virus and indicate areas of viral scarring. Inclusion bodies vary with viral strain. They may be single or multiple, small or large, and round or irregularly shaped. They may also be intranuclear or intracytoplasmic and eosinophilic or basophilic.

Viral persistence

- 1- Chronic infection:** In which the virus can be continuously detected, often at low levels; severe, mild or no clinical symptoms may be evident.
- 2- Chronic carrier:** The patient who has been infected with certain virus continues to produce significant amount of the virus for a long period. eg HBV and HCV.
- 3- Latent infections:** In which the virus persists in an occult or cryptic form most of the time. There will be intermittent flair-ups. HSV type 1 is latent in the trigeminal ganglia.
- 4- Slow virus infections:** Prolonged period between the initial infection and the onset of the disease, which is usually measured in years. Subacute sclerosing panencephalitis (SSPE) which follows several years after measles virus infection, and the second disease is progressive multifocal leukoencephalopathy (PML) caused by JC virus a papovavirus.