MICROBIOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 5

Laboratory Diagnosis and Treatment of Viral Infection

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Treatment and Prevention of Viral Infections

1. As bacteria and protozoa do not rely on host cellular machinery for replication, processes specific to these organisms provide ready targets for developing antibacterial and antiprotozoal drugs.
2. However, because viruses are obligate intracellular parasites, antiviral drugs must be capable of selectively inhibiting viral functions without damaging the host, making the development of such drugs very difficult.
3. Furthermore an ideal drug would reduce disease symptoms without modifying the viral infection so much as to prevent an immune response in the host.
4. There is a need for antiviral drugs active against viruses, for which vaccines are not available or are not highly effective.

Explanations in the next slide

هههه بلشنا إضافة سلايدات :)

Treatment and Prevention of Viral Infections

Targeted/ specific treatment: treatment against the microorganism without affecting the host.

So Microorganisms(except for viruses) like bacteria and protozoa conform to the definition of a cell, as they possess the necessary machinery for independent replication and metabolism outside of a host and it could invade for further pathogenicity however since it has this independent mechanism, we can use it for targeted treatment against them without affecting the host.

~The main target for developing antiviral drugs are severe and serious viral infections that don't have vaccines.

The development of antiviral drugs is difficult because:

1. Viruses obligate intercellular when developing antiviral drugs, we must make it specific to the virus' metabolism and replication so we wouldn't damage the host cell since it depends on it and its machinery so it's not easy to differentiate between them.

2. An ideal drug: 1. would kill the virus and reduce replication of the virus so the immune system can recognize it and build long-term immunity against it 2. targets specific proteins or steps within the viral replication and doesn't affect any part of the host cell.

3. Severe untreated viruses are the priority in developing antiviral drugs in contrast to viruses with mild, self-limiting infection and the viruses that have effective, safe, and available vaccines.

4. Find a mechanism that allows the drug to act intracellularly where the virus is located.

This produces a limited effect on the host since the virus contains that protein but the virus doesn't(specificity), thus decreasing the side(or adverse according to Dr. Yaqoub) effects on the host

Detect and recognize the virus-> Viral Target(the appropriate protein or maybe a replication step that is specific to the virus)-> Studying available drugs and developing new ones-> Screening; viruses are presented to various drugs and whichever eliminates most would be considered the starting step-> Studied and testing its effectivity.

In case we couldn't find that ideal drug we would reside to the next step: viral dominant targets; what does the virus do/ have more of than the host? It could be a protein with a higher concentration in the virus than in host and if targeted it wouldn't affect the host cell or it would cause minimal adverse effects

Example: a drug that targets viral DNA replication, because it's a DNA targeting drug it might affect our own DNA. However, if its effect on the viral DNA replication was greater than on our own, it would be cond=sidered an appropriate drug/ treatment.

Development of an antiviral drug(has to be specific!):

Recognize the virus-> identify the target(unique protein or replication step) -> study available drugs/ develop new ones-> drug screening (viruses are presented to various drugs and whichever eliminates most would be considered the starting step)-> study their safety and effectivity-> focus on viral-dominant features; in case we couldn't find a specific target(we would look for (an example) a protein that is highly concentrated in the virus than in the host-> a DNA replication-targeting drug is viable if its effect on viral DNA outweighs its effect on host DNA

Anti-viral Development

Viruses are now becoming better understood and several viral genomes have been properly mapped. Scientists are now looking for the best drug targets

Whether it's the viral genome, capsid(and its proteins), the envelope and spikes, or even the replication process of each virus.

The main point of interest is any viral protein that the host organism does not normally produce. Once these viral proteins are identified they are tested using a large-scale screening process to test for effectiveness.

Development of an antiviral drug(has to be specific!):

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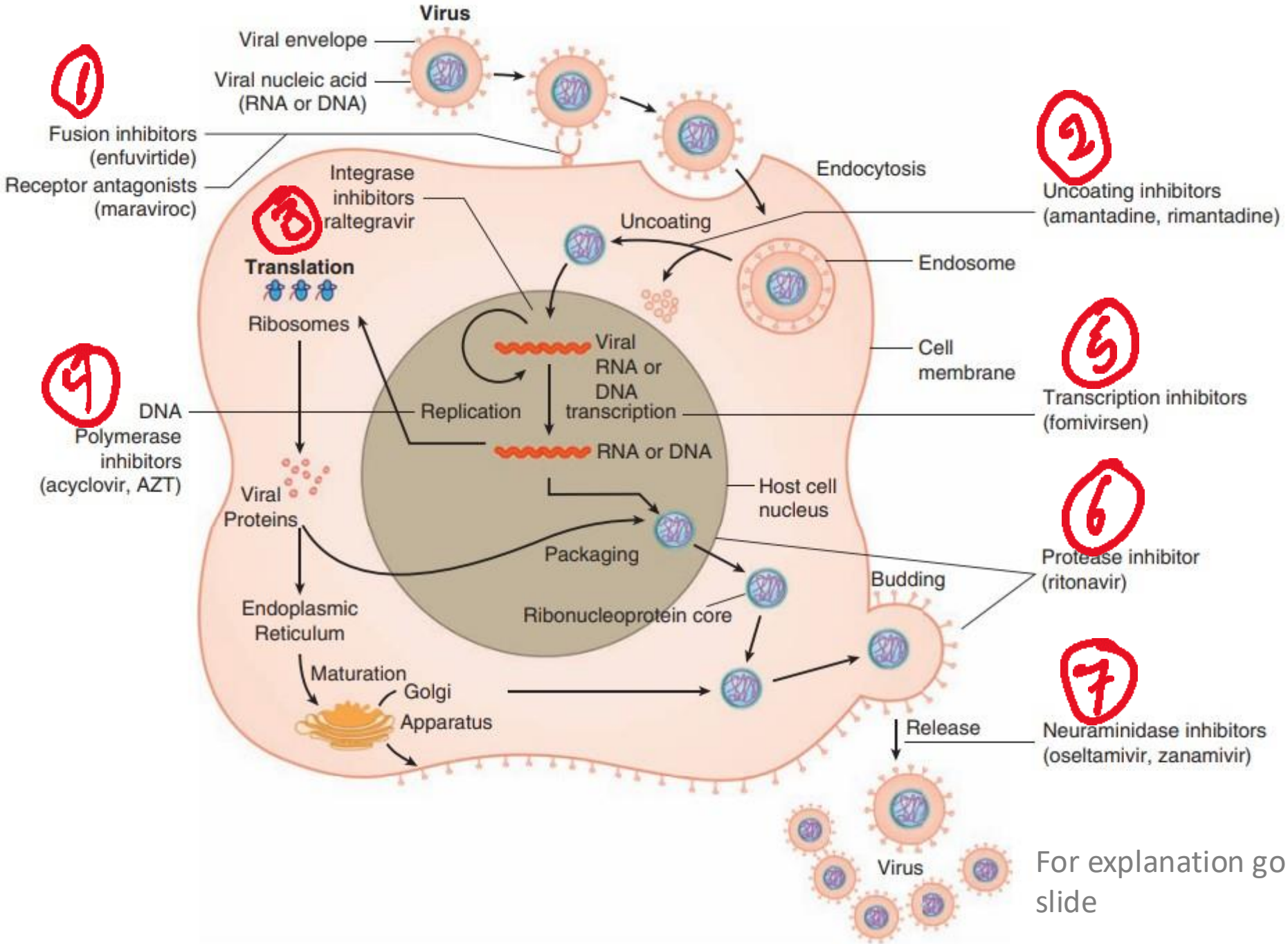
Anti-viral Targets

There are several known methods that the makers of Antiviral drugs are looking at, including:(There is direct connection between it and the replication cycle)

1. Inhibitors of Attachment (when we inhibit attachment we inhibit the whole replication process and the virus won't be able to replicate anymore)
2. Inhibitors of Cell Penetration and Uncoating(the virus gets rid of capsid protein and envelope outside)
3. Neuraminidase Inhibitors
4. Protease Inhibitors(the virus uses it for replication)
5. Inhibitors of Nucleic Acid Synthesis(essential step in the replication is formation of viral DNA which can be inhibited)
6. Nucleotide Analogs
7. Stopping the release of the mature viruses from the host cell (we cut the replication cycle)



For explanation go to The next slide

The virus has genome, capsid,and viral enevlope in this case.
1)The first step in the replication is attachement, so the first target for Anti-viral drug is inhibition of attachement which is very Effective.the attachement of the virus is usually mediated by glycoproteins spikes on the envelope or on the spy that specifically Bind with specific receptor in certain cells
. The inhbition is happened by peptides or proteins or antibodies drug-like
Example: fusion inhibitors :the virus is trying to make attachement .the fusion inhibtors stop this process . An example of it (enfuvirtide drug)
.Receptor antagonist: the virus is trying to bind specific receptor .we develop an antagonist for the virus . The example of it (maraviroc)

2) Endocytosis viral uncoating: there are group of drugs works on uncoating inhibitors which prevent the uncoating of virus (amantadine, rimantadine)
3) The virus will start making transcripition after the release of genetic material It could be our target. We well inhibit transcripition process by transcription inhibtors example of them (fomivirsen)
4) The formation of virus requires connection with certain proteins ,formation of certain proteins by protease enzyme . We could Use protease inhibitor example of it (ritonavir)

5)During synthesis of viral parts we need the formation of DNA or RNA. We have DNA polymerase or RNA polymerase one of The essential enzymes the virus are capable of having it doesn't depend on the host cell it could be with it. These enzymes are Used for the replication of viral DNA or RNA. So, they are good target for treatment . We could develop DNA polymerase Inhibtors or RNA polymerase inhibtor. Example of it (acyclovir). We should notice that DNA polymerase inhibitor it will act on Formation of the virus as well as DNA formation for the host but its effect on the DNA replication about hundred time DNA of the host cells. So it is still successful treatement

6)Some viruses could use integrase which is enzyme for DNA viruses cuts our own DNA and intrgrates the DNA of Them and binds them . So that's why its called integrase , it integrate the viral DNA into our cell geneome DNA When we inhibit integrase the virus will not able to integrate its own DNA into the DNA of the cells so we stop the re cycle

7- the final step is the release:the virus will leave the cell and it will use part of cell membrane to form an envelope

We can inhibit the release of viral shedding

Example: the virus in (slide 8 in the figure) is formed and the final step it makes budding and release . The virus for release It forms certain proteins(neuroaminidase)on the surface of the cell .during it exits from the cell it takes cell membrane+ Neuroaminidase) so it will be fully matured virus

The target is : developing drugs that are neuroamindase inhibitor so it prevents the proper release of the matured virus (oseltamivir)

Antiviral drugs for (the simple
Viral infections) GP can prescribe them
But complicated viral infections we
Leave it to the specialist to treat it

1. Oseltamivir (Tamiflu)

Trade name

Scientific name

from its name its target infleunza virus

- Prevents the mature viruses from leaving the cell(this drug works on the final step which is released of virus from the cell)
- It is a neuraminidase inhibitor, it works on both influenza A and B(it is protein or enzyme
- Neuraminidase is an enzyme found on the virus which cleaves sialic acid from cell membrane, leading to a more effective release (and shedding) of viruses
- Used to battle(treatment) avian flu and influenza

2. Acyclovir (Zovirax)

One of the Trade names

Scientific name

.A widely used antiviral with main implications in the treatment of herpes(can cause mouth ulcers and other group of diseases we will know them latter on and many people are suffering from them especially during cold periods or people at risk)

.Seen as a "new age" in antiviral therapy, Gertrude Elion, its creator, was given the Nobel prize for medicine in 1988

.It is a nucleoside analogue and prevents viral replication in infected cells

. (mechanism of action)Inhibits viral DNA polymerase(specifically)and terminates viral DNA chain growth(even though it works on DNA polymerase it might have a minimal effect on our DNA replication but the effect is mild and the effect on the virus about 100 time more)

Perprations of the drug Come in the form of:

creams

ointments

Injection

tablets

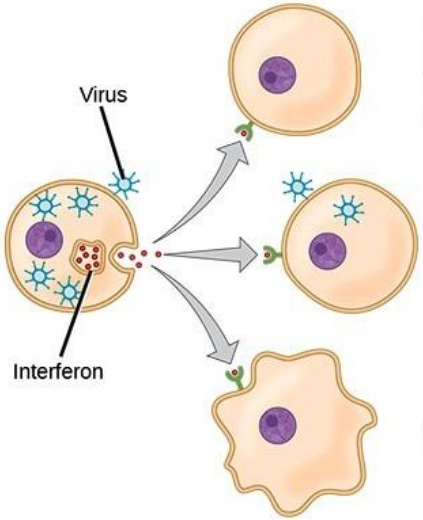
3. Interferons: when we discussed before the immune response against viral infections innate immunity partially depend on Interferons which are effective for fighting viruses non-specifically.

.α and β interferons are produced by all the cells in response to viral infections(immune cells)

.γ interferons are produced only by T lymphocyte and NK(natural killer cells) cells in response to cytokines

.The action of interferons leads to an inhibition of translation(the process of formation of required proteins for the viral capsid)

.Pegylated interferon-α (Peg-IFα) is given for 6 to 12 months to treat chronic hepatitis C disease and B



(mechanism of action Of interferons)

Avaliable drug that mimics Interferons

.One of the treatment opotions for hepatitis B ,C which has Effectiveness(30-50%) specifically at the beginning are the interferons. The patient takes prolonged course (6-12) month

An example of interferon- liked drugs

Viral Vaccines

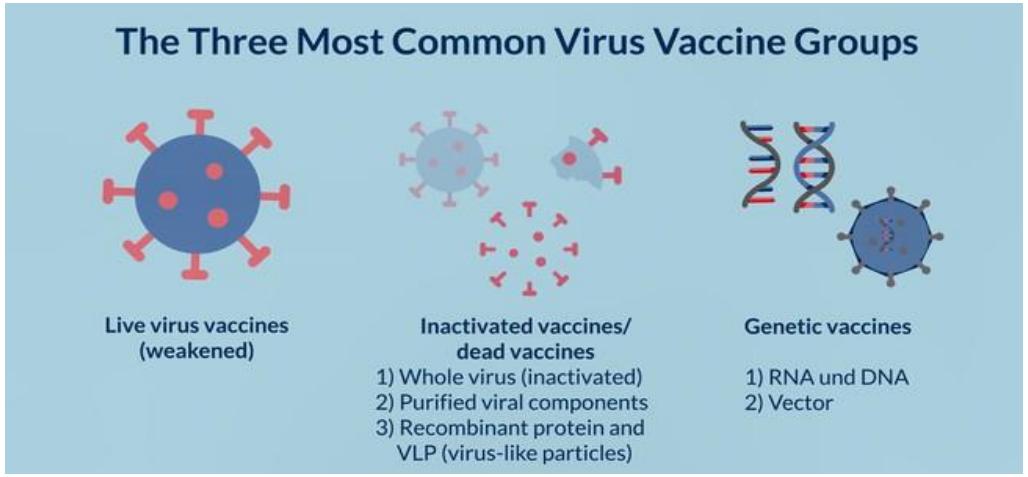
Another important part of prevention of viral infection

- General Principles Types:
- 1-Killed-Virus Vaccines

2.Attenuated Live-Virus Vaccines

3.Genetic vaccines

- Proper Use of Vaccines(we take the vaccines as recommended)
- Vaccine development and future direction



For explanation go to the next slide

.There are large number of effective ,safe viral vaccines that have been used in the world . We all know that large number of Viruses have safe and effective vaccines and vaccination programms have been implemented in all countries. It includes variety Of vaccines which are effective against some serious viral infections. To recall, Many serious viral infections Now they have Vaccines like (meassles, Mumps, Rubella, Hepatitis A and B and Rotavirus)
Common example: smallpox was a catastrophic(leading to death for severl regions) disease.Now the vaccine have been applied world wide for A long time which eliminates the disease completely

Another disease is :poliomyelitis infectes many childern .Unfortunately, it ends with child having paralysis that stays with Them for life. After we have the vaccine the incidence decreases and becomes very rare disease
. In general childern are the ones who give vaccines to. Some vaccines can be given to people ar risk, when we will start Clinical phase they give us booster dose for hepatitisB ,Eldery people may also take vaccines.

.General principles: vaccine :is virus killed attenuated or part of virus that well help to mimic the immune response and peo ple Well have long lasting immunity (B, T cells activation and memory cells) so if the virus enter the body the human is alread y Has recognized by the immunity cells and has the immunity against it
.To form effective vaccine we should know the virus structure, geneome and then it will go through known stages :screening, Animal studies , stages 1,2,3 . If it is effective it will applied.

Vaccines made a breakthrough in the fighting of diseases. They prevent the disease much better than drugs even though They have side effects(simple) so the benefits for them are more than side effects

1. Killed-Virus Vaccines : we recognize the virus and make proper isolation , proper characterization and then we kill it using (form aldehyde, Ultra violet...etc.) . Now we have viral vaccine it is given to the patient. The immune system will recognize the Vaccine and forms the immunity. This type of vaccine doesn't have the risk of activation the virus whatever the virus or the Immunity of the body. It is very safe

.Because it is killed virus practically maybe it doesn't replicate inside the cell and the recognition of the virus by immune system Is weaker which can recognize certain epitopes(the acquired immunity from this vaccine short term and less effective)

(more than one dose)

2. Attenuated Live-Virus Vaccines(weakening of the virus and we don't kill it): we make the studies for this vaccine and make sure That is. Safe (the number of doses it could be less than killed virus vaccines)

The advantage of this vaccine: it is attenuated so it has certain degree of viral activity and replication inside the host. The immune System interacts with virus more and recognize it more. The immunity is more effective long lasting

The disadvantage : because it is attenuated live virus (not killed) there is a chance to the activation of the virus and make The disease itself.it is critical in pregnant females and immune- compromised people :(the attenuated virus is stronger Than the immunity of the individuals and it will replicate and cause disease)

The pregnancies females as well:for the mother the production of certain hormones and the immune state not at its full Effectiveness)
For the baby; the baby can affect by the vaccine through the placenta
. These two groups are not given the vaccine

3.Genetic vaccines: During Covid-19 pandemic we had a new groups of vaccines(mRNA- based vaccine, vector based vaccine)

Instead of giving the whole virus, the genetic material of it is given like: RNA or DNA (which carries the virus's characteristics)

As soon as DNA part or RNA part it enters the cell and has the ability to make its replication cycle and develop immunity
This process is complex (DNA introduction) and we must be ensures that the full replicaion of the virus doesn't occur .

example:mRNA based covid-19 vaccine like: sinopharm COVID-19 vaccine which is chinese killed vaccine .it is the classical one .we make sequencing for it because it is RNA virus
.We bring mRNA part with ceratin additives and vectors which differ from on vaccine to another and we give to the patient
This mRNA forms the spikes of the virus(spike proteins) which helps in the viral attachement with the lung

The mRNA enters the cell and make the transcription for spikes (it isnt infective) so the immune system recognized the spikes As a forigen antigen and we will have antibodies against spikes

What about long lasting immunity and memory? The vision is still unclear with mRNA- vaccine.If you notice ,we took multiple Doses which indicates that it might be short term and requires booster doses

not all vaccines are 100% effective. There are vaccines almost 100% effective such as yellow fever vaccine,89% effectivness (mumps rubella,measles), 50% effectivness is the infleunza vaccine because it makes changes,mutations, change geneome.we have to change it every year and add the new strains for the vaccine

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

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