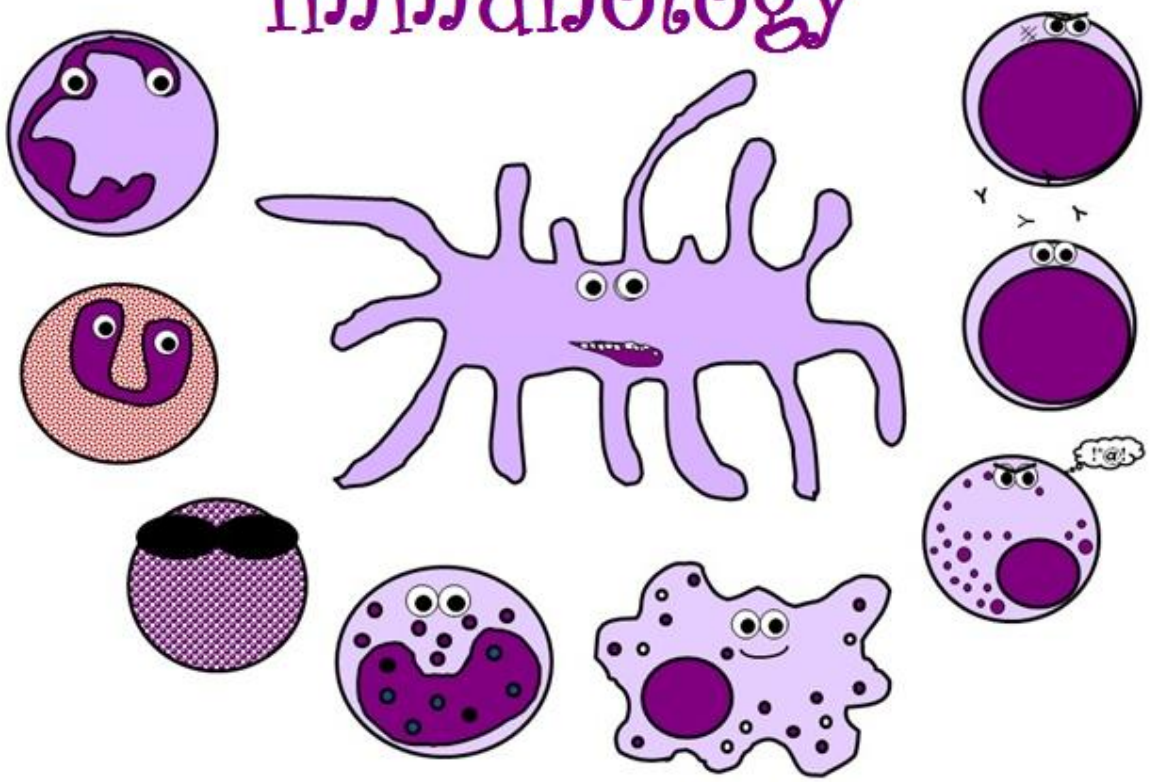
Immunology



Sheet Slides

Number: 1

Subject: Introduction to the Immune System

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بسم الله الرحمن الرحيم

Everything in the slides is included in this sheet and many of the figures.

- **<u>Why is immunology difficult?</u>**

  1. Details: If you open an immunology textbook you will see how many details there are in immunology. These details seem scary at first, but there are some important details you have to memorize, but the important thing is to understand the big picture of Immunology.

  2. Exceptions: Every time you think there is a consensus, new research will show that there are exceptions and the results are dependent on the context.

  3. An evolving science: What was taught in the 80's is different than what is taught today, unlike some other fields such as microbiology and anatomy. There is so much new information in the field of immunology out there today.

  4. Immunology is a network

  What does network mean? Cells communicate with other cells. You don't see a T cell or B cell alone. They all work together. If you look at this NBA player you think that he will score two points, but if you zoom out and look at the big picture you would see another player blocking him from scoring the basket. You have to look at the big picture.

  If you don't look at where the B cell is, what cells are inhibiting it and what cytokines are being released you won't come to the correct conclusion.

- The immune system has many lines of defense. Bacteria is everywhere; on the chairs you are sitting on, your pencil cases, the walls, everywhere! How do you sit here for an hour without getting sick?

LINES OF DEFENSE:

A. First line of defense??? ..... Physical barriers!!!

The physical barriers help to protect our body from disease.

Physical Barriers:
Skin: 2m^2
Mucosal membranes: 400m^2

- **Physical barriers are the first line of defense and include:**
  1. **Skin**: it prevents the organisms from entering the body. It covers the whole surface of our bodies. Skin when spread out has an area of 2m^2.
  2. **The mucosa:** It is something very important that people usually overlook. The mucosa is about 400m^2. We find the mucosa in the GI, oral cavity, urogenital tract, respiratory system.

There will be some cases when these **barriers are breached**. Such as if a pin pricked your toe. When the barriers are breached how will the body protect you? You will find neutrophils, macrophages for example, these are part of the **Innate Immune System .**

B. Second line of defense: The Innate Immune System (جهاز المناعة الفطري)

Innate Immune System
Second line of defense.
500 million years old!

- Invertebrates that existed millions of years ago had an innate immune system. The innate immune system is 500 million years old!!! With time the innate immune system adapted and progressed.

  Note: This is from an evolutionary perspective. If you are convinced with the creationism theories, skip this.

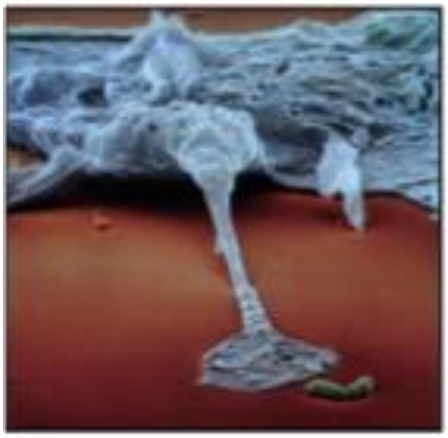
Now the pin pricked your toe. What do you see?

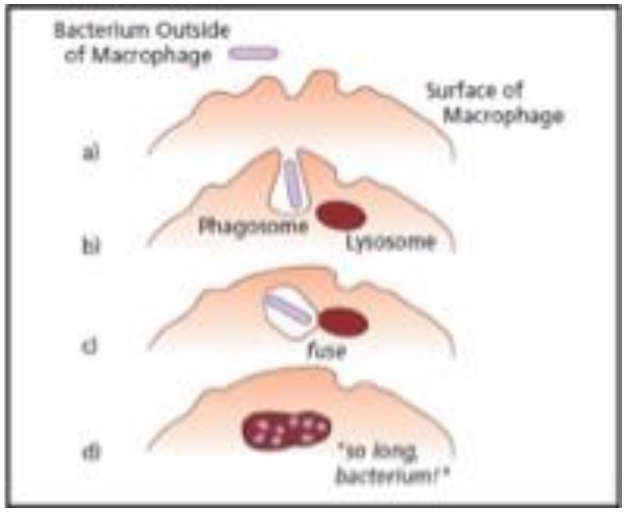
Erythema which is redness and **edema** which is swelling. The redness is due to increased blood flow and the edema is due to the infiltration of cells and fluids. Erythema and edema are the product of the immune system working. The barrier was breached, the bacteria entered,

and the innate system is activated.

The Macrophage:

- Macrophages are one of the cells you mentioned as an example of the innate immune system. The macrophages were monocytes, they left the blood stream and were extravasated. The macrophage from its name is **MACRO** big and **PHAGE** which means eats. It will then present anything it phagocytoses to the other immune cells.





This is a picture of the macrophage in the scanning electron microscope. It extended its plasma membrane towards the bacteria, phagocytoses it and then processes it. There are receptors on the cell membrane of macrophages that discriminate between disease agents and non-disease agents. Once it finds a bacteria, it invaginates it and surrounds it by the plasma membrane into a phagosome.

- **Phagosome:** is a plasma membrane that is invaginating to the inside.
- **Lysosome**: organelle that contains hydrolytic enzymes, enzymes that kill and break down the bacteria. The PH of the cell is 7.5 (7.35-7.45 according to physiology), but the lysozyme is acidic.

There are hydrolysis enzymes and reactive oxygen and reactive nitrogen species. The **reactive oxygen species** such as hydrogen peroxide is very powerful. Nitric oxide is an example of the **nitrogen**

oxygen species. The fusion of the phagosome with the lysosome allows the hydrolytic enzyme to access the bacteria, kill it and break it up into peptides. The importance of breaking the bacteria up is for antigen presentation to the other immune cells. To get antigen presentation you break up the bacteria into smaller peptides for the antigen to be presented.

Where do Macrophages and other immune cells come from?

Macrophages are made in the bone marrow. They differ from the blood cells. If you look at the image you have the hemocystoblast which is the stem cell.

- **Stem Cells:** are undifferentiated cells that can differentiate into many different cell types based on the signals it receives.

- **When the stem cell divides it gives us two cells:**

1. Another stem cell, so it can maintain the number of stem cells.
2. A cell from one of the following cell lines:

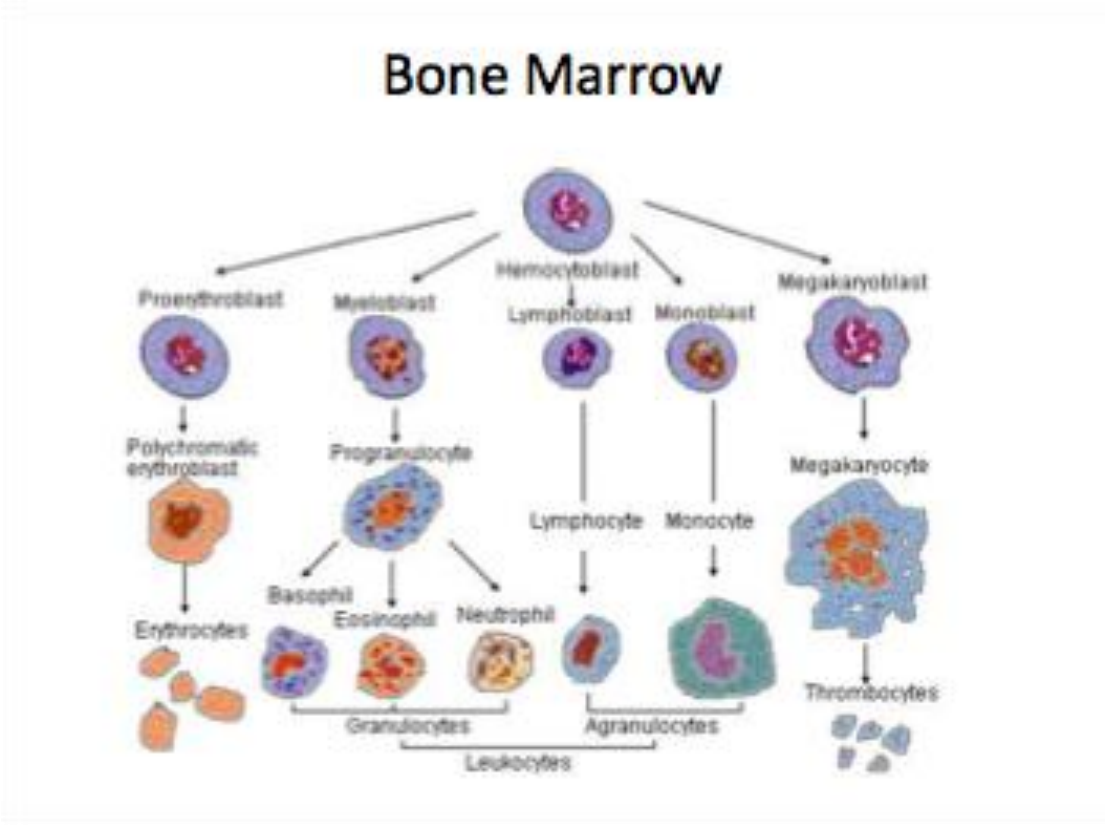
A. **Proerthyroblast**: which gives us erythrocytes

B. **Myeloblast**: which gives us granulocytes, which are cells that contain granules (neutrophils, basophils, and eosinophils).

C. **Lymphoblast**: gives us lymphocytes (B cells and T cells)

D. **Monocyte**: gives us a macrophage

E. **Megakaryoblast**: which gives us a megakaryocyte which gives us platelets.



So the innate immune system has macrophages, neutrophils, dendritic cells which all play an essential role in immunity and will be studying in detail throughout the semester. A lot of times we find resolution of the infection via the innate system. **Pus** for example is dead neutrophils; neutrophils that came, attacked the pathogen and died. Many times the innate immunity system is not enough due to either a huge number of microbes that entered the body, or if they were resistant to drugs. So what would be the third line of defense?

C. Third Line of Defense: The Adaptive Immune System (جهاز المناعة التكيفي)

(most probably developed to protect us against viruses)

Why do we call it adaptive? The innate immune system finds a pathogen and it is programmed via certain receptors to attack these

pathogens. The adaptive immune system on the other hand has specialized cell that attack a specific organism or pathogen and divide based on that recognition.

The adaptive immune system is not present in the invertebrates. It is thought that when viruses evolved they attacked they entered into the cells and hid instead of being outside and exposed in the interstitial fluid. This hiding from the immune system prompted the immune system to adapt and evolve new mechanisms to overcome the viruses.

- Note: This is again evolution stuff, so you can skip it if you don't believe in it.

❖ Edward Jenner 1796 experiment:

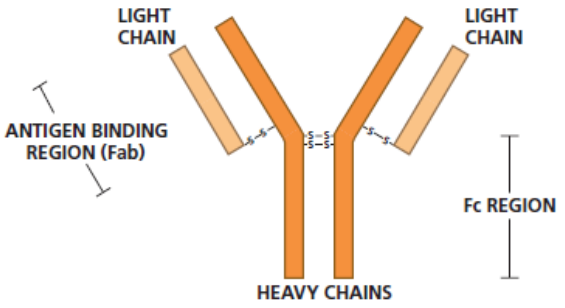
Edward Jenner who was a medical student tried to vaccinate against **small pox**. Jenner noticed that the milk maidens that milked the cows who got infected with cow pox wouldn't get small pox. Cow pox was a much less severe disease than small pox. He wondered if there was a similarity between the small pox and the cow pox that would prevent people from being infected with smallpox. He took from the pustule of the infected person and then inoculated a child with cow pox. A couple days later the child developed cowpox. A month and a half later Jenner inoculated the child with the deadly small pox and found that the child didn't develop smallpox.

What protected the child? What protected the child was the **antibodies** from the adaptive immunity prevented him from getting the small pox. **What causes immunity to smallpox?** Antibodies!

Adaptive Immune system
Most probably developed to protect us against viruses
Edward Jenner 1796 Experiment.

❖ The Antibodies:

(It is very important to focus on the structure of the antibody and know it very well)



The antibody looks like a fork. It is

composed of four polypeptides, it has long heavy chains and smaller light chains. The two heavy chains are bound together by two disulfide bonds and there is a disulfide a between each light chain and heavy chain.

What is the benefit of the disulfide bond?

The disulfide bonds give you the structure and flexibility to bind the antigen. Flexibility is very important for the antibody to bind the antigen correctly.

- **Fc:** The bottom portion of the heavy chains (which looks like a stick) is called the Fc portion, the **c** stands for **constant,** which means that this part is the same for all the antibodies of that category. So if it is IgM all the IgM would have the same Fc portion. If it was an IgG antibody, it would have the same Fc portion of all the IgG's but it would differ from all the IgM's and so on with IgA, IgD and IgE.
- **Fab:** is the antigen binding region. It is the variable part that differs from antibody to antibody.

Antibodies are formed by **plasma cells** which are the differentiated B cell. There are 100 million antigens the body has to identify. We have heavy chains and light chains that compose the antibodies. To cover all the antigens you would need 10,000 genes for light chains and 10,000 genes for light chains because 10,000x10,000 would give you the 100 million you need. So you would need 20,000 genes just to acquire the needed variability.

Generating Antibody Diversity
- Around 100 million different antibodies are needed to cover antigen variety.
- 10,000 heavy chain genes mixed with 10,000 light chain genes.
- Total of 20,000 genes required

- **How many genes do we have in our body?**

Between 16-20 thousand genes. So it is impossible to have all the genes in our body dedicated to making antibodies.

- **How do you explain the high variability with this little number of genes?**

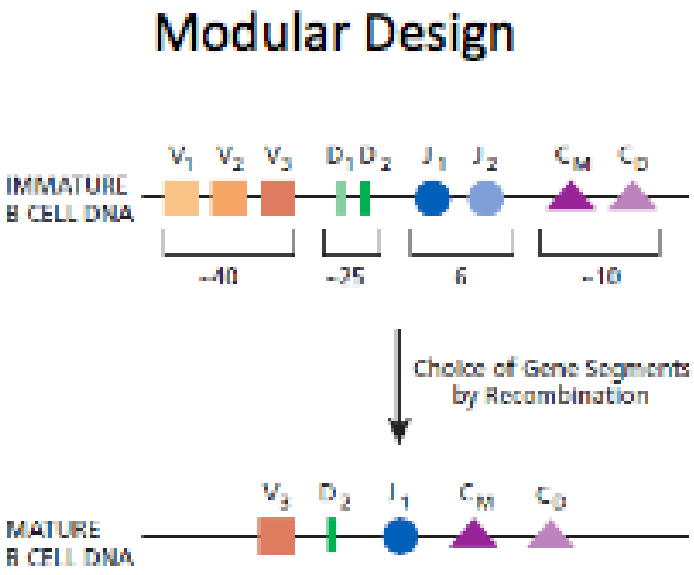
Susumu Tonegawa solved this mystery in 1977 and received a Nobel prize for proposing the **Modular Design.** Susumu Tonegawa compared

DNA in mature and immature B cells. He found that the DNA is completely different!

❖ Generating Antibody Diversity

• Around 100 million different antibodies are needed to cover antigen variety. • 10,000 heavy chain genes mixed with 10,000 light chain genes.

• Total of 20,000 genes required to generate this diversity.



❖ Immature B cell DNA contain:

1. The **constant region** contained 10 genes

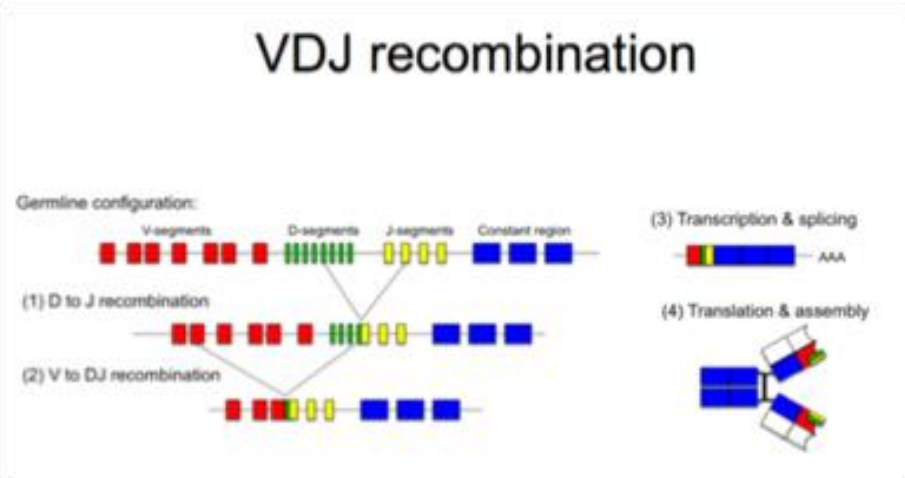
2. The **variable region** was composed of three types:

   V: 40 genes

   D: 25 genes

   J: 6 genes

❖ **Mature B cell DNA:** Had only one type of gene from each of the V,D and J. Cm and Cd code the regions of the first two antibodies that are formed by B cells.



❖ The D and J enzymes are cut and the pieces are ligated together randomly. This DNA is transcribed to mRNA that is spliced and then translated to immunogobulin. The blue part in the image represents the Fc portion, and the red, green and yellow represent the variable region in the figure.

This model shows you don't need 20,000 genes. You need random recombination that happens one time with the heavy chain and one time with the light chain and you end up with million of recombinations to make the antibodies.

Problem of numbers?

• We have around 3 billion B cells in circulation targeting around 100 million antigens.
So, 30 B cells per Antigen.

Clonal Expansion

1 cell division/ 12 hours Within one week..... 20,000 B cells secreting the same antibody!!!

The second problem is if we have one hundred million antigens we need to identify and there are three billion B cells that means that for each antigen there are only 30 B cells to identify it.

So how do we have enough B cells to fight an infection?

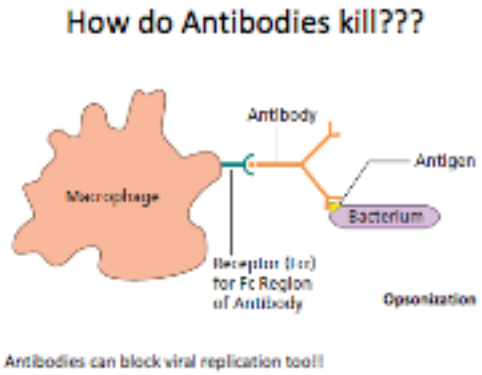
❖ Clonal Expansion

B cells identify the antigen and proliferate and differentiate into plasma cells. These cells divide every 12 hours and within one week you have 20,000 specialized B cells against that specific antigen that produce antibodies. Every second the plasma cell can secrete 2000 antibodies per second.

❖ How do antibodies kill?

1. Antibodies prevent the binding of the virus to the cell membrane

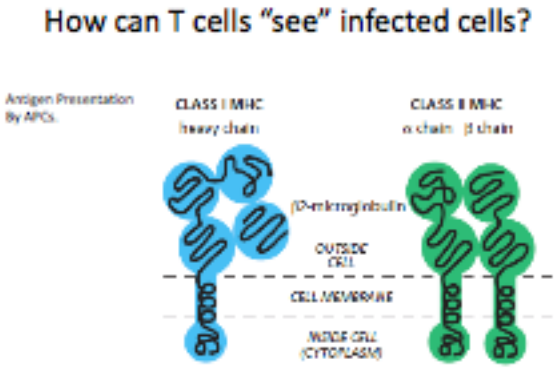
2. Activation of the **complement system,** which is part of the innate immune system .



3. The antibody binds the bacteria. The macrophage that has a Fc receptor will bind the Fc portion of the antibody, and will phagocytose the complex. This is called **opsonization**. This is like putting a tarboosh on a person's head, everyone can see it. It is telling the immune system to come and see me.

The T cells are different, you have many types of T cells:

1. **T Helper Cells**: secrete cytokines, which is the language that the immune cells use to communicate.
2. **Cytotoxic T cells:** identify the infected or cancerous cells and attack it. The infected or cancerous cells are identified using by the cytotoxic T cell by the T cell receptor (TCR) that recognizes the MHC presenting the peptide



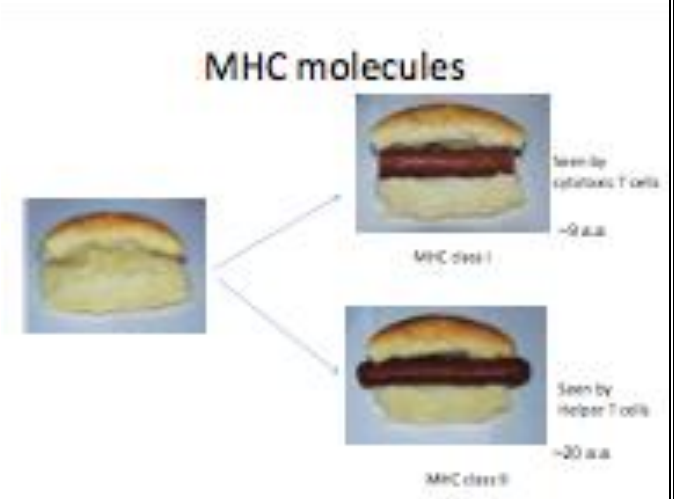
❖ **There are two kinds of MHCs:**

1. **MHC class I:** made of a long chain and small chain called beta2 chain micro-globulin

2. **MHC class II:** made of two peptides, an alpha chain and a beta chain

What is the difference between them?

If we compare MHC to a hotdog:

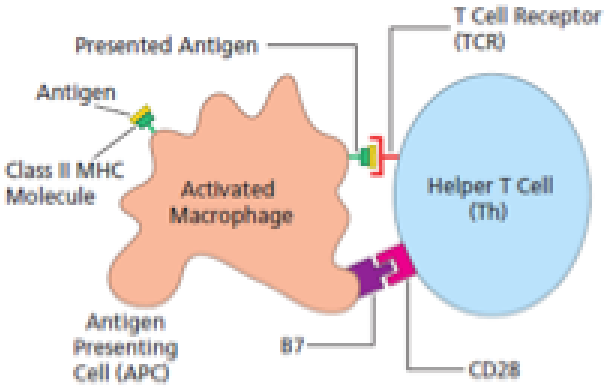


MHC class I the peptide that sits in it is very short (only **9 amino acids**), and it is very picky. The amino acids at the end are very specific. It is important to remember that the MCH class I presents its antigen to the cytotoxic T cells.

MHC class II on the other hand has a longer peptide (20 amino acids), and the amino acids are more flexible on the sides and is seen by the T helper cell.

❖ **The activation of MHC: (very important)**

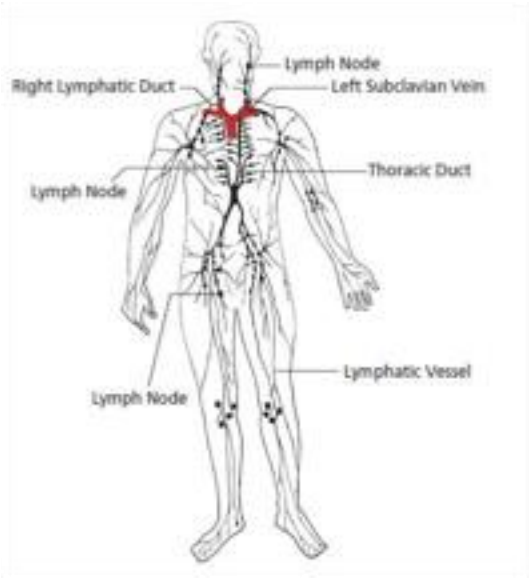
An antigen was presented by an antigen presenting cell and the peptide is presented by MHC molecule. A T cell receptor compatible with that antigen identified the MHC molecule and bound the MHC. This is the first signal, but that first signal is not enough. You have to have a second signal by a costimulatory molecule. Which is B7 with the receptor CD28.



❖ Why do we need two signals?

For protection. To prevent binding to the self antigen and autoimmune diseases. It is like a safe it has a code and a key, for safety . So if someone has the code only or the key only they can't get in. That is the same principle as the immune system. The first signal is like the key to prevent wrong activation the cell has to prove it is an antigen presenting cell and that you are presenting an antigen. The second signal comes for conformation. This is called the **Two-Key System.**

❖ How can APCs and lymphocytes meet?



The cells meet the antigens in the lymphatics. When the antigen presenting cell phagocytoses an antigen they go to the lymph nodes and present the antigen to the cells until there is a match and then activates.

There are 30 types of B cells, one of these 30 B cells will see the antigen has a very low chance, so they meet in the lymphatics. The function of the lymph node is to have the APC go to the lymph node and wait until the B cell recognizes the antigen. So the lymph nodes is where they meet.

Quick comparison between innate and adaptive immune system. Innate system helps identifies general types of the organisms, and buys time for the adaptive immune system to make antibodies, produce T cells and fight off the organism.

❖ Innate vs. Adaptive systems:

• Innate defends non-specifically and buys time for adaptive immune system to kick in if needed.
• Innate immune system decides which cells should respond, where, and when!
• The innate immune system rules!