INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	1
DONE BY	Hebah Shahwan
CORRECTION	Ahmed Quzli
DOCTOR	issa abu-dayyeh

Why is immunology difficult?

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.

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.

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.

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 are everywhere; on the chairs you are sitting on, your pencil cases, the walls, everywhere! BUT not all of them are pathogens, most of them – especially normal flora of the body- are commensals that we need for vitamins synthesis and protection from other pathogens.

Even though, how do you sit here for an hour without getting sick?

First line of defense = **Physical barriers**

The physical barriers help to protect our body from disease, and they include:

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 $2m^2$.

The mucosa: It is something very important that we 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 aren't sufficient, like having high dose of the pathogens or being breached. Such as if a pin pricked your toe. When the barriers are breached how will the body protect you? You will find neutrophils and macrophages, for example, which are part of the Innate Immune System**.**

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

Erythema and **edema** which are redness and 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 products of the immune system working. The barrier was breached, the bacteria entered, and the immune system is activated.

The immune system is composed of:

*The Innate Immune System

*The Adaptive Immune System

The Innate Immune System

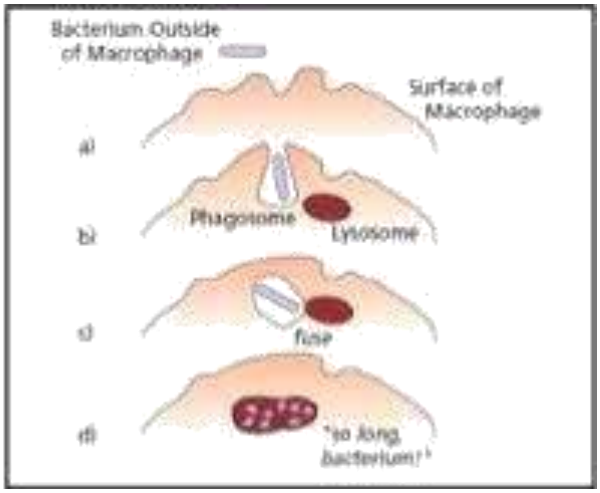
Works in the first 12 hours after the exposure to the pathogen.

Vertebrates 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.

first comes the physical barriers then the phagocytes (neutrophils, **then** macrophages), dentric cells (professional antigen presenting cells), complement system, NKC, and the innate lymphocytic cells.

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 (the big eater). 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 (like toll-like receptors). Once it finds a bacterium, it invaginates it and surrounds it by the plasma membrane into a phagosome.

***Phagosome:** is a plasma membrane that is invaginating to the inside, making a vesicle into the cytoplasm.

***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 hydrolyzing 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 **reactive nitrogen species**. The fusion of the phagosome with the lysosome

(called the phagolysosome) 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. If you look at the image you have the hemocystoblast which is the stem cell:

When the stem cell divides it gives us two cells:

*Another stem cell, so it can maintain the number of stem cells.

*A cell from one of the following cell lineages:

Proerthyroblast: which eventually gives us erythrocytes

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

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

Monoblast: gives a monocyte which gives macrophage/dendritic cell.

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. A lot of times we find resolution of the infection via the innate system alone. 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 immune attacks and drugs. This is why we have the Adaptive Immune System.

The Adaptive Immune System

(most probably developed by a virally carried gene, a transposone.)

starts after the innate
*
*it is composed of B cells (producing antibodies) and T-cells (producing cytokines, mature in the thymus).

*In birds, B cells mature in the bursa of fabricius, a lymphoid organ (this is where the name comes from; B = **B**ursa).

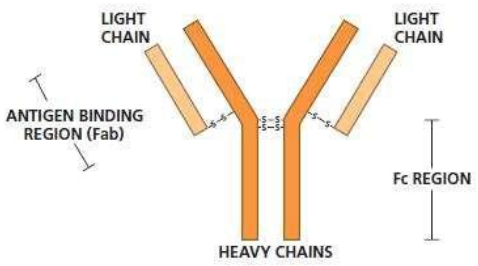
Why do we call it adaptive? The innate immune system finds a pathogen and it is programmed via certain receptors to attack these pathogens. The adaptive immune system on the other hand has specialized cell that attack a specific organism or pathogen and divide based on that recognition.

Edward Jenner 1796 Experiment:

Edward Jenner, who was a British scientist, tried to vaccinate against **smallpox**. Jenner noticed that the milk maidens that milked the cows who got infected with cowpox never got smallpox. Cowpox was a much less severe disease than smallpox. He wondered if there was a similarity between the smallpox and the cowpox that would prevent people from being infected with smallpox. He took liquid from the pustule of the infected person and then inoculated a child with cowpox. A couple days later the child developed cowpox. A month and a half later Jenner inoculated the child with the deadly smallpox and found that the child didn't develop smallpox.

What protected the child? It was the antibodies from the adaptive immunity that protected him from the small pox. What causes immunity to smallpox? Antibodies to cowpox which were also effective in binding smallpox.

1- B cells (produce Antibodies):



The antibody looks like a fork. It is composed of four polypeptides. It has two long heavy chains and smaller two 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.

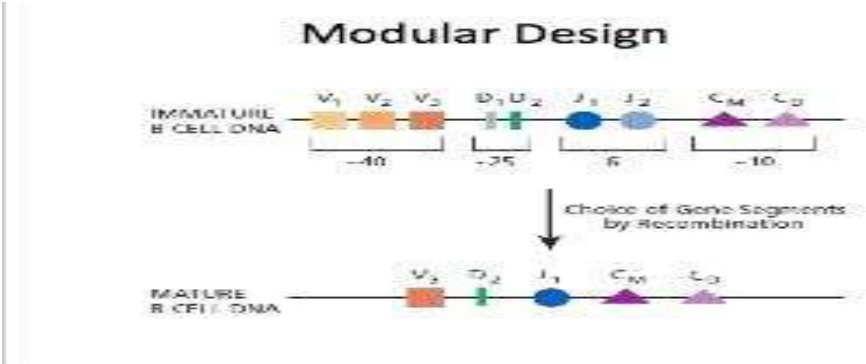
What is the benefit of the disulfide bond?

Fc: The bottom portion of the heavy chains (which looks like a stick) is called the Fc portion; the **c** stands for **c**rystalizable.

Fab: The **a**ntigen **b**inding 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 around 100 million different 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 heavy 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.

We have around 20 thousand genes in our bodies. So it is impossible to have all the genes in our body dedicated to making antibodies alone. So 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 widely different.

Immature B cell DNA contained multiple copies of VDJC genes, that encode heavy chains and light chains.

The **constant region (c)** contained 10 genes (10 copies)

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

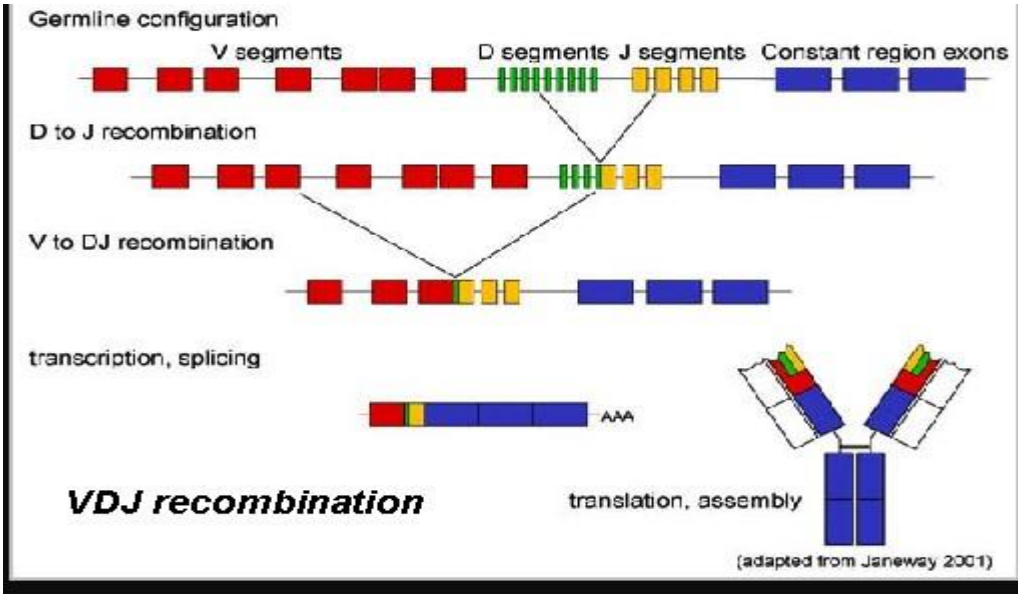
V: 40 genes

D: 25 genes

J: 6 genes

Mature B cell DNA only contained one type of gene from each of the V, D and J, and so on.

This process is RANDOM, choosing of any copy of the Vs, to join any copy of the Js, to join any copy of the Ds.



Firstly, recombination of the D and J segments occurs (random choosing of

one type of D with one J), and the pieces are ligated together. Then this DJ segment is ligated to a chosen V to yield the final VDJ segment. This DNA is transcribed to mRNA that is spliced and then translated to immunoglobulin. The blue part in the image represents the constant portion, and the red, green and yellow represent the variable region in the figure.

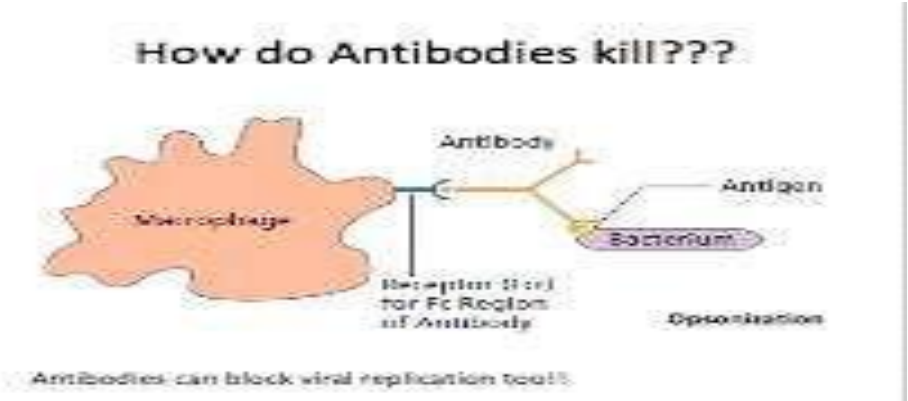
This model shows you don't need 20,000 genes. You need random recombination that happens one time with the heavy chain and one time with the light chain and you end up with millions of recombinations to make the antibodies.

The second problem is if we have one hundred million antigens we need to identify and there are 3 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:

The B cells that identify the attacking antigen and specifically produced antibodies that can bind it are selected and allowed to expand (proliferate fast). The 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?



Antibodies prevent the binding of the virus to the cell membrane

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

The antibody binds the bacteria. The macrophage that has an 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.

2 .<u>T cells (need MHC to recognize the infected cells)</u>

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

T Helper Cells: secrete cytokines, which is the language that the immune cells use to communicate.

Cytotoxic T cells: identify the infected or cancerous cells and attack it. The infected or cancerous cells are identified by the cytotoxic T cell using the T cell receptor (TCR) that recognizes the MHC presenting the peptide

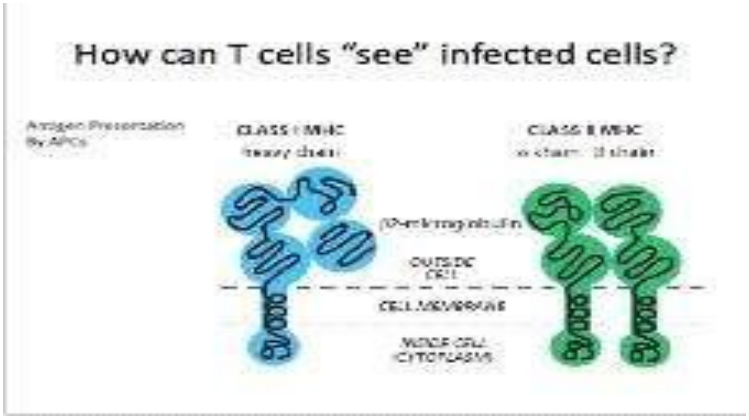
Regulatory t cells

**There are two kinds of MHCs:

MHC class I: made of a long chain and small chain called beta2 chain micro-globulin (we can use the beta2 chain micro-globulin levels as a test for myeloma (plasma cell tumor) due to plasma cells high proliferation in the bone marrow).

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

All cells have MHC I but MHC II is only found in the immune cells.



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 larger fragment of antigen (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 co-stimulatory 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 or the key on same principle as the only code the has 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 B cells for each possible antigen, if this antigen attacked the body, there is a very low chance that one of these 30 B cells, so they meet in the lymphatics to increase this chance. 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 identify 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 System

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 current theory for the evolution of the immune system is due to the entry of some genes from viruses that are called the transposable elements "jumping genes" (they were able to present receptors B cells can detect). Link to the full article:

https://drive.google.com/file/d/0BxYhLxWFav9fMHVTLXZ0a2hrQUpodzdiNTBjU0c2aVFwWFRv/view

Features of Innate and Adaptive Immunity

Characteristics	Innate	Adaptive
Specificity	For molecules shared by groups of related microbes and molecules produced by damaged host cells	For microbial and nonmicrobial antigens
Diversity	Limited; germline encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement, others	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells, innate lymphoid cells	Lymphocytes

The End