GENERAL VIROLOGY 3

Viral Pathogenesis - Host Defenses
&
Viral Genetics

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Viral Pathogenesis

- **The process of disease production following infection.**
- **It may lead to clinical or subclinical (asymptomatic) disease. And this depend on the viral inoculum**
  - **Asymptomatic viral disease (subclinical infection): here the viral inoculum small so it cant cause infection for large num. of cells ,SO we will not see symptoms . Have a characteristic that there is a sufficient antibody stimulation in which it make immunity from further infection**
    stimulate humoral and cellular immunity.
  - **Clinical viral disease:**
    - **Direct** or **indirect viral effects** (e.g. cytolysis, immunologic attack)
    - Size of the **viral inoculum**.

- Direct : cytolysis of cell by virus itself , when it lysis the cell or make a cytopathic effect , the result will be clinical manifestations (symptoms)

- Indirect : immune attack . These things will cause physiologic changes in tissue ,so clinical viral disease start to appear
- Large viral inoculum >>> clinical
- Small viral inoculum >>> subclinical

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Viral aspects of pathogenesis:

1. Viral entry into a host (Transmission): **occur through GIT,RT,GUT**

- Touch, saliva, air. - Blood - sharing contaminated needles.
- Contaminated food and water - sexual contact - Insect bite.

2. Viral attachment proteins (VAPs): **= antigenic determinants =proteins or glycoproteins**

- Interact with cellular receptor. To initiate the infection
- Neutralizing antibodies. If VAPs interacted with antibody , the virus will be incapable to interact with cellular receptor sites ,so the infection will not continue .i.e inactivation of VAPs
  - pH OR Enzymes OR Any host biochemical factors = inactivation of VAPs

3. Viral virulence: * Genetically determined (it means that the virulence strains is known and its genome carry genes responsible for virulence) - decrease with attenuated strains of virus. **These virulence determine the ability of a particular viral strain to cause a disease and the severity of this disease

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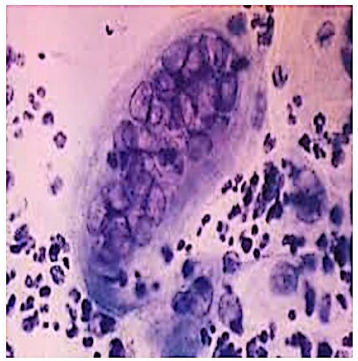
Cellular aspects of pathogenesis:

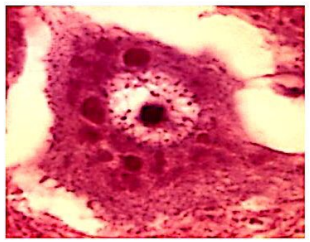
1. **Cellular receptor sites.** **interact with VAPs to initiate the infection which help in determination of cellular tropism**
2. **Target organ.** **Responsible for major clinical signs and symptoms**
3. **Cell tropism.** **Reveals the propensity of virus to infect or replicate in certain cells**
4. **Cellular responses to viral infection**: may be **inapparent** or **may include:**

- **Cytopathic effects:** virus-induced damage to the cell e.g. multinucleated giant cells (some cells are damaged and then aggregated together to form syncytium) as in herpes simplex.
- **Cytolysis** **(response from cell , rupture of cell and release of virus therefore cell will die)** **: Non-enveloped** viruses.

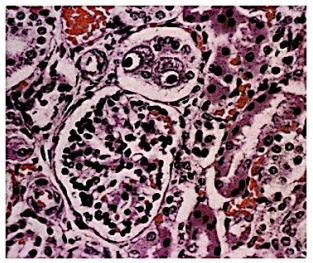
syncytium



- **Inclusion body formation** (things from virus particle found inside cell) : **Intracytoplasmic eosinophilic**: rabies Negri bodies. **Intranuclear basophilic:** owl eyes in cytomegalovirus.



- **Transformation** (occur in chromosomes) : From normal cells into abnormal ones with properties of **cancerous** cells, **here the cell is not dead.**



- **Immune complex diseases** (highly known in cases of hepatitis viruses) : Antigen-Antibody complex is produced that deposit in different places of body (may deposit in kidney , joints , etc) .

- **Interferon (IFN) synthesis.** To persist the viral infection

basophilic

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Types of infections

1. Inapparent infections (subclinical disease):

- can cause immunity from further infections.
- virus inoculum is small.

2. Acute infections :

- **Short IP (**Ds/Ws**).**
- **localized** or **disseminated. Depend on the virus if it travel through blood and reach a target organ or travel through the body from site of implantation to its target organ (disseminated) or its stay in the same site (localized)**
- **Recovery □□elimination** of the virus.
- **Persistent (person has infection and there is a continuing presence of the infectious virus particle in the body for extended time perhaps lifelong ,clinical symptoms may or may not be present** or **latent** infections may follow.

- Localized infection : occur when viral multiplication and cell damage are localized at the site of virus entry the body , may associated with systemic manifestations such as fever , occur after short inoccupation period , viremia doesn't usually occur , site may be in RT (such as influenza and rhinoviruses)or in GU (such as papilloma) or eye (such as adenoviruses) or alimentary tract (such as Picornaviruses), it cant speared in the body , weak immune response because it related to the site

- Disseminated : there is speared of infection from entry site to the target organ , may associated with primary and secondary viremia , inoccupation period is moderate , high immune response

- Viremia : viral infection in the blood

3. Persistent infections :

- Clinical symptoms ??.
- Carriers.
- High antibody titers for some antigens.

4. Latent infections:

- Periodically reactivate □□ **recurrent disease.**

5. Slow infections:

- **Prolonged IP (**Ms/Ys).
- **No clinical symptoms** during **incubation** but can **produce some infectious agents.** (and it stimulate immune response and there is production of antibody against it , such as in HIV case)
- **Chronic, progressive,(fatal viral diseases.** In CNS as in Jacob disease)

- **Persistent infection : person has infection and there is a continuing presence of the infectious virus particle in the body for extended time perhaps lifelong ,clinical symptoms may or may not be present , such as in case of hepatitis B or C the patient in some times present in good state and other times in bad state , persistently infected individuals are called carrier ,there is continuous viral antigenic stimulation which cause immune system to respond to continuous stimulation so there will be high antibody titer**

- Latent infection : occur when the infecting virus persist in the body in the non infectious form and these non infectious form can be periodically reactivated to infectious viruses and produce clinical disease , cause recurrent disease , antibody stimulation being only during initial or primary infection and during recurrent periodically reactivation , in between them there is no antibody stimulation , sometimes subclinical reactivation may occur . This infection is difficult to be seen in the cell , it consider as a silent period

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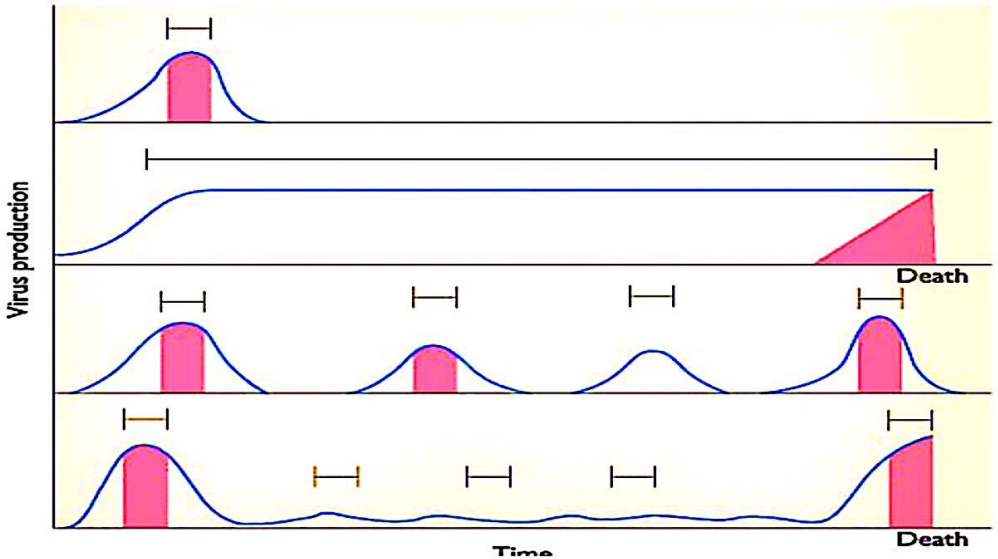
General patterns of infection



Acute infection
- Rhinovirus
- Rotavirus
- Influenza virus

Persistent infection
- Lymphocytic choriomeningitis virus

Latent, reactivating infection
- Herpes simplex virus

Slow virus infection
- Measles SSPE
- Human Immunodeficiency virus

From Flint et al Principles of Virology

- Curve in blue : represent virus in blood
- IN acute infection : عند اول تعرض للفيروس ترتفع كميته داخل الدم و تظهر الاعراض لفترة محددة و بعد ذلك يختفي تماماً
- IN Persistent infections: تبدأ كمية الفيروس في الدم بالارتفاع كما في النوع الاول لكن لا يختفي بل يبقى متواجد في الدم حتى الوفاة و طيلة فترة تواجده بالجسم يقوم بتحفيز الجهاز المناعي
- IN Latent infection : تكون على شكل ايبيثودز و اول مرحلة هي اسوأ مرحلة و تكون شبيهة باول نوع و بعد ذلك تبدأ حدة التأثر بالفيروس تنخفض و بين كل اصابة بالفيروس و الأخرى لا يوجد اي شيء من الفيروس في الدم
- IN Slow infection : البداية تكون شبيهة باول نوع و بعد ذلك تنخفض , تنخفض ولا تختفي و هذا سبب وجود الخط الازرق في المنتصف ليدل على وجود و افراز اجزاء من الفيروس في الدم

- Extra examples :
- 1) Persistent infection : hepatitis B and C
- 2) Latent infection : Epstein-Barr virus

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Host defense mechanisms

Nonimmune defenses:

1. **Innate immunity: anatomic** (such as dead cells in the epidermis) and **chemical barriers.** (such as mucous layer limit the contact between virus and susceptible cell)
2. **Cellular resistance: non-permissive cells.** (lacking certain factors, lacking viral receptor site ,lacking certain enzymes or anything is needed by the virus)
3. **Inflammation.** (limitation of virus spread due to unfavorable condition and unfavorable environment such as low pH ,antiviral substance , high temp.)
4. **IFN: inhibits viral replication.** (host specific viral induced glycoprotein , inhibit viral replication)

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immune defenses:

- **Humoral immunity (antibody) : neutralizing (protective) and non-neutralizing antibodies** (enhance phagocytosis and degradation of infectious agint □□**opsonins**) .
- **Cell-mediated immunity: Cytotoxic T lymphocytes, NKcells**, and **activated macrophages**□□ lymphokines and monokines.
- **Viral-induced immunopathology:** antibody-antigen **complexes**, or through release of cytokines…virus isn't cytopathic but it make immune system reactive against antibody and this reaction will cause diseases
- **Viral-induced immunosuppression (if the virus infect the immune cells): lymphocyte infection by the virus**.

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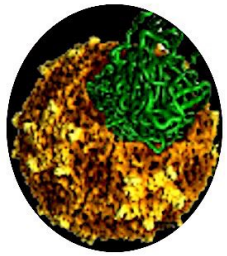
Viral Genetics



Viral genetics includes:

- **Mutations** : effect on replication and pathogenesis.
- **Interactions:** of two genetically distinct viruses infect the same cell.

Mutations

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Types of mutation:

Point mutation ---- **Deletion** ----- **Frame shift** mutation.

Examples phenotypic changes seen in virus mutants: (there is many viral mutants can much mild or no symptoms compered to the parent or wild virus)

- Attenuated mutants. (have an important role in vaccine development)
- Antigenic variants or antigenic drift. (most common in influenza virus, certain mutation occur in genome of the virus which will produce antigenic variants so the patient will have repeated attacks of influenza due to presence of new mutant strains, the previous antibody isn't able to resist them so new attack will occur .i.e there is alteration in the antigenicity)
- Drug resistant mutants.(it make the viral strains insensitive to antiviral drugs due to modification in target of the drug)
- Conditional lethal mutants. (certain mutation occur in virus this mutation make it alive under certain conditions, if these conditions changed it may die e.g temperature sensitive mutants, because other temperature will alter the active or functioning protein)
- Defective interfering particles. (cant replicate unless its deleted function supplied by the helper virus and it can play role in viral infection through interfering with the production of the pro-gly virus)

INTERACTIONS BETWEEN VIRUSES

- **Recombination/ Re-assortment.**
- **Complementation.**
- **Phenotypic mixing.**

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• Recombination/ Re-assortment:

Exchange of genetic information between two chromosomes that is based on crossing over within regions of significant base sequence homology.

- "Classic" recombination: break/join recombination.(breaking of covalent bond in N.A then exchange of genetic information and finally reforming of covalent bond. Its most common in DNA viruses rather than RNA viruses , if it occur in RNA viruses they must have DNA phase such as retroviruses)
- Reassortment: viruses with segmented genomes, such as Influenza virus, exchange segments (**major antigenic changes**). (here, there is high frequency of gene exchange and more than recombination ,because it can take from more than one segment - at the end it may produce virulent strain such as in influenza virus)

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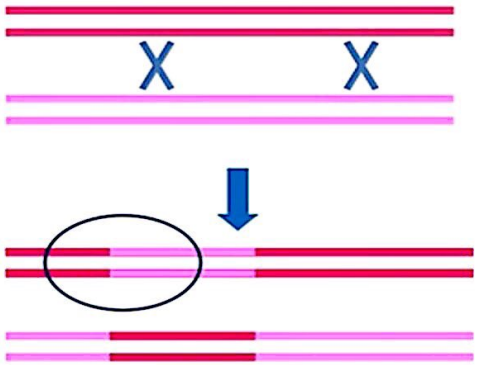
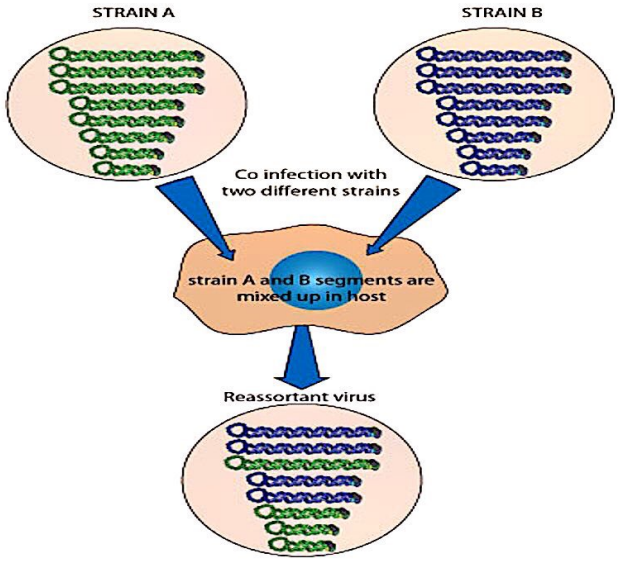
Classic recombination

Common in DNA viruses



Reassortment



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- **Complementation:** **(similar to helper virus)**
- **Interaction at a functional level NOT at the nucleic acid level.**
- It can occur when either **one or both of the two viruses** that infect the cell have a **mutation** that results in a **non-functional protein**.

(two viruses enter the cell on of them have a defective function , the other one will help in the defective function to be completed but it will not and it cant take any part of its genome – if there is mutation in two viruses, the mutation in each one must be different and not in the same gene)

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- **Phenotypic mixing:** **(occur in different members of Picornaviruses family and between genetically unrelated viruses , for example : between Rhabdoviruses and Paramyxovirus)**

➢ If two different viruses infect a cell, progeny viruses may contain **coat components** derived from both parents and so they will have coat properties of both parents. (i.e the two viruses when they enter the cell , if one of them took some antigens from the other virus and then become in one coat and this coat has on the surface its antigens and other virus antigen but the entire gene is for one of them , the virus which has two types of antigens now can infect two type of cells : the original one which is used to infect it and one other which has its antigens to infect the new type of cells from the other virus when they enter together .**which one of them can multiplicate ? the parent virus which has one gene and two antegens

➢ **It involves no alteration in genetic material.**

There is interesting thing here , the virus can take antigens on its surface from other virus and it can take complete coat . Two viruses enter the cell and after their multiplication they exit with different coats , each one of them took the coat of the other and soooo , pseudovirion will form.

In this case the virus from out (coat) will entirely of the anther virus, example : retrovirus nucleocapsid enter with rhabdovirus , RVN will take surface coat of RV , this process called phenotypic masking

Thank You

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