LESSON 10: VACCINES and ANTI-VIRALS

The goal of a vaccine is to imitate the natural process of recovering from a viral infection, without actually experiencing the infection. When we recover from an infection, most of our B cells will receive signals from other immune cells to stop producing antibodies and to go through the process of apoptosis (programmed cell death). However, a small number of B cells will turn into memory cells, and will live on for years, ready to be activated if the need should arise. The first time the B cells are activated to attack a new virus, the process can take up to two weeks. The next time around, the memory B cells can shorten the activation time to just a few days, and the virus will be overwhelmed with antibodies before it can do any damage. Our immune system deals with pathogens (viruses, bacteria) every day, and most of the time we just go about our activities unaware of all the battles our immune system is winning.

A vaccine simulates infection by delivering whole viruses, or pieces of virus, to macrophage cells. The macrophages roam around looking for things to eat, so anything you inject will eventually end up being discovered by macrophages. The macrophages process the viral proteins and then present them to T helper cells who then find the matching B cells. These B cells will start producing antibodies (but not quite to the degree necessary for a real infection). Most importantly, some B cells will turn into memory cells.

Vaccines are classified as either active ("live") or inactive. Active vaccines are whole viruses that have been weakened, or "attenuated." Usually this means that their genome has mutated, as we saw with polio. Albert Sabin discovered a natural mutation of one letter in the IRES part of polio's RNA genome. We call these "live" vaccines even though viruses are non-living, because the virus retains a substantial part of its ability to replicate. What it can't do is actually cause harmful disease. In the case of polio, the virus in the Sabin vaccine could still infect the intestinal cells, but it could not attack nerve cells. In the intestines, polio is harmless. You don't even know it is there. It's when it travels to the neurons that you begin to see poliomyelitis symptoms. Other active vaccines include measles, mumps, rubella, yellow fever, and chickenpox.

Inactive vaccines are either whole viruses that have been "killed" by chemicals, or just small pieces (fractions) of viral protein such as bits of spike or capsid. The first inactive vaccine was the polio vaccine invented by Jonas Salk. He used a chemical called formalin to damage the viruses so badly that they no longer functioned. He found that the immune cells would still react the same way to these inactivated viruses. Using just tiny pieces of viral protein removes any concern that the vaccination will be able to actually cause disease. Recently, advanced genetic techniques have allowed virologists to make plants cells or yeast cells produce either empty capsids, or pieces of viral genome, which can be used for a vaccine that can't possibly cause disease. These vaccines are called "recombinant."

Sometimes, a vaccine that contains only pieces of a virus will not cause a strong enough response to get B memory cells produced. Virologists have found that if they add something to the vaccine to cause a microscopic amount of inflammation, this can trigger the desired memory response. Added substances are called "adjuvants." A common adjuvant is alum (aluminum hydroxide). Another option is to use inactivated bits of bacteria that fit into those TLR sensors.

In the past few years, some researchers have raised concerns about whether aluminum adjuvants can have side effects. They are generally considered safe by the FDA, but aluminum has been suggested as a possible contributing factor to the development of Alzheimer's in elderly people. Veterinarians have noticed that (a small number of) cats can develop tumors in the places where they receive shots, though there isn't any obvious reason why this should be so. It doesn't happen in dogs.

Anti-virals are medications you take after you come down with a virus. The tricky part is to find a chemical that will harm the virus without harming body cells. Viruses are made of the same stuff we are (proteins, lipids, DNA, RNA), and a general toxin would kill the host cell as well as the virus. You have to find a molecule that will stick to a particular viral shape, a shape not found in body cells. Before virologists were able to map out the exact shape of a virus, it was a matter of trial and error, collecting and experimenting with any new substance they could find. The would take samples of anything--dirt, plants, bacteria, fungi, minerals-- and do an assay to see if they killed viruses. Amazingly enough, they found a chemical from a Caribbean sea sponge that would stop herpes viruses! They did not know it at the time, but this chemical, which they sold under the name Acyclovir, was so similar to the guanine rung in DNA or RNA that the virus would use Acyclovir instead of the real guanine. Acyclovir had no attachment point for the next rung, and thus genome replication would come to a halt. Many anti-virals work like this, being an analogue (a mimic) of a nucleoside (A, T, U, C, G).

The strategy used to treat influenza infections is a chemical that sticks to the NA, neuraminidase, and prevents it from cleaving (cutting) the HA spike free as the virus is trying to leave the cell by the process of budding. The medicines molecules (sold as Tamiflu or Relenza) bind to the active site of NA, preventing its scissor action. The influenza viruses are stuck. (They will eventually be digested by macrophages.) The protein shape of NA is complicated and various drug binding sites can be used.

One of the many anti-virals that is used against HIV is called Fuzeon. It is a protein containing only 127 amino acids (short enough to be called a "peptide"). It binds to HIV's spike at just the right place so that it is not able to connect to the cell receptor that allows it to expose its fusion protein and join with the cell membrane.

A strategy that worked for a while on influenza was a chemical (sold as "Amantadine") that locked onto the M2 channel and blocked it. Unfortunately, influenza mutates quite quickly because of its segmented genome and the lack of a spell checker, and soon a new version of influenze arose where the shape of the M2 channel was just enough different that the chemical was no longer able to lock onto it.