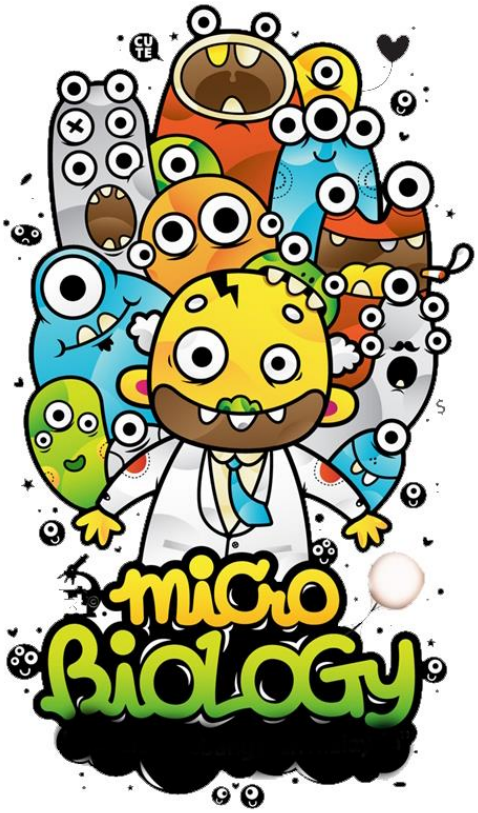

VIROLOGY

Subject: Pathogenesis of viral infection, and viral genetics

Lecture: 5

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REMEMBER

Cytopathic effect: changes occur in the cell as a result of viral infection.

Virokines vs viroreceptors

Virokines are proteins encoded by some large DNA viruses that are secreted by the host cell and serve to evade the host's immune system. Such proteins are referred to as virokines if they resemble cytokines, growth factors, or complement regulators; the term viroceptor is sometimes used if the proteins resemble cellular receptors. The doctor did not discuss them; but kept them as homework and said they are important. These definitions are taken from Wikipedia.

Patterns of Viral infection

1-unapparent

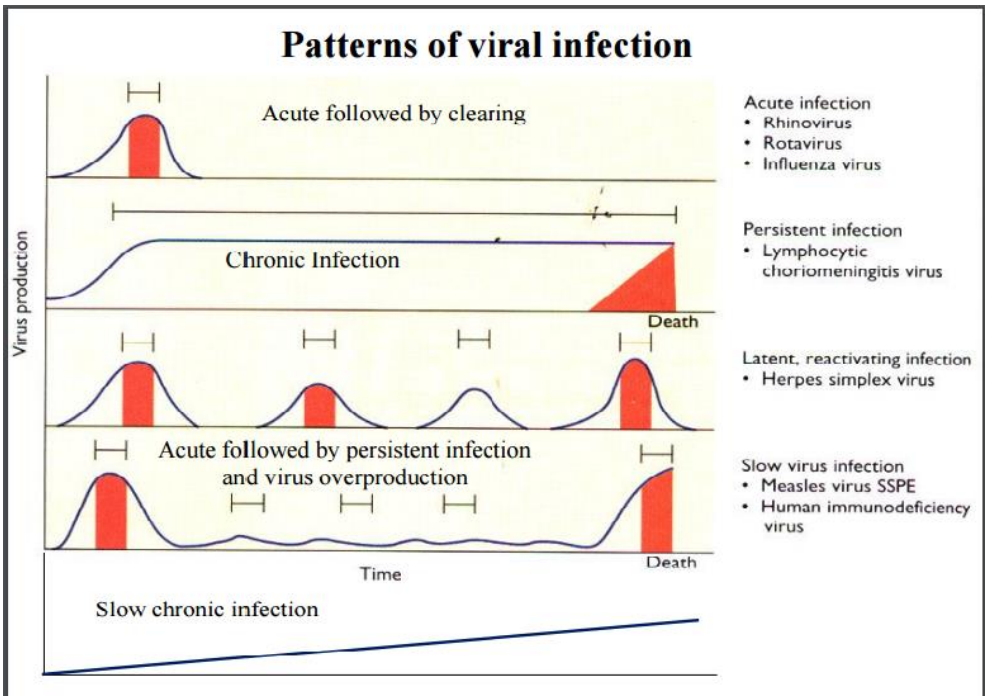
Subclinical, asymptomatic, you never know that you are infected

2-apparent

a- Acute

b- Persistent which includes (chronic, latent and slow viral infection)

Now look at this picture that describes these patterns:



What these patterns represent?

The first one: Acute infection

There is a short incubation period –days- then illness occurs. The red color represents *the symptoms* which lasts (5-7) days and the line represents *the viral load*. In this pattern the virus has been totally irradiated from the body (viral load = zero). It means total recovery. After the virus has been cleared, we can know that the virus has infected the person by looking for antibodies of the virus in his blood.
**Remember that most infections are subclinical but here we talk about apparent **

The Second one: Chronic infection

Symptoms might take a longer period to appear and there is no clearance. The example can be used to represent Hepatitis C virus –which can be characterized by delayed symptoms* such as jaundice- but not accurately Hepatitis B, because hepatitis B has an acute phase in which the patient is symptomatic followed by a chronic phase "a peak of the acute phase, then it gets lower to make the chronic phase plateau".

**the symptoms appear at the end of the chronic phase*

The third one: Latent infection

Examples on this type are HERPS-1, HERPS-2 and Vercelli Zoster "herpesviridae family", which are lying dormant in the dorsal nerve ganglia (the place may differ depends on the virus).

Conditions of latency:
1- no complete irradiation of the virus/ no clearance
2- It is in the form of episome "dormant" which is circular extra chromosomal DNA. It could be either the whole genome or part of it, most probably the whole genome. Inside the nucleus but not integrated with the chromosomes
3- The production of early protein only.

And there is reactivation in response to the drop in immunity resulting from predisposing factors such as exposure to sunlight, UV light ,fever, illness,…
(reactivation not re-infection, because the lately indicates different virus coming from outside)

The theories of reactivation

1- This theory contradicts the conditions given for the latency and it states that the virus is present in the dormant cell and it's replicating at a very slow pace until the cell no longer can tolerate the viruses inside so permit their release. This is a week hypothesis.
2- A stronger theory states that once there is a drop in immunity system, chemical changes occur inside the cell that has a dormant virus and trigger its activation and replication and then release the viruses through the peripheral nerves until it reaches the equivalent dermatome* – shingle.
*dermatomes are the superficial innervations of the skin; those innervations come from the back to the chest in horizontal lines. The virus can affect one side or both sides.

Notice in the picture above that the reactivation could be symptomatic or asymptomatic.

In the dormant phase between the peaks in the curve, the virus is not cleared; but it is also not detectible; but antibodies of the virus can be found. Antiviral drugs work on replicating viruses only; so they cannot work in the dormant phase of latent viruses.

The fourth one: HIV

No complete clearance

First there is an acute phase, the viral load increase, the patient is symptomatic with flu-like symptoms which might last for weeks or few months then the viral load drops *(looks like hepatitis B; it drops but never reaches the baseline).*After the acute phase there is an incubation period (10-15) years in which the virus is always there and is continually replicating at a slow level. This phase exactly can be elongated by highly active antiretroviral therapy. And the last phase in the picture is AIDS (differentiate between HIV infection and AIDS which means the collapse of the immune system, the CD4 count has dropped below 200/mm3), here, the immune system collapses and the virus load increases. Symptoms become noticeable.

The fifth one: slow virus infection

Such as prions, which are infectious proteins (this is the most widely accepted theory) and Polyoma virus.

Overall fate of the cell

- The cell dies in **cytocidal** (lytic/death) infections either by:

1- Acute infections: characterized by brief and self-limiting "ex. ciliated cells death in influenza infection".

2- Chronic infections: characterized by drown-out, longer, only few cells infected while the rest proliferate such as hepatitis. (Let's take the liver as an example, at one time only certain percentage of the liver is infected while the other part is good, the infected ones will die and then regeneration occurs. And if we take this liver for a long period of time, each cell must be infected at certain point in this period). This loop of infection-regeneration can lead to liver cirrhosis in the short term and liver cancer in the long term.

- The cells that live in a **persistent infection** may be productive or non productive *(refer to whether or not virions are being produced*) or it may alternate between the two ways of latency and reactivation.

  So the persistent infection may be latency+reactivation or it could give us productive and non productive.
  (Remember permissive -a cell that support the virus replication- and non-permissive cells -most probably the virus enter them by accident, and they only produce early proteins so the fate of the cell here is either death or transformation-.)

- Transformation "oncogenic viruses": change from normal cell type to a cancerous cell. It could occur in both (RNA and DNA viruses) but generally in

DNA viral infections.
***All DNA viruses are capable of transforming cells in natural host (human) or animals (other species) or cell culture in the lab at a certain point of time except **parvovirus**.

Let's have a look at the DNA viruses and whether they cause transformation in the natural host or not:

1-human papilloma virus: leads to transformation in the natural host, cause cervical cancer (associated with latency).
2- Adeno virus: it doesn't lead to transformation in humans (natural host) but capable of transforming cells of other species or in the lab (associated with latency).
3- POX virus: it doesn’t lead to transformation in the natural host.
4- Polyoma virus: it doesn't lead to transformation in the natural host.
5- Hepatitis B: it leads to transformation in the natural host.
6- herpes viridea: it leads to transformation in the natural host (associated with latency).
7- Parvovirus: it does not.

<< The ones that do not lead to transformation in humans are APP>>

DNA tumor virus infections are often cytocidal; thus transformation is associated with abortive or restrictive infections in which few viral genes are expressed. The persistence of at least part of the viral genome within the cell is required for cell transformation. This is accompanied by the continual expression from a number of viral genes.

***They found retrospectively in experiments that cancer patients had a previous infection and the viral genome in that infection has been integrated with the cellular genome. So basically, when there is an integration of the viral genome with the cellular genome in the latent viruses there will be higher chance of transformation -cancer-.

The Mechanisms of the oncogenesis for both RNA and DNA is not fully understood, but one of the mechanisms in DNA viruses is the effect on the P53 gene and retinoblastoma gene. And these both genes are cell cycle regulators.

retinoblastoma gene: prepare the cell for division and then starts the S phase, when a virus come and affect this gene, they will put a cell in continuous replication which leads to transformation. The same happens with **P53**. P53 regulates the cell cycle; functions as a tumor suppressor that is involved in preventing cancer. These two conditions are seen in human papilloma viruses.

- RNA viruses that can lead to transformation: HIV, hepatitis C.

RNA tumor viruses usually transform cells to a malignant phenotype by integrating their own genetic material into the cellular genome and may also produce infectious progeny. In this sentence we are talking specifically about HIV.

- How **HIV** cause transformation?
  It prolongs the life span of the infected cells (T-CELLS), so a longer life span means continuous viral production and a higher chance of producing mutations in the cell itself. Also when the virus controls the cell machinery to its own benefit can aid in the process of transformation.

- There are three mechanisms by which **Retroviruses** can transform cells:

1- Acute transforming virus

Normal cells have proto-oncogenes in their DNA; which code for specific proteins that function in cell cycle regulations. However, gene-mapping studies on retroviruses genome shows that 4-7% of these genomes are shared with human genome; and those shared genes are of human origin. And because viruses divide rapidly, many mutations result over time. Such mutations lead to the transformation of proto-oncogenes "normal" which are shared between human cells and the viral genome, to oncogenes. If these viruses which contain the oncogenes infect human cells, oncogenes will code for proteins that resemble the original proteins' receptors in the cell, and lead to disrupt the original function; which is cell cycle regulation. This entire scheme may lead to transformation.

c-Src are the proto-oncogenes of the normal cells, while v-Src are the oncogenes of the viruses.

2- **Insertional mutagenesis:**
inappropriate expression of a proto-oncogene adjacent to integrated viral genome. Promoter is a sequence on the DNA that activates the transcription of the gene that the promoter precedes it. After the insertion of the viral genome into the cell genome, a promoter may precede a proto-oncogene; whiuch leads to the activation of the proto-oncogene, and over production of it, which affects the cell cycle regulation, making it continuously replicating "= transformation".

3- **Transactivating factor:**
certain genes in retroviruses such as tax gene use the cell resources in order to increase its production and increase production of other cellular genes that help in cell regulation. So, this results with overproduction of such genes and disruption of cell cycle regulation.

Now what are the mechanisms by which **Hepatitis** can transform cells?

1- Chronic infection

2-Cytosidal infection- the fate is death- which leads to cirrhosis as mentioned before.

3-The presence of certain enzymes such as a NSE3 (non structural enzyme 3) in hepatitis C

** remember that the liver is capable of regeneration**

VIRAL GENETICS

Viruses grow rapidly in different rates and the maximum number of viruses a host cell can produce is called the burst size. Hepatitis C for example grows very rapidly and a single infected cell is able to produce millions of viruses.

DNA viruses seem to have access to the proof reading (check for errors) while RNA no. This is because the DNA viruses replicate in the nucleus which has many mechanisms of auto-correction of the errors, While RNA viruses replicate in the

cytoplasm and they use their own enzymes that lack proof reading (RNA dependent RNA polymerase and RNA dependent DNA polymerase "reverse transcriptase"). This explains why RNA viruses are more prone to mutations and errors; every 2500-10000 base there will be a mutation.

Nature of the genome: DNA or RNA, SEGMENTED (influenza and rota, reo) or NONSEGMENTED.
*each segment represents a gene and after translation a protein.

Mutation:

Spontaneous mutations arise from variety of sources physically or chemically induced.
* Codon is the three letters code that codes for one amino acid*
* there are 4 bases; A, T, C and G*

Types of mutations:

1- *Point mutation: replacement of one base*
   - If the change in the base number 3, most probably the amino acid will stay the same because the majority of amino acids have 4 codons that code for them. The protein is the same in terms of structure and function. This is what is called **silent mutation**.
   - If the change is in the base number 1 or 2, this leads to the production of a different amino acid. This is called **missense mutations** and the effect on the protein in this case depends on the new amino acid, it could be no loss, partial loss or complete loss of the function and structure.
   - If the change leads to the production of a stop codon, then such mutation is called **nonsense mutation** which has a massive effect "no continuing in the amino acid sequence of the protein".

2- *Insertional: adding base/bases and it causes frame shift*

3- *Deletion: removing base/bases and it causes frame shift*