LESSON 5(a): HOW VIRUSES ENTER CELLS

There are three basic steps that a virus must go through to enter a cell. The first step is to attach securely to the cell. The second is to somehow get their payload of DNA or RNA into the cell. The third step is only for enveloped viruses because in this step they merge their envelope with the cell's membrane.

The first step is to attach to the cell. The surface of all cells is a "forest" of tiny proteins sticking up everywhere. Most of these proteins are receptors of some kind. Some are like ID tags and function to identify the cell as "self," meaning belonging to the body. Some are used for attachment to other cells. Some are there to take in nutrients that the cells needs, or to receive chemical messages sent out by other cells. Some receptors are actually not receiving but sending messages but we call them receptors anyway. Chemical messages are in the form of hormones made of lipids (fats), or proteins, sugars, or even small ions such as calcium atoms.

The first feature we draw is actually a mechanism that cells don't attach to: the proton pump. This little "machine" constantly pumps positively charged protons from the inside to the outside of the cell. (The protons probably came from a hydrogen atom that lost its electron. Hydrogen's nucleus is nothing but a proton, so when it loses its electron the nucleus floats around as a single proton.) The proton pump is a key factor for many viruses in their entry process.

Another feature on the cell surface that is not a major target of virus attachment is MHC 1 (also known as HLA) which looks like a little flag and is used to identify the cell as belonging to the body. Immune system cells called NK (natural killer) cells patrol the body, feeling the surface of cells, looking for those ID tags. If they don't find them, they kill the cell with a little protein "gun" that shoots a hole in the cell. Cells that are infected with viruses often are not able to put their flags out, so they are killed by the NKs.

Cell receptors that are commonly known as viruses receptors are:

1) Sialic acid: a tiny sugar found on the ends of many long glycoprotein chains, especially on cells found in the respiratory tract.
2) ACE2 (Angiotensin Converting Enzyme 2): part of the blood pressure regulation system, it tells arteries to relax and open, thus lowering blood pressure. (ACE is the opposite and works to constrict vessels and raise blood pressure.) ACE2 receptors are found in the lungs, heart, blood vessels, and intestines. The coronavirus attaches to ACE2, so it can enter anywhere these receptors are found, including the intestines. This is why people are told to wash their hands thoroughly, so corona is not swallowed.
3) CD155, also known as **PVR** (Polio Virus Receptor): used as a connection between cells, found mainly in epithelial cells in the skin, lungs and intestines. (CD stands for Cluster of Differentiation, a technical-sounding way to say "clump that is different.")
4) CD4: a receptor found on T cells allowing the T cells to communicate with macrophages. Both of these cells are types of white blood cells and are part of your infection-fighting immune system. HIV attacks T cells and enters using CD4. This is why HIV is such a serious disease-- it disables germ-fighting cells.
5) CAR: Coxsackie-B Adenovirus Receptor, which is not designed for these viruses, but for body processes such as proper formation of the heart during embryonic development, and for cells to attach to each other in the heart and lungs.

We also drew a 7-pass receptor, as they are a very common feature found in the membrane. Most 7-pass receptors are also called G-Protein Coupled Receptors. This type of receptor has some very complicated and interesting mechanical features under the surface of the membrane. About half of all prescription medicines are designed to target some type of GCPR.

The most important concept to understand in drawing 1, is that viruses are able to latch on to a receptor because their protein spike or knob just happens to fit perfectly into a receptor. It is all about shape matching. Sometimes the phrase "lock and key" is used to describe it. The virus (unfortunately) has a copy of the correct key shape to open the lock.

Viruses need to get their genome into the cell. Some naked viruses, like polio, open a small pore right at one of the vertices (corners) of their icosahedral capsid, using a fusion protein, and the genome threads through the hole and into the cell.

Other naked viruses wait until they are taken into the cell, inside a "bubble" called an endosome. The endosome is made of a piece of membrane, so it still has proton pumps in it. The pumps are still pumping protons, so the endosome begins to fill with protons. This causes the pH to drop, and the endosome becomes acidic. This is just what the virus needs, as the low pH causes the capsid to disassemble and the endosome to burst open.

If a virus has a lipid envelope, it will need to merge the envelope with the cell membrane. Since the virus's membrane is actually stolen cell membrane (from the cell it came out of) the two membranes will merge naturally if they can be brought together. Some viruses merge their membranes at, or close to, the surface. Others wait until they are in an endosome. In either case, a fusion protein will be needed.

The fusion protein is not accessible (hidden) until the virus attaches to the receptor. The attachment of the receptor triggers the release of the fusion protein and it sticks down into the cell membrane. Again, the low (acidic) pH inside the endosome is a key to making this happen. When the viral membrane fuses to the endosome, the result is sort of a C shape, and the genome suddenly finds itself outside the endosome, in the cytoplasm of the cell. Influenza virus is the best example of this, so we will study the influenza process in lesson 5(b).