LESSON 8(a): HERPES SIMPLEX-- A DNA VIRUS

Every virus has its own unique life cycle pattern, so what you learn here may or may not apply even to other DNA viruses. However, herpes simplex is a very good example to use because we'll see quite a few key features of viral replication.

The herpes family of viruses gets its name from the Greek word "herpein," which means "to creep." This is thought to refer to the way the rashes produced by herpes creep along the skin. Herpes viruses enter the body though epithelial cells, primarily skin cells. The outer layer of skin is actually a layer of dead cells, which herpes cannot attach to. The skin must be cut or damaged in some way for the virus to enter. Many herpes viruses causes rashes or sores on the skin, but they can produce other symptoms, as well.

There are hundreds of herpes viruses which infect a wide range of animals. There are 8 types that infect humans:

1) HSV-1: herpes simplex 1, which causes sores in and around the mouth
2) HSV-2: herpes simplex 2, which causes warts and sores in and around the genital region
3) VZV: Varicella zoster, or "chickenpox" which causes fever and pox-like sores on the skin
4) EBV: Epstein-Barr virus, a
5) HCMV: Human Cytomegalovirus, often causes no symptoms, but can also cause pneumonia and rash
6) HHV-6: ("Roseola," a common and mild infection in infants and toddlers)
7) HHV-7: a relatively mild virus unless the person's immune system is not working well
8) HHV-8: causes Karposi's sarcoma (skin tumor)

Herpes viruses are relatively large, from 150 to 200 nanometers in diameter. They have very large genomes (from 120,000 to 240,000 base pairs) made of double-stranded DNA.

A major feature of herpes viruses is their ability to become latent (dormant). After initial infection, they will often travel to the nearest sensory neuron and hide inside the cell body of the neuron. The circle of DNA might or might now become part of the host cell genome, but even if it does not, the cell still can't ever rid itself of the viral DNA. A very well-known example of this is the varicella zoster virus which, in its initial infection causes "chickenpox." Then it goes into neurons and lies dormant for decades. If it comes out again, this time the infection will be called "shingles" and will involve both neurons and skin cells. Because of neuron involvement, the virus causes more pain than it did the first time around. The triggers for varicella becoming lytic again are not well understood, though the probability does increase with age.

Almost every adult on the planet carries at least one type of herpes. Most people are exposed to HSV-1 during childhood and 67 percent will go on to test positive for it as adults. If you or someone you know gets small, white mouth sores from time to time, HSV-1 is the likely cause. HSV-2 is a concern for people who are sexually active since that is how it is passed from person to person. Women who are infected with HSV-2 run a greater risk of getting cervical cancer. A large section of the population carries cytomegalovirus (HCMV) though they've never had any symptoms. HCMV doesn't cause problems for people with healthy immune systems. Roseola (HSV-6) is a very common childhood disease, and mild enough that making a vaccine for it is very low priority.

After doing this drawing and seeing how complex the assembly process is, you might wonder if anything ever goes wrong. The answer is yes, things often go wrong and with some viruses, only one in several hundred attempts at creating a virion will actually produce a perfect virion capable of future infection. However, the infected cell is churning out thousands of virions, so it doesn't matter if not all of them work.

The "life cycle" of herpes simplex viruses

This information goes with drawing 8(a).

1) Attachment: One of the receptors that Herpes simplex uses is "heparan sulfate," found in abundance on epithelial (skin) cells.
2) Entry: A second set of receptors allows the virus to fuse its membrane with the cell membrane.
3) A tegument protein called "vhs" (virion host shutdown) goes out into the cytosol and starts chopping up mRNA. (Proteins that chop up DNA or RNA are called "endonucleases.") The action of vhs is thought to help the virus by getting rid of a lot of the host cell's mRNAs so that there will be many available ribosomes when the viral mRNAs come along.
Also, mRNAs for making interferon (the cell's first anti-viral response) will be destroyed.

4) The capsid is transported by motor proteins to the nucleus.
5) Uncoating: The DNA goes into the nucleus, along with a protein called VP16, which will help to transcribe immediate early genes.
6) The DNA goes from linear to circular.

7) A decision is made (after sensing environment) as to whether to follow the lytic or lysogenic pathway.
7A) If lysogenic is chosen, proteins will attach to the DNA at the location of "latent" genes, and mRNA will be made that will result in the virus NOT reproducing itself. The viral DNA will just sit there doing nothing for a very long time, perhaps for the rest of the lifetime of the host. Some herpes come out of lysogenic stage and become lytic for a short time, then go back to latency.
7B) If the lytic pathway is chosen, other proteins will attach to places on the DNA where there are genes for "immediate early" proteins. RNA polymerases make mRNA from these immediate early (I.E.) genes.

8) The "immediate early" mRNA leaves the nucleus and goes out to ribosomes in the cytosol. The ribosomes make proteins using the code in the viral mRNAs. These are called "immediate early" proteins.
9) Some of the "immediate early"proteins stay in the cytosol because they mimic a cellular protein called interleukin 10 (IL-10), which is a chemical message that tells the cell not to make any "pro-inflammatory" proteins. When there is inflammation, this alerts the immune system that there is trouble, and the immune cells come running. So if no pro-inflammatory signals are sent out, the immune system will not be alerted.
10) Some of the I.E. proteins go back into the nucleus and attach to the DNA at places where there is code for "early" genes. These sections of DNA are read by host cell RNA polymerases, and mRNA is made.
11) The early mRNAs go out into the cytosol and are read by ribosomes, and several early proteins are made. One protein that is made is a DNA polymerase. Other proteins will be for making late mRNAs.
12) These early proteins go back into the nucleus. The DNA polymerase starts making copies of the DNA. The copies are all connected, in one long string (called a concatamer).
13) Other early proteins attach to the DNA (including DNA copies) where there is code for "late" genes, and "late" mRNAs are made (again by the host cell's RNA polymerases).
14) The "late" mRNAs go back out into the cytosol. Some of these "late" mRNAs code for the capsid proteins, some tegument proteins, and some "helper" enzymes that will help to assemble the capsid. These proteins are made by ribosomes in the cytosol and then transported back into the nucleus.
15) Other "late" mRNAs attach to ribsomes that are embedded in the ER, and thus the proteins they make go into the ER. One of these proteins is a "wrench to throw in the works" and it will stop the cell's MHC flags from leaving the ER to go to the surface. The MHC flags have a clip on the top that can hold a sample of proteins that are being produced inside the ER. If the MHCs get to the surface, immune system cells will recognize viral proteins and will kill the cell in order to stop the virus from reproducing.
16) Some of these will be proteins for the glycoprotein spikes (but at this point they are just the protein part).
17) Vesicles containing spikes will bud from the ER and go into the Golgi body.
18) Inside the Golgi body, the sugars will be added to the spikes, making them glycoproteins.
19) Vesicles containing glycoprotein spikes will bud off the Golgi bodies and go to the surface of the cell.
20) Then they will be brought back inside as part of an endosome's membrane. This seems silly (to put them out and then bring them right back in) but this allows for recycling. Some of the spkes brought back in might have been originals from step 2.

21) Capsids are assembled and tegument proteins are stuck to them.
22) A protein scissor cuts apart the long DNA concatamer, and each copy of the genome goes into a capsid as it is assembling.
23) Finished capsids bud out of the nucleus and into the cytosol.
24) The capsids will run into the endosomes with the glycoproteins and be taken inside the endosome. This will create the envelope. The enveloped capsid is now inside an endosome that will take it to the surface.
25) The endosome merges with the plasma membrane and the new virion is released.