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Introduction to

Microbiology

Title :

Virus Pathogenicity- virololgy

Professor:

Dr. Ashraf Al-Khasawneh

: 14

- ○ Slides
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Done by: Sally Khateeb

Price: .....

Designed by:
Waseem Kamal

M.D University of Jordan Class of 2018

groups/Doctor2012
http://medstudygroup.weebly.com

Microbiology
Dr. Ashraf Khasawneh
Lecture – 15 –

Ω Retroviruses:

- Concerning the ***replication*** of **retroviruses**: certain mRNAs become the new genome for the newly synthesized progeny viruses, and other mRNAs go to the ribosomes and become translated into proteins.

  Just make sure you correct this in the sheet; if it was wrong in the first place.

Ω Replication Challenges for DNA Viruses:

- **Access to nucleus:**
  - Certain types of small DNA viruses, like parvoviruses, the whole nucleocapsid enters into the nucleus.
  - If the capsid is large, then the capsid will dissociate in the cytoplasm, and the genome will enter in to the nucleus.
- **Competing for nucleotides:**
  - It competes for the cellular nucleotides, because we generating new strands of RNA or DNA.
- **Cell cycle control in eukaryotes – S phase dependent materials for some viruses (Parvoviruses):**
  - S-phase is the phase at which the cell can provide all the enzymes and machinery required for replication.
  - We said that Parvovirus waits for the cell to enter the S-phase to use its machinery.
  - On the other hand, other viruses produce certain enzymes that induce the cell to enter the S-phase. Or they might interfere with certain enzymes in the cell like retinoblastoma and p53.

Ω Assembly:

- This is the next step of viral replication after macromolecular synthesis.
- Assembly involves the collection of all the components necessary for the formation of the mature virion at a particular site in the cell.
  So we replicate the genome and we translate the genetic code into structural and non-structural protein.
- During assembly, the basic structure of the virus particle is formed.
- The site of assembly depends on the site of replication within the cell and on the mechanism by which the virus is eventually released.

- In picornaviruses, poxviruses, and reoviruses assembly occurs in the cytoplasm.
- In adenoviruses, polyomaviruses, and parvoviruses it occurs in the nucleus.

- **Mechanism of Assembly:**
  1. At a **certain place** in the cell, either in the cytoplasm or in the nucleus, we have all the components of the new viruses.
  2. These components accumulate at a **certain location** within the cell, and the first thing we get are the glycoproteins on the surface of the cell.
  3. After that, we get the M-protein or the Matrix Protein.

     The matrix protein and the glycoproteins: their location is correlated with the assembly of the virus.

  4. All the other components of the virus (capsid, genome, nucleocapsid, enzymes, and proteins) go to **that certain place**, and the process of budding starts from there.
  5. The next step is release.

Ω Capsid Assembly:

- **Helical Capsid Assembly:**
  - Capsid is composed of capsomers, which are arranged as a barrel-shape.
  - The capsomers arrange ring by ring; they stack on top of each other.
  - Once the barrel-shape forms, the genome comes and attaches from the inside, and elongates in both directions.

- **Icosahedral Capsid Assembly:**
  - The building units are protomers, which form the capsomers.
  - These protomers start as building blocks forming a scaffold, thus forming a hollow structure closed from all sides except from the top, so the top of the icosahedral structure remains open.
  - After the whole icosahedral structure is ready (except for the top part), the enzymes and the genome get inside.
  - After all the genome gets in, the icosahedral structure closes.

→ **Note:** there are certain DNA viruses, like Herpes virus, which form their genome as a *linear DNA*, so the virus can't fit it inside the scaffold of the icosahedral structure.
This linear DNA is called a **Concatemer**.
Part of this concatemer will enter into the scaffold icosahedral structure, and nucleases will cut the concatemer into pieces, which will rejoin & unite together at a later stage.

Ω Maturation:

- Maturation is the stage of the replication-cycle at which the virus becomes infectious.
- Maturation usually involves structural changes in the virus particle, which may result from specific cleavages of capsid proteins conformational changes in proteins.
- Virus proteases are frequently involved in maturation, although cellular enzymes or a mixture of virus and cellular enzymes are used in some cases.

→ After the step of assembly:
Sometimes before and sometimes after the release of the virus, there has to be multiple steps for the virus to become infectious, and certain cellular enzymes and viral proteases have a role in this maturation step.

Ω Release:

- Apart from plant viruses which have evolved particular strategies to overcome the structure of plant cell walls, all other viruses escape the cell by one of two mechanisms:

1. **For lytic viruses (most non-enveloped viruses):** release is a simple process - the infected cell breaks open and releases the virus. So, in short, naked viruses are released by the lysis of the cell.

2. **Enveloped viruses:** they acquire their lipid membrane as the virus buds out of the cell through the cell membrane or into an intracellular vesicle prior to subsequent release. Virion envelope proteins are picked up during this process as the virus particle is extruded - this process is known as budding.

Pathogenesis of Viral Infections
New Topic

Ω Viral Epidemiology:

- **Endemic:**
  - It means that a disease is present at fairly low but constant level.
  - This doesn't apply for viruses greatly.
  - Example: Malaria, Schistosomiasis (bilharzia) it's present in Egypt, and it's present around the world with the same percentage.

- **Epidemic:**
  - Infection is greater than it's usually found in a population.
  - Example: Influenza during winter months increases than during the whole year.

- **Pandemic:**
  - A disease that starts in one country and spreads to other countries. They are infections that are spread worldwide.
  - Example: Swine flu.

- **Infectivity:**
  - The frequency with which an infection is transmitted when contact between a virus and host occurs.
  - It reflects the transmission of the disease or getting the disease upon exposure to the virus, whether you got the disease (that is an infective), or you didn't get it (it is not infective).
  - **Getting the disease can be classified into:**
    1. **Subclinical Infection:** You might get the disease or become infected with the virus, but at the same time you don't get the disease itself. You're infected with the virus, but it passes unnoticed.

    2. **Apparent Infection:** Symptoms might appear, and you develop the disease.

- **Disease index:** the number of people who developed the disease/total infected.
  Because some people develop the diseases, and others pass the disease unnoticed.

- **Virulence:** number of fatal cases/total number of cases.

- **Incidence:** number of new cases within a specific period of time. It's usually in a percentage.

Example: If the incidence of the disease is 10%; then for each 100 cases of the illness, 10 cases are new over that certain period of time (usually per year).

- **Prevalence:** the number of cases of a disease that are present in a particular population at a given time.
  Example: It's the 100 cases that we mentioned in the incidence.

Ω What does a pathogen have to do?

1. Infect or infest the host, but since we're talking about viruses then we're talking about infecting the host.
2. Reproduce or replicate itself.
3. Ensure that its progeny are transmitted to another host or to neighboring cells.

Ω Viral Routes of Entry:

1. **Horizontal Route: from person to another person.**

   A) Inhalation: through aerosols (sprays) or droplets via the respiratory tract.
   Examples: respiratory syncytial virus (RSV), measles, mumps, rubella (MMR), Virus Herpes Zoster, and rhinoviruses that are responsible for the common cold.

   B) Ingestion: via the GI tract (oral or fecal). Most of these viruses cause gastroenteritis,
   Examples: rotavirus, astrovirus, calicivirus, and hepatitis A.

   C) Inoculation: can be through skin abrasions or mucous membranes, transfusion, injections, transplant, and sexual transmission
   Example: HIV (mucous membranes, transfusion, injections, transplant, sexual transmission), Hepatitis C, and Hepatitis B.

   For HIV, contraction through blood transfusions and transplants doesn't happen anymore because there's screening.

2. **Vertical Route: from the mother to the fetus.**

   Transplacental:
   - Examples: CMV, Rubella Virus, and HIV virus.
   - Women get screened for the presence of those viruses, in order to prevent contraction to the fetus.

During Delivery:

- Examples: Hepatitis C, Hepatitis B, Herpes Simplex, HIV, and Human Papilloma Virus.

During Breast Feeding:

- Examples: CMV, hepatitis B, and HIV.

Notice that HIV can be transmitted through all these routes in the vertical transmission.

3. **Zoonotic Route: from animals to humans, or through vectors such as bites.**
   - **Animal bite:** rabies (rapid dog to human).
   - **Insect bite:** Dengue, and West Nile.
   - **Animal Excreta:** such as Arenavirus, and Hantavirus. They can be transmitted through bird droppings, where the feces of the birds might get dry and get airborne, and you might inhale them and get the infection.

Ω Sites of Virus Entry:

1. **Skin:**
   - Skin abrasions, cuts, and wounds.
   - Arthropod vectors: mosquito bites.
   - Injections.

2. **Eyes:**
   - Through the conjunctiva of the eye.

3. **Mouth:**
   - Fecal route.
   - Oral route.

4. **Respiratory Tract:**
   - In the respiratory tract we have: ciliated epithelium, mucous secretions (it contains IgA antibodies), and low temperature.
   - All these act as a defense mechanism against any invading microorganisms, whether viruses or bacteria.

5. **Alimentary Canal:**
   - Fecal route or oral route.
   - There are the gastric acids and bile salts, which act as defense mechanism against pathogens.

6. **Urogenital Tract:**
   - It's the most susceptible to infections, because it doesn't have many defense mechanisms, except for the continuous flushing by urination.

Ω Terminology:

- **Incubation Period:** time between exposure to the pathogen and the appearance of the first symptom of the disease.

  Examples:
  Influenza, common cold, and bronchiolitis:
  - They are viruses that cause respiratory tract infections.
  - They are seen mostly in the winter months.
  - They have the shortest incubation period.
  - Incubation period for some viruses:

  Dengue, and Herpes simplex virus: about 1 week.
  Enteroviruses, Poliovirus, and Measles virus: about 1 – 2 weeks.
  Mumps, Rubella, and Chicken pox viruses: about 2 – 3 weeks.
  Mononucleosis virus: about 1 – 2 months.
  Hepatitis A: about 15 days – 1 and a half months.
  Hepatitis B: about 2 – 5 months.
  Rabies Virus: about 10 days – 1 year.
  Papilloma virus: about 2 – 5 months.
  HIV: about 1 – 10 or 15 years.

Doctor said that he might ask us "Which one has the shortest incubation period? Which one has the longest incubation period?"

Ω Terminology:

- **Communicability:**
  - The ability of the virus to shed into secretions.
  - It goes like this: the virus infects the host, then there's the incubation period during which the virus is preparing itself to start replication. Once the virus starts replicating, producing new viruses, and goes to the secretions, then the beginning of production of new viruses is the communicability period.
  - It's the period during which the person becomes infectious to others.

- **Localized infection:**
  - Infection limited to site of entry.
  - Certain viral infections are limited to the site of entry.

- **Disseminated infection:**
  - Viral infections that spread throughout the body.
  - This leads us to primary viremia and secondary viremia.

- **Primary Viremia:**
  - Once the virus enters the body at the site of entry, it goes to the regional lymph nodes, and after that it goes to the blood.

- **Secondary Viremia:**
  - Once the virus enters the body, it goes to another organ (liver, and spleen).
  - The virus is released once again from these organs into the blood.

Primary and secondary viremia leads us to primary and secondary replication.

- **Primary Replication:**

  - Having gained entry to a 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 a systemic infection.
  - The virus enters, then the nature of the virus determines whether the infection will be localized or systemic (spreads to other organs).
  - Localized infection: Influenza virus enters through the upper respiratory tract, causing symptoms related to the infection of the upper respiratory tract. It's a lytic infection that destroys the cells in the upper respiratory tract, and the symptoms you see are related to their destruction.

- **Secondary Replication:**

  - It occurs in systemic infections when a virus reaches other tissues in which it's capable of replication.
  - Poliovirus: the infection starts in GI tract, then it goes to the blood then to the CNS.
  - Retroviruses (Lentivirus: HIV): infection starts in the macrophages, then it might go to the CNS and other tissues as well.
  - *If a virus can be prevented from reaching tissues where secondary replication can occur, generally no disease results:* If we can control the virus at the primary site of enter before it reaches the secondary organ of infection, then we can prevent the disease from occurring in the other tissues.

Localized Infections	
Virus	**Primary Replication**
Rhinoviruses	Upper Respiratory Tract
Rotavirus	Intestinal Epithelium
Papillomavirus	Epidermis

Systemic Infections		
Virus	**Primary Replication**	**Secondary replication**
Enteroviruses	Fecal or oral route	Lymphoid tissue, and CNS
Herpesviruses	Oropharynx (Herpes Simplex type I), or the urogenital tract (Herpes Simplex type II)	Lymphoid cells, and CNS

Localized infection viruses: These are acute viruses, and they remain localized to the site of infection

Herpesviruses: they start by an acute infection, after that they are not shed or excreted or cleared from the body, they are latent or dormant viruses.

Ω **Spread Throughout the Host:**

- Apart from direct cell-cell contact through junctions, there are 2 main mechanisms for spread throughout the host:
  1. Via the bloodstream.
  2. Via the nervous system.

- **Via The Blood Stream:**
  - 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 blood cells (Orbiviruses), platelets (HSV), lymphocytes (EBV, CMV) or monocytes (Lentiviruses).
  - Primary viraemia usually proceeds and is necessary for spread to the blood stream, followed by more generalized, higher titre secondary viraemia as the virus reaches other target tissues or replicates directly in blood cells.
  - The virus enters, goes to the site of entry, regional lymph nodes, and reaching the blood. This is primary Viraemia.
  - Secondary Viraemia: it comes after primary viraemia. The virus goes to another organ, and in that organ it replicates. This replication process generates more viruses, which are spread once again to the blood.
  - Tite → equivalent to the number of viruses present.

- **Via The Nervous System:**
  - General Rule: Spread to nervous system is preceded by primary viraemia. So first it starts in the blood.

- In some cases, spread occurs directly by contact with neurons at the primary site of infection, in other cases via the bloodstream.
- **Example about a virus that might start directly in the CNS:** *Rabies virus*.
  Once a rapid dog bites a human, the bite site might involve the presence of nerves, and the virus might travel along the nerve directly to the CNS.
- Once in peripheral nerves, the virus can spread to the CNS by axonal transport along neurons (classic – HSV, and also the rabies virus).
- Viruses can cross synaptic junctions since these frequently contain virus receptors, allowing the virus to jump from one cell to another

- **Concerning Rabies virus:**
  - Once a rapid dog bites a human, the bite site might involve the presence of nerves, and the virus might travel along the nerve directly to the CNS.
  - The incubation period is long, from 10 days up to 1 year.
  - If you treat the patient once the bite occurs by vaccination (5 doses of vaccination), then you can prevent the infection.
  - If you didn't administer the vaccine, and the virus reaches the CNS, then fate is death within a couple of months.

- **Herpes Simplex Viruses:**
  - They also spread through the nerves.
  - The most famous example that combines *latency* and *spreading through the nerves* is: shingles (Herpes Zoster).
  - This virus can travel through the nerves or dermatomes, and cause an illness.
  - Dormant or latent: the virus has entered previously into the body, but it wasn't shed or cleared from the body, it remained there. Under certain conditions, the virus might become reactivated.

  - Shingles starts as chicken pox in infancy, but it's not cleared from the body, and it goes to the dorsal root ganglia in the nerves, and remaining dormant there.
  - With age (above 50 or 60), or with depression in the immune system of the person, the virus might be activated once again.
  - This virus goes through the nerve that supplies the area that it becomes dormant in.
  - Most of the time it appears in the thoracic region, where you can see the line of damage as a belt where the nerve moves along the dermatome.
  - When it's reactivated, it might cause damage to the nerve, so you might see the lesion on the skin, as well as, post-herpetic neuralgia or severe pain due to this reactivation and replication within the nerve cells.

Ω Virulence & Cytopathogenicity:

- **Virulence:**
  - The ability of the virus to cause disease in an infected cell. If it contract the disease it a virulent virus, if it does not it is avirulent.

- **Infections:**
  1. Acute Infection: such as influenza virus, which comes and causes a disease, then within 10 days the person completely recovers.

  2. Persistent Infection.
     a. Chronic.
     b. Latent.

  3. Slow Infections.

- **Permissive Cells:**
  - Cells that support the replication of the virus, and these are virulent viruses. (productive response)

- **Virulent Viruses:**
  - Infect target cell and causes disease, and give what is called productive response.

  Permissive cells, virulent viruses, and productive response are all related.

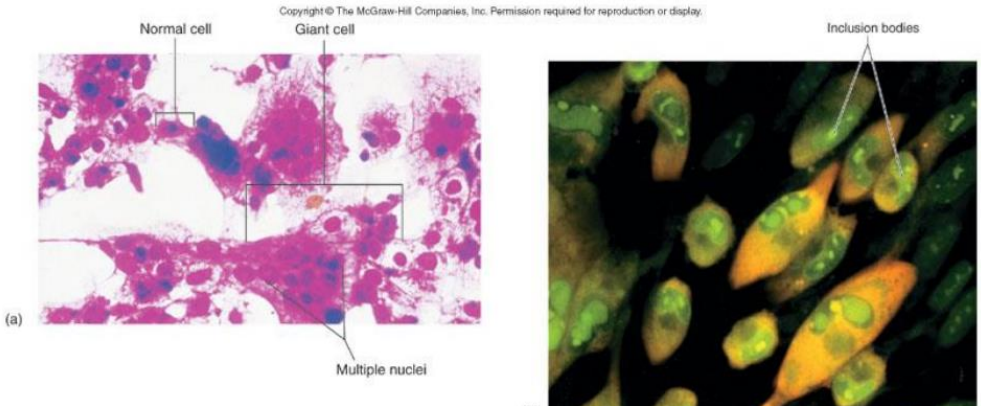
- **Non-Permissive Cells:**
  - They do not permit the replication of the virus, but the viruses can transform the cell.
  - At the beginning of the replication cycle, the cell can support the virus' replication, but the end products of replication produced by the virus might transform or kill the cell. This is what we call abortive infection.
  - Non-permissive cells and abortive infection are related.
  - Abortive infection: there is no viral replication, and early virus proteins cause cell death or can transform the cell.

- **Cytopathic Effect:**
  - Abnormalities that might happen in cells infected by a virus.

Ω Cytopathic Effects:

1. Change in the size and shape of the cell.
2. Cytoplasmic inclusion bodies.
3. Nuclear inclusion bodies.
4. Cells fused to form multinucleated giant cells.

5. Cell lysis and death.
6. Changing the genetic material within the cell.
7. Transform cells in cancerous cells.



- **The picture on the left:**
  - It shows multinucleated giant cells, where there is one giant cell with multiple nuclei.
  - Examples: HIV, and respiratory syncytial viruses.
  - It's seen especially in enveloped viruses, not in naked viruses.
  - Mechanism:
    1. During the entry of an enveloped virus by fusion, the viral envelope becomes part of the cell membrane.
    2. Viral glycoproteins present on the viral envelope remain on the cellular membrane.
    3. These viral glycoproteins will attach to their receptors on adjacent cells.
    4. This causes fusion between these cells.
    5. A giant multinucleated cell is formed.

- **The picture on the right:**
  - These are inclusion bodies within the cytoplasm.

I didn't have the slides when I wrote this sheet, so forgive me for any mistake, but I hope it will be good enough =D

- The End -