Immunology Ambassador Guide

Immunity and Disease

We will talk today about the immune system and how it protects us from disease. Also, we'll learn some unique ways that our immune system uses our DNA to recognize the millions of potential pathogens around us that could make us sick.

What is DNA Day?

On DNA Day we commemorate some very important events in the history of our knowledge about DNA. In April 1953, scientists Watson and Crick described the double helix structure of DNA. Fifty years later, in 2003, scientists published the entire SEQUENCE of the human genome which has enabled many advances in our understanding of how our genes function, but also in how we can treat diseases.

What is the immune system?

DNA is important for the proper functioning of the systems of our body. One of the systems that can be influenced by our DNA is the Immune System. We'll begin by defining the immune system and then we'll discuss how our DNA influences it. The immune system is what protects your body from disease. Some diseases are caused by pathogens. A pathogen is an organism that can cause disease. Some examples are: bacteria, viruses, fungi, and parasites. Are humans the only organisms with an immune system? No. Other mammals, plants, fish, and even insects have an immune system. Image: Immune cell (macrophage) enveloping and digesting bacteria)

What happens when we get an infection?

Our system destroys the pathogen 2 ways.
One of these ways is through a cell mediated response. This involves the use of macrophages, which eat pathogens and debris, and neutrophils, which eat pathogens and kill them by releasing toxic particles.

A second way our immune system destroys pathogens is through a humoral response, which involves B cells that produce antibodies. What is an antibody?

Antibodies are proteins

So how does DNA influence our immune system? The information in our DNA is transcribed to RNA. RNA is then translated to protein. Antibodies are proteins, so the information in our DNA leads to antibody production.

Antibody structure

2 identical light chains (which are proteins) come together with 2 identical heavy chains to form an antibody. Variable region binds pathogens and can differ between antibodies from different B cells. Constant region- varies much less between B cells and does not bind pathogens

What do antibodies do?

1. Pathogens can bind to the outside of cells and lead to cellular damage. Antibodies can bind to pathogens and prevent them from binding to cells. Description of picture: bacteria covered in antibodies that can bind the host cell shown

2. Antibodies help other cells of the immune system recognize that pathogens are foreign. Antibodies will help immune cells such as macrophages and neutrophils recognize pathogens and eat them up. Description of picture (bacterium covered in antibodies eaten by a macrophage on the left, same description for neutrophil on the right)

Questions.
Can you name some pathogens that can infect us and cause disease? Some examples of pathogens that can infect us include viruses like Influenza or bacteria like Salmonella. There are several types of pathogens, do they all look the similar or different? They all look different.
If there are several pathogens that are different from each other, how do our antibodies recognize and bind them all? The answer is V-D-J recombination, which we will discuss shortly.

Demonstration
Now we'll do a demonstration to help us visualize what it looks like when our immune system encounters invading pathogens. SEE HANDOUT.

Recognizing Different Pathogens
Our bodies encounter many different pathogens, and it's important that we have antibodies that recognize the proteins on each of these pathogens. How does our body recognize so many different pathogens?

Remember, B cells are the cells of our immune systems that make antibodies, which are the proteins that are able to recognize pathogens.

Not all B cells are making the same antibodies, however – in fact, every B cell makes a unique antibody, and is therefore able to recognize a unique pathogen. These antibodies differ from each other in their variable regions - that's the part of the antibody protein that specifically interacts with proteins on the pathogen's surface.

Amazingly, our B cells are able to generate 100 Billion different antibodies! If you remember, proteins like antibodies are encoded by genes in our DNA – so do you think we have a single gene for each individual antibody our B cells produce?

Well, the entire human genome has been sequenced, and our entire genomes only contain 30,000 genes – not enough to encode all of those 100 Billion different antibodies. And of course, most of those genes have to be making other proteins besides antibodies. So how do our B cells make so many different antibodies from a much smaller number of genes?

Every Cell Has the Exact Same DNA
First, it's important to understand that even though every cell in your body contains the exact same set of DNA, different cells use that DNA differently.

For example, in a nerve cell, a lot of genes are turned off – that is, they're not making proteins. Nerve cells will turn on the genes that are important for their job as part of the nervous system – so they may turn on genes to make proteins that will act as neurotransmitters – but they'll turn

off other genes for proteins they don't need. This is true for B cells too – they specifically turn on a set of genes that are important for their job – fighting off pathogens.

In B cells, there is a set of genes that is important for making antibodies that is turned on, while those same genes are inactive in other cells. B cells are able to manipulate these genes in a very unique way, allowing them to generate billions of different antibodies from much fewer genes.

Producing Variable Regions of Antibodies

Now, we'll continue to discuss how B cells are able to produce different variable regions of antibodies. You've just learned about how B cells can turn genes on and off in order to produce diversity in antibodies, but we are also able to make so many different antibodies due to another phenomenon known as VDJ recombination. VDJ recombination is the process by which V, D, and J genes are randomly selected and combined to form the heavy and light chains that make up antibodies. VDJ recombination is unique in that it only occurs in specific cells of the immune system, and not in any other cell types within our bodies.

You've now learned that the genes that encode antibody proteins are found in our DNA. You've also learned that antibodies are made up of 2 identical light chain proteins, and 2 identical heavy chain proteins. The genes that encode these proteins are found in your DNA and are referred to as V, D, and J genes, as shown in the bottom right hand corner of the slide. The heavy chain DNA sequence contains V, D, and J genes, while the light chain DNA sequence contains only V and J genes.

VDJ Recombination

So how does V, D, J recombination work? There are 45 V genes (shown in blue), 27 D genes (shown in green), and 6 J genes (shown in orange) that make up the DNA that codes for heavy chains.

During VDJ recombination, the cell must randomly choose 1 V, 1 D, and 1 J gene to combine to make the heavy chain. In this example, the V36 and D5 genes (as shown by the red arrows) have been chosen to recombine.

During recombination, the intervening genes are now removed, and V36 and D5 genes can now be joined together.

Next the D5 and J3 genes are chosen to recombine, as shown by the red arrows

Once again, the intervening genes are removed, and now the D5 and J3 genes can be combined.

So, now the cell has undergone VDJ recombination, and V36, D5, and J3 genes have been combined, the heavy chain DNA can now be transcribed into heavy chain mRNA, and finally translated into heavy chain protein. Only the V36, D5, and J3 genes have been turned on, while the remaining genes are turned off

Light Chain Recombination
The V and J genes of light chains also undergo recombination. Once VDJ recombination has been complete, both the light and heavy chain genes can be translated into protein, in the cytoplasm of the cell (as shown in the far left hand corner). The proteins are then assembled into antibodies and are transported to the surface of the B cell (as shown in the far right-hand corner) and are now able to bind to the pathogen.

Immunodeficiency
So, you've just learned that VDJ recombination is necessary for B cells to produce many different antibodies, with different variable regions. It's also important to know that the inability of immune cells to perform VDJ recombination can have very serious consequences. Individuals that have a defect in VDJ recombination, lack diversity in their antibody production, and as a result have a severely weakened immune system (referred to as immunodeficiency). This means that they are unable to be exposed to their environment because they are unable their immune system is unable to fight off infection caused by pathogens. Some of you may have seen the movie, "The Boy in the Plastic Bubble," which is based on someone born with defects in their immune system, and as a result was not able to mount a proper immune response to pathogens in the environment.

VDJ Recombination Demonstration
So, now that you've learned about VDJ recombination, you, along with your classmates, will play a game which will further demonstrate how VDJ recombination works. SEE HANDOUT.

Clonal Expansion
We have just finished playing a game to demonstrate how VDJ recombination can allow our immune system to produce different antibodies to respond to patterns on different pathogens. But what happens after an antibody binds to a pathogen? How do B cells trigger an immune response? Once a B cell binds to an invading pathogen, in this case a virus, shown on the left, the B cell interacts with other immune cells, a helper T cell is shown here, and becomes activated. Once the B cell becomes activated, it can now release antibodies and undergo a process called clonal expansion.

A single B cell is incapable of producing enough antibody to clear the pathogen and save our bodies from infection. In order to resolve this problem, an activated B cell will make exact genetic copies, or clones, of itself. Each of these clones will produce the same antibody, the specific antibody that recognizes the pathogen trying to infect. This process is called clonal expansion.

As shown here, an activated B cell will create a clone of itself, resulting in two cells specific for that infection. Each of those two cells will create clones as well, resulting in 4 clones, and so on and so forth. Over the course of 4-5 days, the process will continue resulting in 1000 clones or greater formed from the original B cell that became activated.

<u>Demonstration</u>
We will now return to the balloon demonstration from earlier to demonstrate how clonal expansion helps our immune system to evade infection.

Memory B Cells
Now we've seen how our immune system can address an infection, but it's important to note that our immune system can also help protect us from future infection by the same pathogen. How does this occur? Not only do activated B cells undergo clonal expansion, but they also create Memory B cells. These specialized B cells will remain in our bodies for years, much longer than other B cells. They create antibodies that are specific for the pathogen that was trying to infect and if they re-encounter the same pathogen they are able to respond very rapidly and strongly. This allows our immune system so greatly shorten the 4-5 day process for clonal expansion and respond so strongly that we avoid becoming sick altogether.

If these cells are so specialized to protect us from future infections, is there any way we can use them to protect us from illness that we have not yet encountered?

Yes, in fact, vaccines are a method of creating memory B cells to prevent us from future infections without ever getting sick.

Vaccines
So how do vaccines work? Vaccines contain portions of a pathogen that do not make us sick. They can be designed in different ways. They can be made of broken-up or incomplete subunits of a pathogen. The can be vaccines that are the same as a pathogen on the outside, but cannot actually infect us, and these are called killed vaccines. Or they can be live vaccines, which are pathogens that do infect, but are modified so that they don't make us sick.

Can you name some diseases that we are vaccinated against?

Some examples include: Measles, Mumps, Rubella, and the Chicken Pox. In general we only need to be vaccinated against these diseases once, often when we are very young, and the vaccine will create memory B cells that will protect us for our whole lives.

Flu
But what about the flu, another disease that we are vaccinated against? Why do we have to get the flu vaccine every year?

While we've focused on ways that our immune system can adapt to a large variety of pathogens, using for example VDJ recombination, pathogens, like the flu virus, can also adapt and change their genes to evade our immune system. The flu is an example of a pathogen that rapidly changes its genes, so much that in one year the memory B cells that our immune system has developed will often no longer recognize the new, changed, version of the flu virus.

H1N1
Often, large disease outbreaks (pandemics) occur when a virus that normally infects another species, acquires a mutation that enables it to infect humans. Since human immune systems have not seen this specific pathogen before, there are no "memory cells" in the population, and therefore large numbers of individuals get sick. In the case of swine flu (H1N1), scientists

believe that genes from flu virus that infects swine, chickens, and humans combined to form a new version of the virus that was infectious for people.

Summary

So what have we learned today? We've learned that antibodies are proteins created by our B cells that bind to pathogens, which is a key step in our immune response. We've also learned that we are able to create a large variety of antibodies using VDJ recombination and by turning genes on and off. We've also learned that B cells can mount an immune response by undergoing clonal expansion, and that we are protected from future infections by memory B cells. We have also talked about how vaccines are a method of creating memory B cells without causing illness.

Vocabulary
(in order of appearance)

Immune system- system that protects your body from disease

Pathogen- a pathogen is an organism that can cause disease

Cell-mediated response- destroying pathogens using macrophages and neutrophils

Macrophage- an immune cell that eats (phagocytose) pathogens and debris

Neutrophil- eats (phagocytose) pathogens and kill by releasing toxic particles

Humoral response- destroying pathogens using antibodies produced by B cells

B cells- immune cells that produce antibodies

Antibody- protein that binds pathogens

Variable region- part of the antibody that binds pathogens

VDJ recombination: the process by which V, D, and J genes are randomly selected and combined to form the heavy and light chains that make antibodies.

Immunodeficiency: an innate, acquired, or induced inability to develop a normal immune response

Clonal Expansion: A process that an activated B cell undergoes to create many (>1000) exact genetic copies of itself to respond to encountering a pathogen.

Clone: An exact genetic copy of a cell or organism.

Memory B Cell: Specialized B cells that develop following clonal expansion and remain in our bodies for years to protect from future encounters with the same pathogen by responding immediately and very strongly.

Vaccines: A method of creating memory B cells to protect us from future illness without first becoming sick. Can be designed in thee major ways: subunit vaccines, killed vaccines, and modified live vaccines.