Human Immun System

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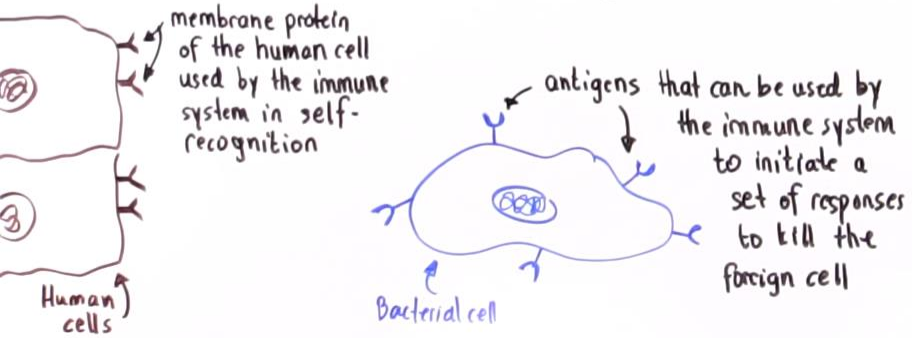
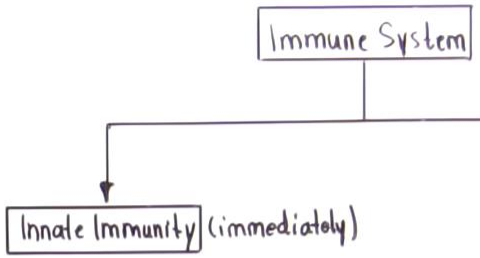
Human Immune System

- Unlike most other systems, the immune system is not localized to a single location. Instead it is spread out through the entire body. The immune system utilizes a series of internal defense mechanisms that help protect cells of the body from pathogens. A pathogen is any agent, living or non-living, that can cause harm to the cells of the body.
- These pathogens can only cause harm if they enter our body. They can enter the body through the air we breathe, the food we eat, through the wounds and cuts in our skin and so forth.
- In order for the immune system to be effective, it must be able to distinguish between its own cells of the body and foreign agents that can bring harm. Such recognition is possible because the cells of the body contain unique macromolecules on the membrane. The immune system can use these unique biomolecules to recognize its own cells
- Pathogens such as bacterial cells have their own membrane macromolecules. These foreign macromolecules stimulate the immune system to initiate a response that can destroy the pathogen. Any substance, such as the macromolecule, that can initiate an immune response is called an antigen.



- The human immune system and its defense mechanisms can be divided into two types - non-specific (innate) immunity and specific (acquired) immunity.



① Physical Barrier
- Our skin creates a physical barrier that prevents pathogens from entering

② Mucous Membrane
- Our air passageways contain mucous that traps pathogens that enter along with the air we breathe in.

③ Fluid Secretions
- Stomach secretes HCl that kills off pathogens entering with food. The skin, mouth and eyes secrete an enzyme that kills of bacteria.

④ Phagocytes and Neutrophils
- Specialized cells that can engulf and destroy pathogens.

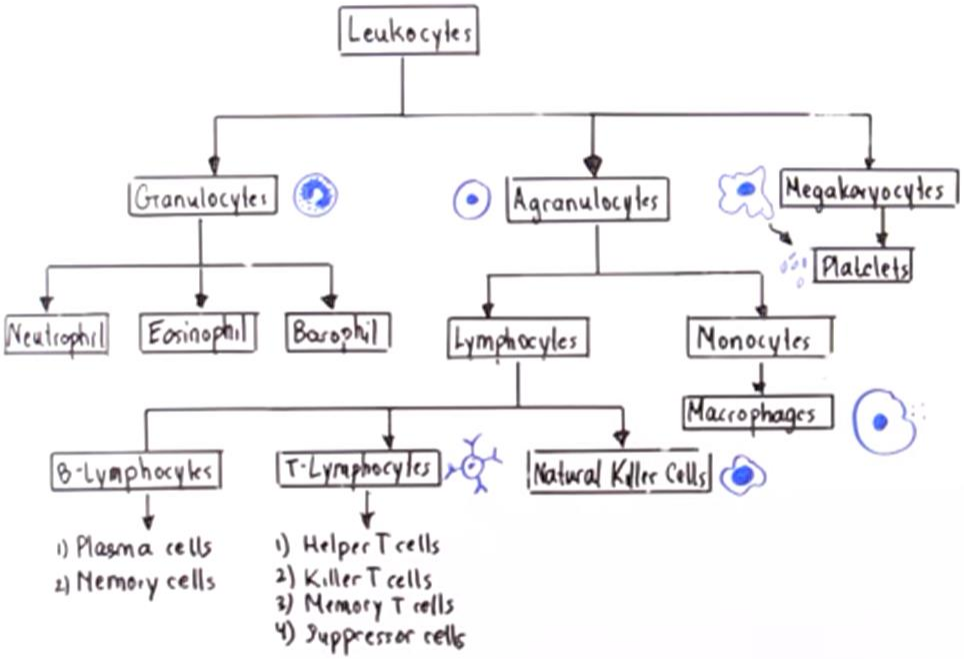
⑤ Inflammation and Fever
- Special chemicals can lead to inflammation and fever, which can kill of pathogens.

① Cell-Mediated Immunity
- This immune response involves special defense cells called T-lymphocytes. There are several types of T-cells, including killer T-cells, suppressor T-cells and helper T-cells.
- These cells have a special protein on their membrane that can recognize foreign antigens and kill off the pathogens.

② Antibody Mediated Immunity
- This involves B-lymphocytes (plasma and memory B cells). These cells are responsible for producing special defense molecules called antibodies.
- Antibodies can circulate in the blood and will bind to specific antigens and initiate a defense response.

Cells of Human Immune System

- Leukocytes or white blood cells are specialised cells that can defend our body from pathogens. All leukocytes originate from cells in the bone marrow called hematopoietic stem cells. Leukocytes can in turn differentiate into a variety of different cell types that each have their own unique function.



- Leukocytes are amoeba-like cells that are capable of moving independently. They can move against the flow of blood and can slip through the walls of capillaries and enter our tissue in a process called diapedesis.

1) Granulocytes

- These cells are characterised by the presence of granules in their cytoplasm and by their lobe-shaped nuclei. Neutrophils are phagocytic cells that can seek out and engulf bacterials cells that infect our body. Eosinophils are involved in allergic reactions and parasitic infections. Basophils contain special chemicals (i.e. histamine) that are involved in inflammation and also contain an anti-clotting agent called heparin.

2) Megakaryocytes

- When pieces of megakaryocytes break off, they form structures called platelets (thrombocytes). These platelets lack a nucleus. When a cut in a blood vessel develops, platelets will bind to the cut and aggregate within minutes to form a temporary patch.

3) Agranulocytes

- These cells lack granules and have spherical or kidney-shaped nuclei.
- Monocytes enter tissue and develop into macrophages, which are large scavenger cells that engulf pathogens via phagocytosis.
- Lymphocytes are cells involved in our acquired immune response. They differentiate into three types. Natural killer cells seek out and destroy infected cells and cancer cells. B-lymphocytes are cells that are part of the antibody mediated response. They further differentiate into plasma cells that produce the antibodies and memory cells that protect the body from re-infection. T-lymphocytes are part of cell-mediated response. These differentiate into killer T cells, which recognise foreign antigens and destroy pathogens, Helper T cells, which release chemicals and assists maturation of other cells, memory T cells, which also protect from reinfection and suppressor cells, which regulate and suppress the immune system.

Innate Immune System

- The innate immune system consists of non-specific defense mechanisms that act immediately following infection. This is the primary line of defense against pathogens. Non-specific implies that it does not depend on presence of specific antigens; that is, the innate immune system attacks all pathogens with equal likelihood.

Physical Barriers

- There are several anatomical structures that act as physical barriers to pathogens.

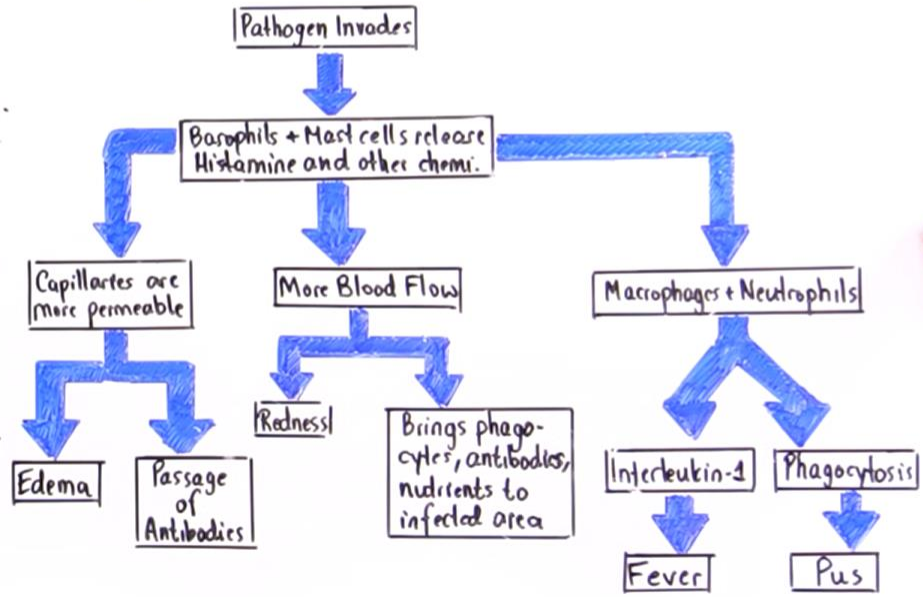
1) Skin: Our skin consists of several layers that create a first line of defense against invading pathogens. The skin also contains glands that secrete fatty acids and this creates an environment in which most bacteria cannot grow.
2) Mucous and Cilia: Goblet cells found along our air passageways produce a sticky and slimely layer of mucous that traps pathogens. Cilia can then be used to move the pathogens to the outside or to our stomach.
3) Acidity of Stomach: Parietal cells release HCl, which creates a highly acidic environment that kills off most pathogens that enter the stomach via food or via mucous.
4) Tears and Saliva: Lysozyme found in tears and saliva helps breakdown cell walls of bacterial cells.

- These barriers don't only prevent the pathogens from entering but they also create an inhospitable environment in which pathogens cannot grow.

Inflammation

- Once the anatomical physical barriers are breached and the pathogen enters our tissue, the innate immunity then initiates the process of inflammation. In this process, blood flow is increased to the infected area. This blood brings several important white blood cells - neutrophils, eosinophils, basophiles and macrophages.

1) Neutrophils - these cell are recruited to the infected area and engulf bacterial cells and other harmful agents and kill them intracellularly. They can eat up to 20 bacteria before dying.
2) Basophils: Release histamine, which causes the dilation of blood vessels leading to the infected area (causing redness). The capillaries in the infected area also become more leaky, which causes edema (swelling).
3) Eosinophils: These granulocytes are specialized to fight certain parasites.
4) Macrophages: The increased blood flow also carries large phagocytes called macrophages that can engulf about 100 bacteria before dying.
5) Mast Cells: These cells are situated within the tissue and release histamine and other chemicals called cytokines that promote inflammation.
6) Natural killer Cells: Although these are not really involved in the inflammation response directly, they do kill of infected cells and cancer cells non-specifically.

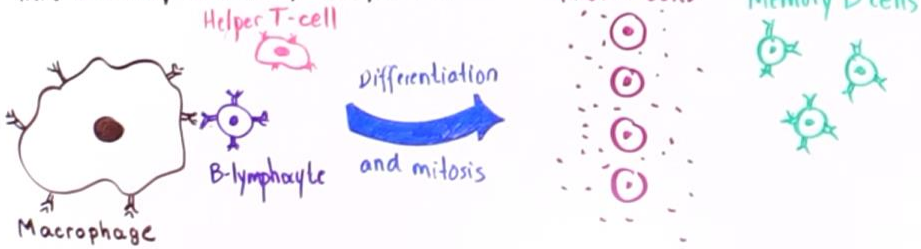


Adaptive Immune System

- When infection begins, the innate immune system kicks in immediately and uses non-specific mechanisms (i.e. inflammation) to destroy the invading pathogens and keep them from spreading. During this time, the adaptive immune system is mobilized and begins to gear up to fight the infection. Several days may be needed to activate the specific defense mechanisms of the adaptive immune system.
- The adaptive immune system can be subdivided into antibody-mediated (humoral) immunity and cell-mediated immunity.

Antibody-Mediated Immunity (Humoral)

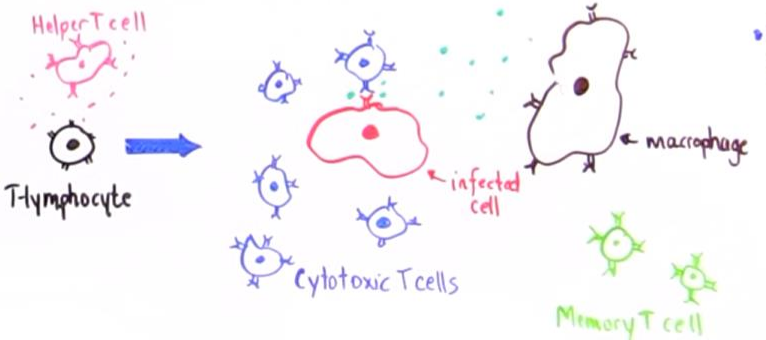
- Humoral immunity involves leukocytes called B-lymphocytes. B-lymphocytes are produced and mature in the bone marrow and are usually found in the lymph nodes.
- During the innate immune response, macrophages engulf and destroy pathogens. However they keep the pathogenic antigens and display them on their membrane. The B-lymphocytes contain B-cell receptors on their membrane that can bind to these macrophage-bound antigens.
- Once the B-lymphocyte binds to the specific antigen, it calls upon the helper T-cell that helps it differentiate further. The B-lymphocyte then undergoes many cycles of mitosis to produce plasma cells and memory cells.
- Plasma cells are "factories" that produce antibodies that are specific to the antigen that the B-lymphocyte was bound to. Memory cells however keep a copy of that antibody in case of reinfection.



- Antibodies, also called immunoglobulins, bind only to specific antigens. Once bound, they call upon other leukocytes or they can aggregate to form large insoluble complexes via a process called agglutination.
- Humoral immunity is effective against bacterial cells, parasites, fungi, viruses, and toxins.

Cell-Mediated Immunity

- This involves leukocytes called T-lymphocytes. They are formed in the bone marrow but mature in the thymus. In the thymus, T-lymphocytes are tested to ensure that they do not attack the body's own cells.
- One type of T-lymphocyte is the helper T cell. Helper T cells release chemicals called interleukins and interferons. These chemicals help B-lymphocytes mature into plasma cells and memory B cells.
- T-lymphocytes contain membrane T-cell receptors. These cells can bind to antigen complexes and with the help of Helper T cells, differentiate into cytotoxic T cells (killer T cells). These cytotoxic T cells travel to the infected area and bind to specific antigens. Once bound, they release powerful proteins (perforins) that can drill holes and kill the pathogen.
- In addition, T-lymphocytes can also form its own memory T cells as well as suppressor cells that can regulate and tone down the immune response.



- Cell-mediated immunity is effective against infected cells.

Innate Immune System (non-specific)

① Mast Cell

- Located in certain tissues and along the mucous membranes, they can be stimulated by pathogenic antigens to release histamine, heparin and other chemicals into the blood.
- These in turn stimulate vasodilation of blood vessels, increase permeability of capillaries, decrease blood-clotting and call upon other white blood cells + reduce inflammation.

② Dendritic Cell

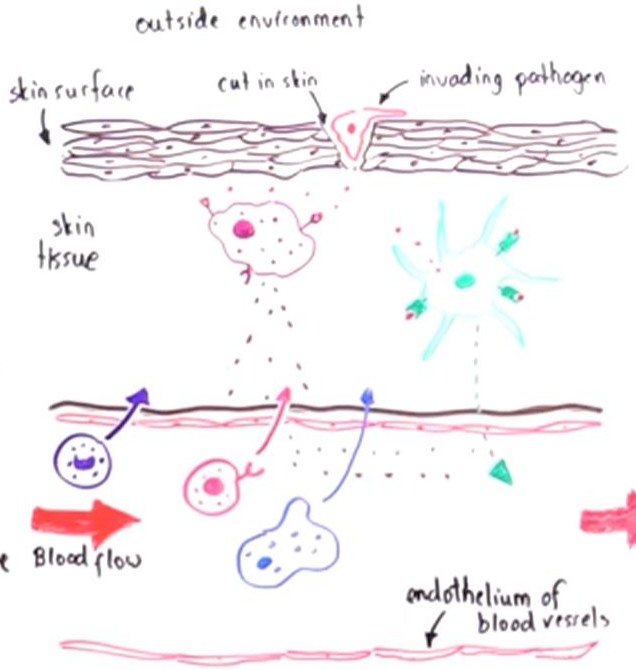
- Located in the epithelial tissue, these cells link the innate immune system to the adaptive immune system. They engulf antigens and present them on the membrane to B-cells and T-cells.

③ Neutrophils

- These are the first-responders to trauma. They are phagocytic cells that can engulf pathogens. They migrate from blood and into infected tissue.

④ Basophils

- These respond to infections due to parasites or allergic reactions. They move from blood to tissue and release histamine and heparin.



⑤ Eosinophils

- These have lots of vesicles that release chemicals that kill of parasites. Also involved in allergic reactions.

⑥ Natural Killer Cell

- Circulates in blood and moves into affected tissue. Bind to infected cells and cancer cells, releases chemicals and kills them off.

⑦ Macrophages

- These are large phagocytic cells that engulf pathogens, infected cells, cancer cells and any debris found in the tissue.
- Moves from blood and into infected tissue.

Adaptive Immune System (specific)

B-Lymphocytes

- By interacting with other blood cells, such as dendritic cell, they differentiate into plasma cells (produce antibodies) and memory cells (store antibodies).

T-Lymphocytes

- These cells differentiate in four types:

Helper T-cells

- Assist with B and T-cell differentiation and release chemicals that calls upon macrophages and othe cells.

Cytotoxic T-cells

- Bind to specific cells and release chemicals that lyse them (i.e. infected cells).

Suppressor T-cells

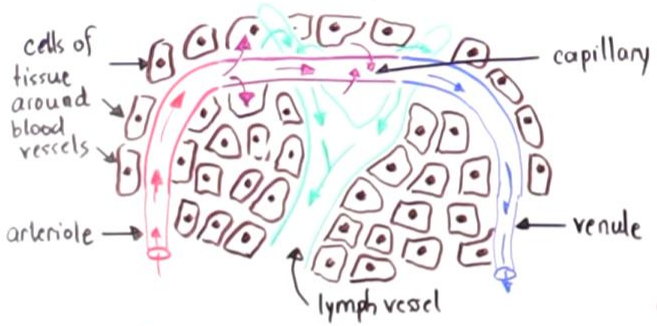
- Regulate other immune cells and use negative-feedback mechanisms to turn down our immune response.

Memory T-cells

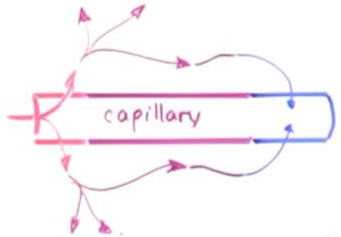
- Similar function to memory B cells; help with reinfection.

Lymphatic System

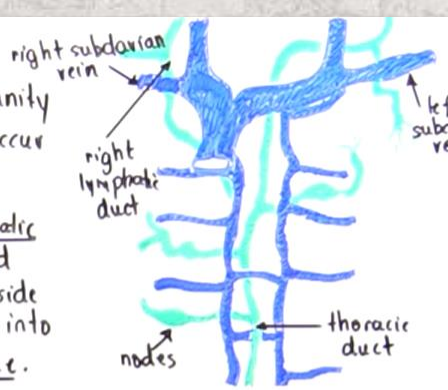
- The lymphatic system is network of vessels that plays a role in fluid immunity and fluid homeostasis. Without this system, fluid build-up would quickly occur in our tissues, leading to many serious complications.



- Recall that hydrostatic pressure forces blood out of the arteriole side of the capillary and into the interstitial tissue.
- When the blood plasma enters the tissue space, it brings nutrients and oxygen to the cells of the tissue.



- On the venule side of the capillary, osmotic pressure pulls the blood plasma back into the blood vessel. However, this pressure is not great enough and cannot pull all of it in. About 10% of the fluid remains in the surrounding interstitial space.
- What happens to this 10% fluid? If it remains in the tissue space, it will lead to a continual build-up. To prevent this from happening, our body uses lymph vessels to drain this fluid out of the interstitial space. The fluid then travels into larger lymph vessels called lymph veins. Eventually the lymph vessels reconnect with the blood vessels and the fluid is returned back into the blood through the thoracic duct and right lymphatic duct.



- The thoracic duct collects lymph from lower right part of the body, the GI system and the left side of the body and it connects to the left subclavian vein.
- The right lymphatic duct collects lymph from the right side of the head, the neck and the chest and empties it into the right subclavian vein.

along many parts of the lymphatic system are small masses of tissue called lymph nodes. Within these lymph nodes are cavities called sinuses. Lymph carrying leukocytes such as dendritic cells enters these cavities. Inside these cavites other leukocytes such as plasma cells produce antibodies and these antibodies leave the lymph sinuses from the other end. In addition, leukocytes such as macrophages found inside the nodes filter the lymph and engulf pathogens.

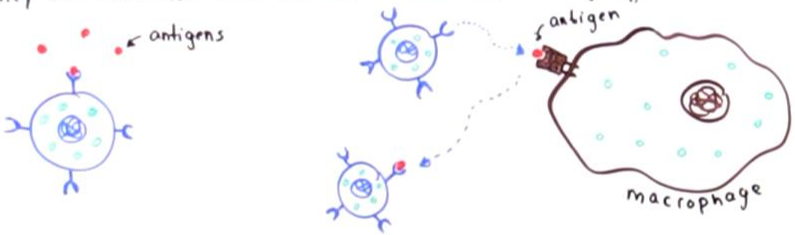
- The walls of lymph vessels consist of endothelial cells that overlap slightly. When there is a build up of fluid in the tissue space, that creates fluid pressure that pushes on the cells. This forces the fluid to move into the lymph vessels.
- Inside the lymph vessels is a system of one-way valves. These valves as well as the endothelial cells open one way, which keeps the lymph inside and keeps it moving in one direction
- The movement of skeletal muscle pushes against these lymph vessels and helps keep the lymph moving.

B-Lymphocytes

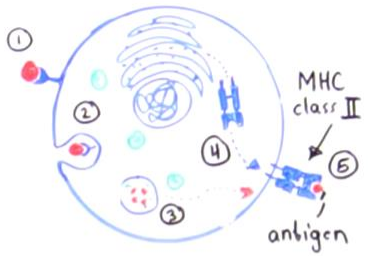
- B-lymphocytes or simply B-cells are the white blood cells of our humoral immunity that are responsible for synthesizing and storing antibodies.

Mechanism of Action

- Each B-lymphocyte is made specifically to bind to a particular pathogenic antigen. That means that B-lympocytes contain receptors on their membrane called B-cell receptors that can attach to these antigens. These antigens:
  (1) are either floating freely in our tissue or
  (2) they are attached onto the membranes of macrophages or dendritic cell.

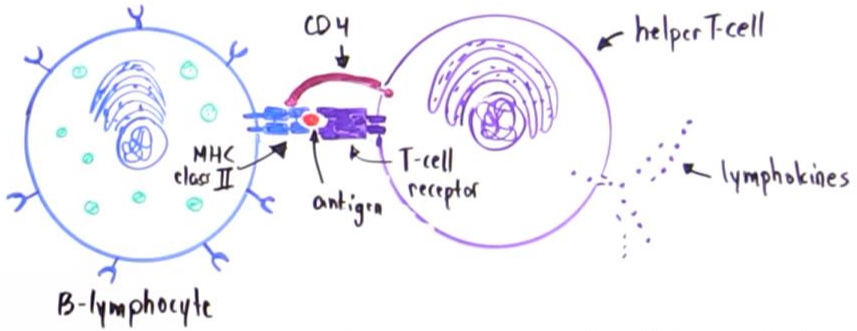


- The B-lymphocyte can either bind to a free-floating antigen or grab the antigen off of another leukocyte. What happens once the antigen binds to the B-cell receptor?
- The cell then undergoes cell-mediated endocytosis, which is the process by which the B-cell engulfs the antigen into the cell. It then uses its digestive enzymes to break the antigen down into smaller pieces and at the same time, the B-cell begins to synthesize a membrane protein complex called major histocompatibility complex class II (MHC class II). The B-cell then inserts the MHC class II protein along with the antigen onto the cell's membrane.



① Antigen binds to specific B-cell receptor on the B-lymphocyte.
② Receptor-mediated endocytosis takes in the pathogenic antigen.
③ Digestive enzymes break down antigens.
④ ER / golgi synthesizes and modifies the MHC class II protein.
⑤ Antigen binds onto MHC class II protein.

- Next, a helper T cell with a complementary T-cell receptor (CD4+ glycoprotein) locates and binds to the antigen-MHC class II protein on the B-cell.



- This interaction causes the helper T cell to release lymphokines which:
  1) stimulate the B-cells to divide via mitosis and produce many clone copies with identical B-cell receptors specific for that antigen.
  2) stimulate differentiation of B-cells into plasma cells, which begin producing plasma-soluble and mobile versions of the B-cell receptor (i.e. antibodies specific for that antigen).
  3) stimulate differentiation into memory B-cells.

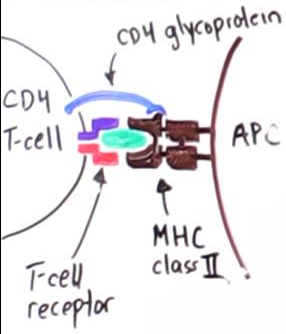
T-Lymphocytes

- T-lymphocytes or simply T-cells are the white blood cells that make up our cell-mediated immunity. Like B-cells, T-cells also have their own membrane-bound receptors called T-cell receptors.
- There are two types of T-cells that can be distinguished by their T-cell receptor. Alpha-Beta ($\alpha\beta$) T-cells contain a T-cell receptor that has an alpha and a beta subunit while gamma-delta (γ-δ) T-cells have receptors consisting of a gamma and delta subunit.

$\alpha\beta$ T-Lymphocytes

- Recall that the antigen-presenting cells (APCs) of our immune system such as B-lymphocytes, macrophages and dendritic cells engulf antigens and attach them onto protein complexes called major histocompatibility complexes (MHC). Once the pathogenic antigen is bound to the MHC, its the job of the T-cell to recognize the particular antigen-MHC complex and bind to it.
- Along with the $\alpha\beta$ protein dimer, $\alpha\beta$ T-cells can have one of two types of glycoproteins found on the membrane. These include the CD4 and CD8 glycoproteins.

A) CD4 T-cells



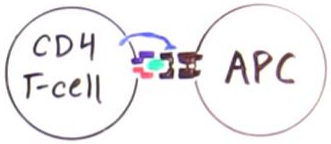
- T-cells that have the CD4 glycoprotein only bind to the MHC class II protein membrane. Once they bind, the T-cells can either stimulate the

(1) humoral-immunity

Helper T-cells are $CD4^+$ cells that bind to B-lymphocytes and stimulate them to differentiate into plasma cells and memory B cells.

(2) cell-mediated immunity

CD4 T-cells can bind to APCs such as macrophages and dendritic cells, release lymphokines and call upon other white blood cells to the infected area.

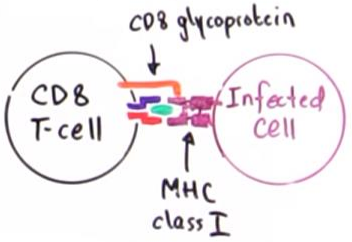


→ humoral immunity

→ cell-mediated immunity

B) CD8 T-cells

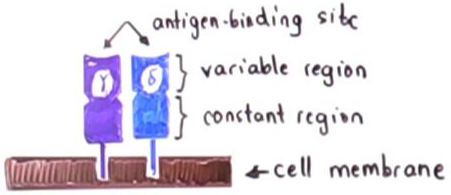
- These T-cells contain the CD8 glycoprotein next to their $\alpha\beta$ protein receptor. These cells can only bind to the MHC class I complex. Recall that this is the complex used to differentiate between healthy cells and infected cells of our body.
- Cytotoxic T cells are examples of $CD8^+$ T-cells. Generally speaking, the role of these T-cells is to find the cells of our body which have been infected.
- Suppose a virus, such as influenza, infects our cell. That cell will take an antigen from that virus and attach it to its MHC class I membrane protein. When a cytotoxic T cell locates and attaches to the infected cell, it will release powerful proteins that will destroy the infected cell



→ Release chemicals that kill the infected cell

Gamma-Delta T-cells

- T-lymphocytes can be categorized based on the type receptor that is found on their membrane. Alpha-Beta T-cells contain receptors made of an alpha and a beta subunit that can bind to MHC class I and MHC class II regions of antigen-presenting cells (APC).
- Gamma-Delta (γ-δ) T-cells are the second type of T-lymphocyte. They have a membrane receptor that is made up of one gamma and one delta unit.



- The variable section of the receptor contains an antigen-binding site that can bind to foreign antigens.
- What types of antigens can these gamma-delta receptors bind to?

(1) Fully intact antigens that have not been degraded by other white blood cells into smaller ones. In this way, they resemble free-floating antibodies

(2) Any antigen that is not bound to the MHC class I or MHC class II molecules found on other white blood cells.

(3) Antigens that are not bound to the membrane of antigen-presenting cells such as macrophages, dendritic cells and B-lymphocytes.

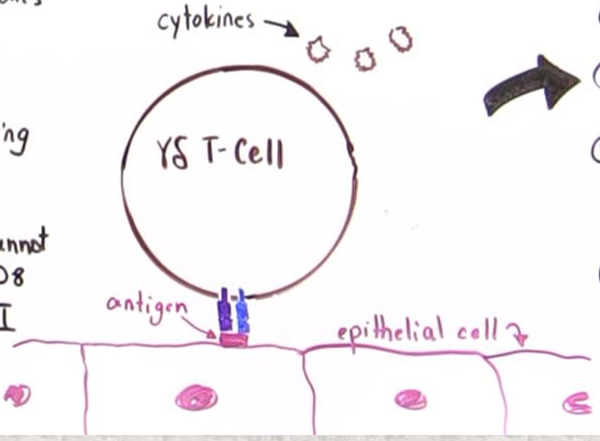
- Therefore gamma-delta T-cells bind to antigens that alpha-beta T-cells cannot bind to. In fact, most gamma-delta T-cells do not have the CD4 or CD8 glycoproteins, which means that they cannot bind to MHC class I or class II molecules.

Location

- Just like alpha-beta T-cells, gamma-delta T-cells are produced in the bone marrow and differentiate in the thymus. However, once they are formed and tested in the thymus, they move into the tissue of our body that interfaces with the outside environment.
- Therefore, gamma-delta T-cells are usually found next to the epithelial tissue of our skin, lungs, intestine, etc.

Function (?)

- Since these T-cells do not bind onto the MHC molecules of antigen-presenting cells, they do not depend on APCs to function and carry out their immune response.
- Although their exact function and mechanism of action is still not very well known, they are believed to be part of the first line of defense and seem to react faster than αβ T-cells. In addition, the antigens to which these cells respond to are not only found on pathogens themselves but also on infected cells.



① Stimulates repair of epithelium.

② Immunosurveillance

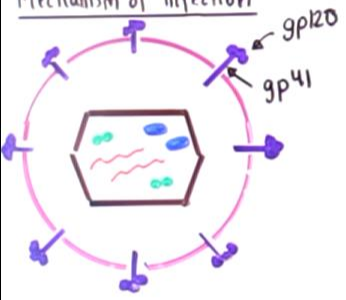
③ Seem to indirectly affect the cytolysis of local antigen-presenting cells

④ Regulate the influx of other white blood cells to infected area.

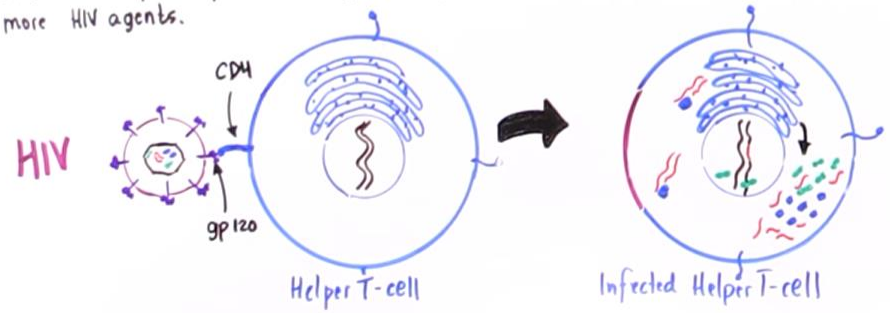
AIDS

- One particularly pathogenic agent that readily affects our immune system is the human immunodeficiency virus (HIV). Transmitted through bodily fluids such as semen or blood, it invades certain lymphocytes and turns them into virus-producing cells that lose their functionality as immune cells. This leads to a medical condition we call d acquired immune deficiency syndrome (AIDS).

Mechanism of Infection



- HIV contains a glycoprotein (gp120) that can binc onto the CD4 protein of immune cells. Recall that helper T cells are CD4+ cells, which means HIV attacks these white blood cells.
- Once bound, a second glycoprotein (gp41) stimulates cell-mediated endocytosis. This fuses the cell membrane with the viral membrane and releases viral contents into the cytoplasm.
- HIV is a retrovirus, which means it has an enzyme called reverse transcriptase that can form DNA from the viral RNA. Another enzyme called integrase then integrates the viral DNA with the cell's own DNA. This turns the immune cell into a viral factory that begins to produce viral proteins needed to form more HIV agents.



Helper T-cells

- We see that HIV directly affects the functionality of Helper-T cells, a type of T-lymphocyte that is part of our adaptive (acquired) immunity. So whats the big deal these helper T-cells?
- Helper T-cells are extremely important and oversee a multitude of different processes that allow our immune system to function effectively and efficiently. Although they do not attack pathogens directly, they:
  (1) bind to T-lymphocytes and stimulate them to differentiate into specialized T-cells such as cytotoxic T-cells.
  (2) bind to B-lymphocytes and induce differentiation into plasma cells and memory B cells. These produce and store antibodies.
  (3) release chemicals (cytokines) that stimulate macrophages, neutrophils, basophils and other cells to initiate a defense response.
- therefore, by destroying our population of functional helper T-cells, HIV ultimately weakens both the innate immune system and the adapted immune system. As a result, most individuals infected with HIV die from other infections (i.e. common cold, pneumonia, etc) because of our bodys inability to mount a proper immune response.

Stages

- A person infected by HIV experiences three stages:

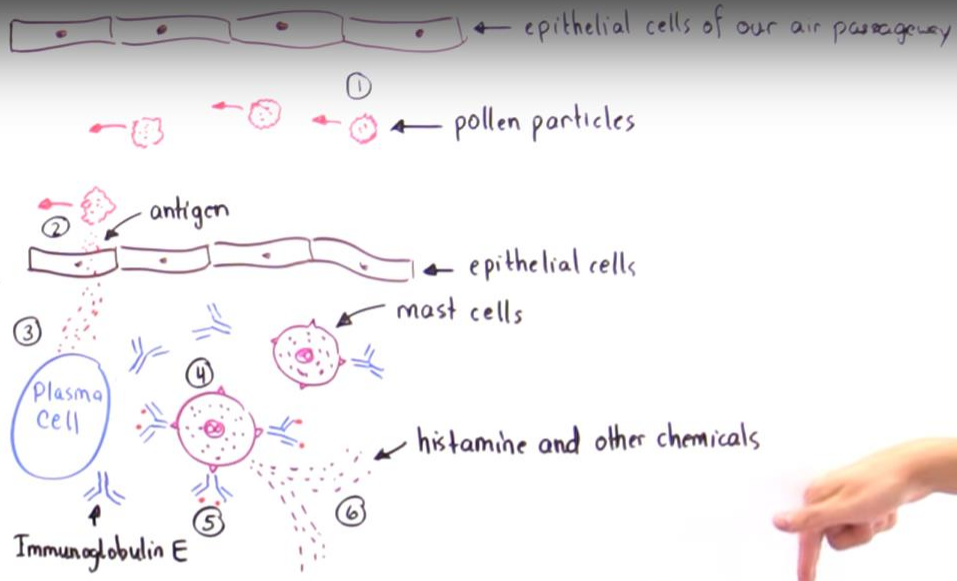
1) Early Stage: (~2 weeks)
   - The individual experiences flu-like symptoms (fever, aches, etc) and has a high level of virions in the body.
2) Middle Stage: (Months - Years)
   - No visible symptoms, low levels of virus, presence of antibodies and a slow but continual decline in # of helper T-cells.
3) Late Stage: (AIDS)
   - Rapid decrease in helperT-cells and increase in rate of infection and cancer.

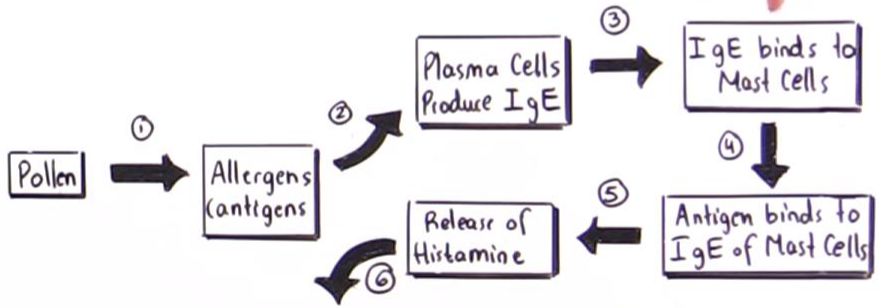
Allergic Reactions

- The overall goal of our immune system is to protect our body from pathogens. However, the immune system is not perfect and sometimes incorrectly labels a non-harmful foreign substance as pathogenic. This causes a defensive immune response that is called an allergic reaction and the causing agent is called an allergen.
- Allergens differ from one individual to another. They can include substances found in the air such as pollen, certain foods such as peanuts or drugs such as penicillin.

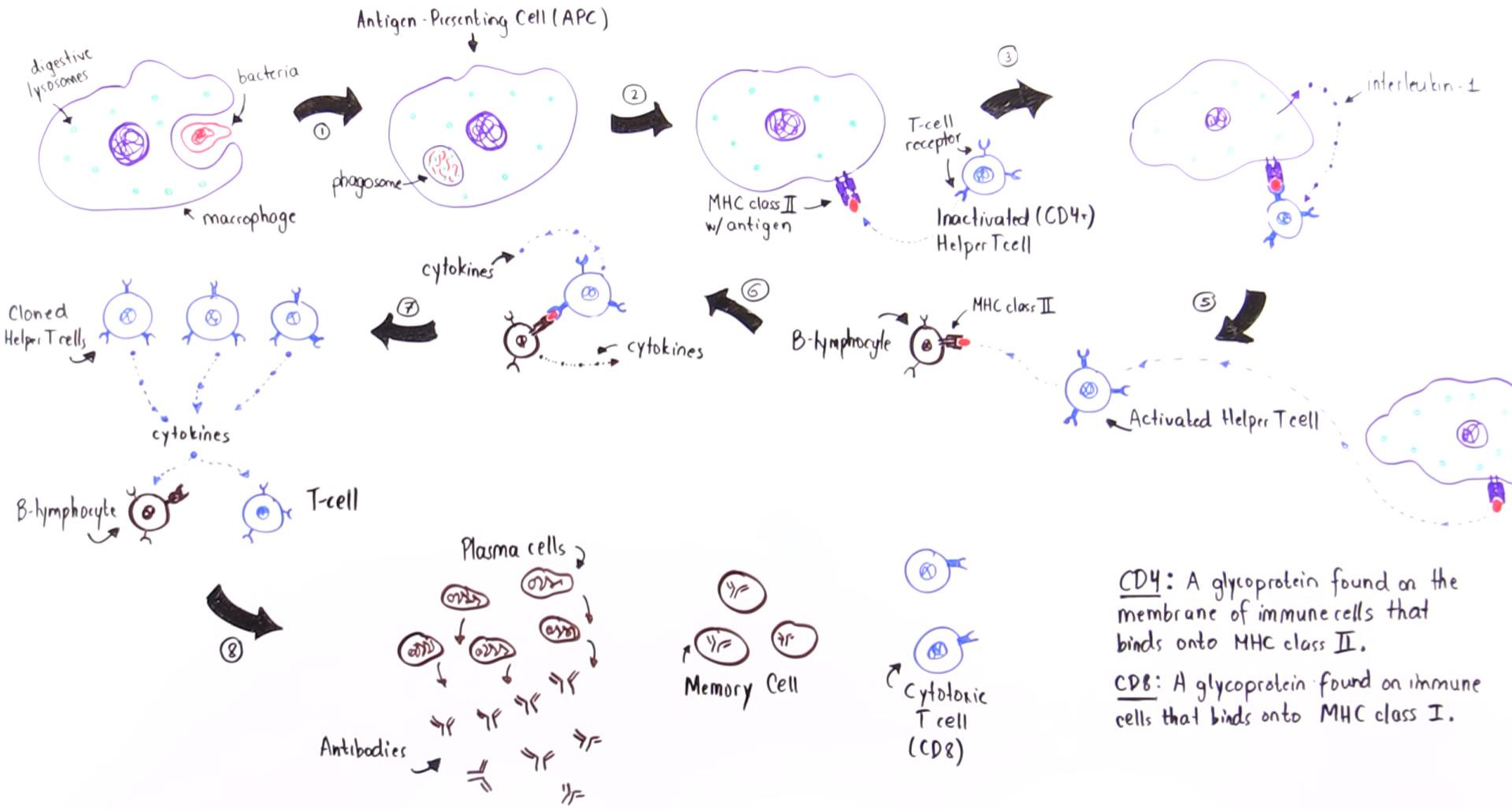
Mechanism of Allergic Reaction

- One very common allergic reaction is hay fever, which is the way our immune system responds to grass pollen. When the allergic individual inhales pollen particles, these microscopic particles are recognized as antigens by our immune cells. Plasma cells of our adaptive immunity begin to release antibodies called immunoglobulin E (IgE). These antibodies bind onto white blood cells of nearby tissue called mast cells. These mast cells contain granules (tiny vesicles) with a variety of immune chemicals such as histamine. When antibodies bind onto the mast cell, the allergen can bind onto the variable section of the antibodies.
- These chemicals in turn cause:
  (1) vasodilation of blood vessels leading to the "infected" area.
  (2) increase in permeability in nearby capillaries
- This can cause edema (swelling), runny nose, redness and respiratory problems as a result of air passageway constriction.





- This dilates the blood vessels, which brings more blood to that area (causing redness). It also increases the leakiness of the capillaries, which can lead to edema (swelling) and causes a "runny" nose.

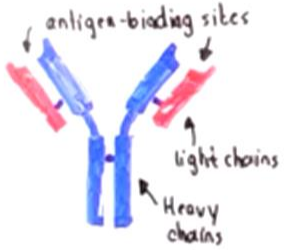

Antigen-Presenting Cell (APC)
digestive lysosomes
bacteria
macrophage
phagosome
MHC class II w/ antigen
T-cell receptor
Inactivated (CD4+) Helper T cell
interleukin-1
Activated Helper T cell
B-lymphocyte
MHC class II
cytokines
Cloned Helper T cells
cytokines
B-lymphocyte
T-cell
Plasma cells
Antibodies
Memory Cell
Cytotoxic T cell (CD8)
CD4: A glycoprotein found on the membrane of immune cells that binds onto MHC class II.
CD8: A glycoprotein found on immune cells that binds onto MHC class I.

Antibodies and Antigens

- Antibodies are highly specific proteins that are produced by plasma cells of our immune system in response to pathogenic antigens. The primary function of an antibody is to bind to its specific antigen and "label" it for destruction by our immune system.

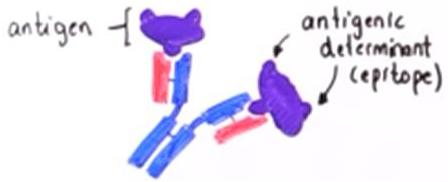
Structure

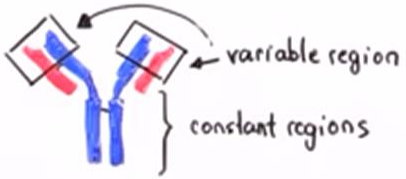
- Antibodies, also called immunoglobulins (Ig), consist of four polypeptide subunits



- These four polypeptides connect via covalent bonds called disulfide bridges and form a Y-shaped structure. This Y-shaped structure contains a constant region and a variable region. As the name implies, the constant region does not really change from one antibody to another but the variable region does.

- The variable region is built to contain a specific sequence of amino acids that can bind to the specific antigen that it was built for. Therefore, the variable segment contains the antigen-binding site. The region of the antigen that binds to the antigen-binding site is called antigenic determinant or epitope.





- The constant regions are usually used to bind onto other structures, such as the membranes of immune cells. The constant region determines the type of antibody.

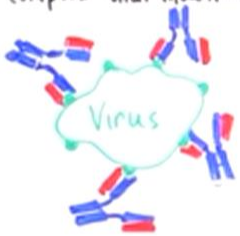
Function

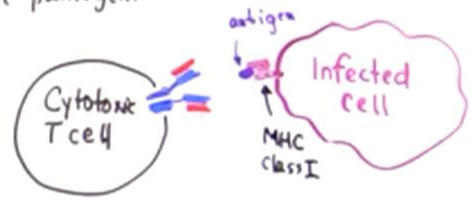
- Antibodies can either be found attached to cells or they can be found circulating in our blood. Either way, when an antibody locates and binds to its specific antigen, the antibody-antigen complex elicits a response that will inhibit the pathogen. Several defense mechanisms exist.

① The antibody-antigen complex may inactivate the pathogen. For instance, a free-floating antibody that binds onto a virus may inactivate its ability to bind onto receptors of healthy cells.

② By binding onto the antigen, the antibody can label that pathogen or infected cell for destruction by white blood cells.

③ Several antibody-antigen complexes can aggregate to form an insoluble complex that inactivates the pathogen.





Types

- There are five classes of antibodies - IgD, IgA, IgM, IgG and IgE. They are grouped by their sequence of a.a.'s on their constant region.

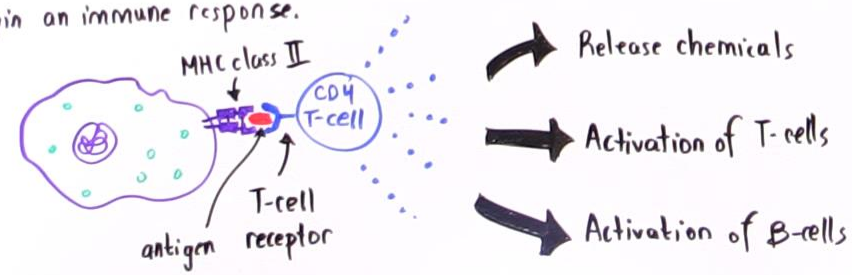
1) IgG: The antibodies found in the blood that are involved in immunity against pathogens. Make up the majority of antibodies in our blood.
2) IgM: Found on B-lymphocytes and highly effective against viruses.
3) IgE: Involved in allergic reactions. Binds to mast cells/basophils and causes the release of histamine.
4) IgD: The antigen receptor found on B-lymphocytes (plays role in antibody pro.)
5) IgA: Primary antibody found in air passageways and digestive tract.

Antigen-Presenting Cell (APC)

- All pathogenic antigens that make their way into our body must be presented to T-lymphocytes of our cell-mediated immunity. T-lymphocytes however cannot bind to antigens directly. Instead the antigens must be presented to the T-lymphocytes by antigen-presenting cells such as marrophages, dendritic cells, and B-lymphocytes.

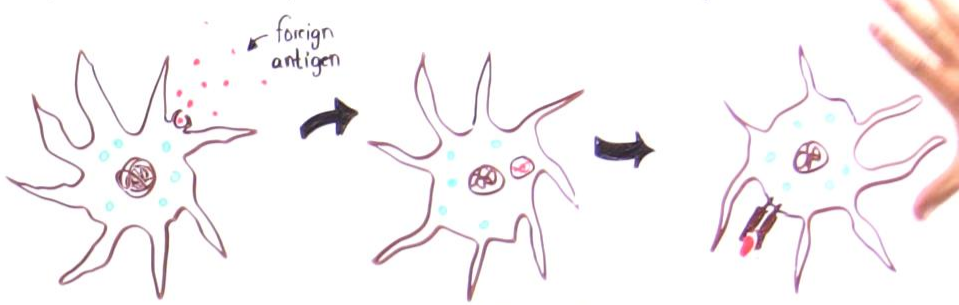
Marrophages

- When infection begins, the innate immune system calls upon marrophages. These cells engulf the pathogen, digest it inside vacuoles and present the pathogenic antigen on the MHC class II (major histocompatibility complex) found on the membrane.
- T-lymphocytes such as helper T cells that contain CD4 glycoproteins on their membrane can bind to these MHC class II-antigen complex and begin an immune response.



Dendritic Cells

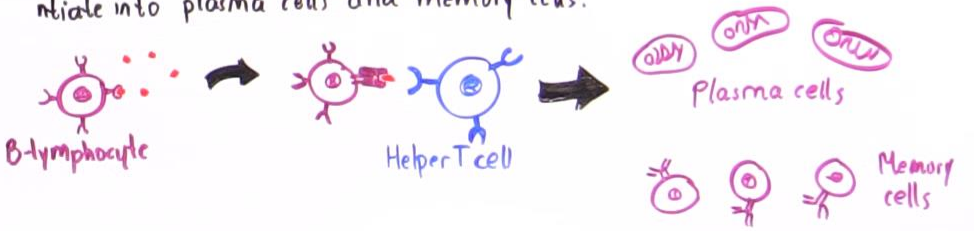
- These are immune cells found in the tissues of our skin, lungs and GI tract



- When they encouter antigens, they engulf them, break them down and display them on their MHC class II membrane protein. They then travel to the lymph nodes or spleen and interact with the T-lymphocyte that has the correct T-cell receptor (CD4). They then stimulate other defense mechanisms.

B-lymphocytes

- B-lymphocytes are part of our humoral immunity. When they approach foreign antigens floating around the tissue, they bind to them via special receptors and take them in via receptor-mediated endocytosis. They then break them down and display an antigen fragment on MHC class II molecule. When a helper T cell binds to the B-lymphocytes, it then induces it to multiply and differentiate into plasma cells and memory cells.



The Complement System

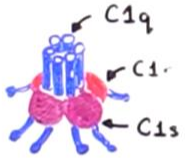
- The complement system consists of a series of mechanisms that ultimately protects our healthy cells from antigens and pathogenic infections.

Classical Pathway

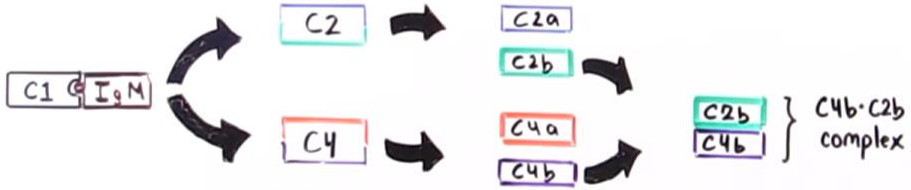
- The classical pathway is triggered by the formation of an antibody-antigen complex.
- There are over 30 inactivated proteins floating around the blood that can be activated as a result of antibody-antigen complex formation. These proteins can then create a cascade of events that ultimately destroys that antigen or pathogenic agent.

C1

- C1 is a protein complex consisting of:
  - 6 molecules of C1q.
  - 2 molecules of C1s.
  - 2 molecules of C1r.



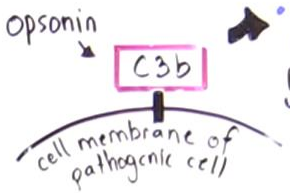
- The constant region of certain antibodies (IgM and IgG) can bind onto the C1q molecule of C1 complex. This in turn activates C1r and C1s molecules. The C1s is a serine protease and can activate the C2 and C4 complexes.



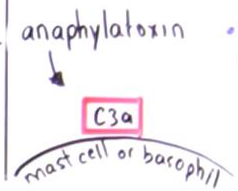
- The C4b·C2b complex, also called C3 convertase, now goes on to activate the C3 protein complex.

C3

- This is the most abundant protein of the complement system. The C4b·C2b complex acts as a serine protease and cleaves C3 into two units, thereby activating it.



- Binds covalently to membrane glycoproteins and calls upon phagocytic cells.

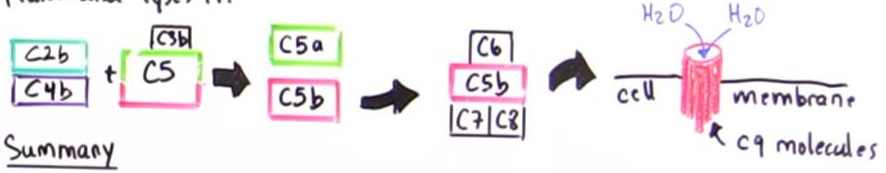


- stimulates immune cells to release chemicals such as histamine.

- C3b can also bind allosterically to another complement protein called C5 and prepare it for cleavage by the C4b·C2b complex.

C5

- The C5 complement protein guides the formation of the membrane attack complex
  1. C4b·C2b complex cleaves C5 into C5a and C5b.
  2. C5a acts as an anaphylatoxin and also acts in chemotaxis, which means it can attract immune cells such as neutrophils.
  3. C5b serves as the foundation for the membrane attack complex. C5b binds to C6, C7 and C8 molecule to form the C5b·6·7·8 complex.
  4. The C5b·6·7·8 complex stimulates many C9 molecules to bind to the membrane of pathogenic cell. This forms a channel that fills the cell with fluid and lyses it.



Summary

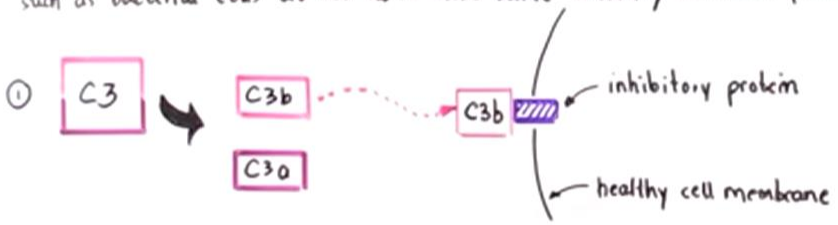
1. Cell lysis of antibody coated cells
2. Chemotaxis by C5a.
3. Opsonization by C3b molecules.
4. Agglutination
5. Promotes formation of antibodies

Complement System

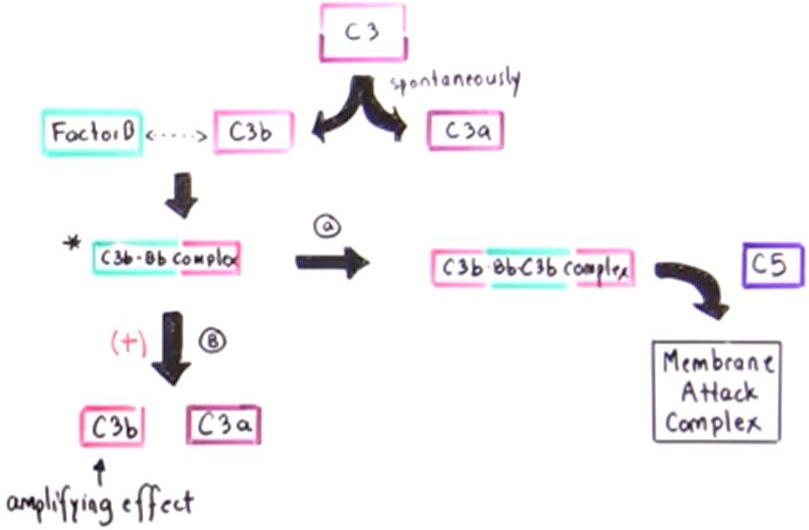
- The complement system consists of the classical pathway and the alternative pathway. The classical pathway requires antibody-antigen complexes while the latter does not.

Alternative Pathway

- This pathway is triggered even in the absence of antibody-antigen complexes! How? Protein C3 can actually spontaneously convert into C3b. When around healthy cells, it can bind onto healthy cell membranes & be inactivated. However, pathogens such as bacterial cells do not have these same inhibitory membrane proteins.



- The C3b·Bb complex is a C3-convertase and can act:
  - ⓐ on C5 molecules to form the C3b·Bb·C3b complex which can go on to activate C5. The C5 then forms the membrane attack complex.
  - ⓑ on C3 to form more C3b, which amplifies the cascade.



Regulation of Complement System

Many proteins are use to control the complement cascade.

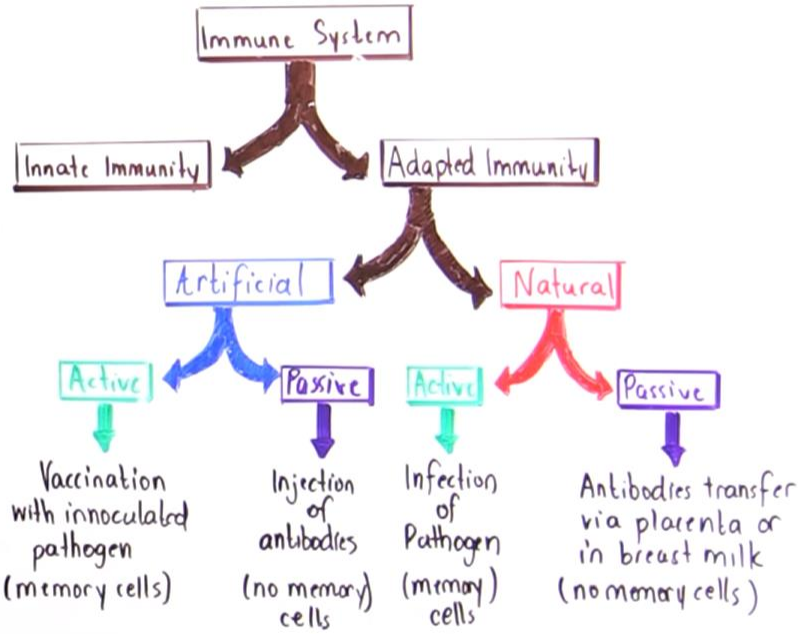
① Factor I - inactivates C3b.

② Factor H - removes Bb protein from the above pathway.

③ C1-Inhibitor - binds to C1 complex of classical pathway and inhibits activation of C2 and C4.

Immunization

- When our body is exposed to pathogenic antigens, it begins to produce antibodies specific for that antigen. These antibodies bind to the antigens, thereby labeling them for destruction by our white blood cells. If we are ever reinfected with the same antigen, our body will already have the antibodies to deal with the pathogen.
- Such a process in which our body develops immunity to the pathogen by being directly exposed to the antigens is called <u>active immunity</u>. For example, people who are exposed to chicken pox gain activity immunity and will be very unlikely to ever feel the same effect if they are exposed to it again.
- Active immunity can be achieved either:
  (1) naturally through some sort of exposure to the pathogen (infection).
  (2) artificially via the process of <u>immunization</u>, which normally involves the injection of a <u>vaccine</u>.
- Vaccines are normally developed in laboratories by many different methods. Typically the pathogen is <u>innoculated</u>, which means that it is changed in some way so that it does not damage the body as severely as it normally would. In many cases, the person does not show any visible effect when they are vaccinated.
- In order to reduce the effects of the pathogen, medical researchers usually use some small part of the antigen in the vaccine. This way, the body can still produce antibodies but the body is not hurt in the process.
- Another form of immunity is called <u>passive immunity</u>. In passive immunity, antibodies are developed in a laboratory that are specific to some pathogenic antigen. These antibodies are then injected into the body and can persist in the blood for months before being degraded. In this way, we can develop an immunity to a certain pathogen temporarily. Note that since the body is not actually exposed to the antigen, it does not produce memory cells.
- Passive immunity can also be developed naturally. Pregnant women give their developing fetus passive immunity by producing immunoglobulin G. IgG can easily pass across the placental membrane and can protect the fetus while their own immune system is still developing. Another example of natural passive immunity is breastfeeding, which passes down immunoglobulin A (IgA) to the baby via the milk.



Grafts and Organ Transplants

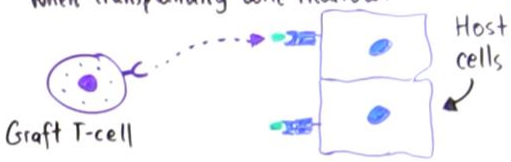
- Many different tissues and organs can now be transplanted from one individual to another and such a procedure is known as an allograph. If the tissue is transplanted from one location to another on the same individual then we call it an autograph. Many organs have been transplanted successfully including the heart, kidneys, lungs, liver, pancreas, skin, ovaries, bone marrow as well as our blood and structures like the cornea of the eye.
- Grafting and organ transplants are extremely complicated procedures and require a a great deal of preparation and analyzation. The primary reason for this is because of our immune system.

Issues with Allographs

1) Graft Rejection
- When a tissue or organ is transplanted, it has a very high chance of being rejected by the host individual. Recall that our immune system attacks anything that it recognizes as being foreign or pathogenic. If the MHC self-antigens of the transplanted tissue cells do not match and are not compatible with the host cells, then the host immune system will mount a defensive response and destroy the allograph.

- When white blood cells do not recognize the self-antigens presented on the MHC complexes of transplanted organs cells, the cell-mediated immunity will respond by producing cytotoxic T-cells that will bind to and destroy the graft cells.

2) Graft-versus-Host Disease (GVHD)
- When transplanting tissue that contains a high concentration of white blood cells such as T-cells, there is a very high probability that the graft T-cells will recognize the host cells self-antigens as foreign and will begin attacking and destroying the host cells. This is of particular significance when transplanting bone marrow.



3) Infections
- The donated tissue or organ may contain dangerous pathogens such as HIV, hepatitis B, rabies, syphilis and many others. Nowadays this problem is very rare because organs are routinely checked for these pathogens before donation.

Tissue-Typing and Immunosuppression

- The best way to ensure that an organ or tissue transplantation is successful is to use that individuals own tissue or, if possible, the tissue of an identical twin. Of course, these instances are very rare. A more common technique includes tissue typing and immunosuppression.

1) Tissue Typing
- This process involves determing the major histocompatibility complex antigens of the host individual and find a donor that is most compatible.

2) Immunosuppression
- Chemical agents can be used to interfere with the production of host white blood cells. This suppresses the immune system and prevents it from mounting an attack on the graft.
- Unfortunately these chemicals can also affect other cells of the host individual. In addition, suppressing the immune system can also lead to infection and cancer.

Immunosurveillance and Cancer Cells

- According to the current theory on immune surveillance, certain cells of our immune system keep a watchful eye for abnormal cells such as cancer cells.

Development of Cancer Cells

- When healthy cells are exposed to radiation, chemical agents, pathogenic agents and other carcinogens, they can develop mutations in their DNA. These abnormal cells are called cancer cells and if not destroyed, they can divide rapidly and uncontrollably to form large visible masses called tumors.

Immunosurveillance

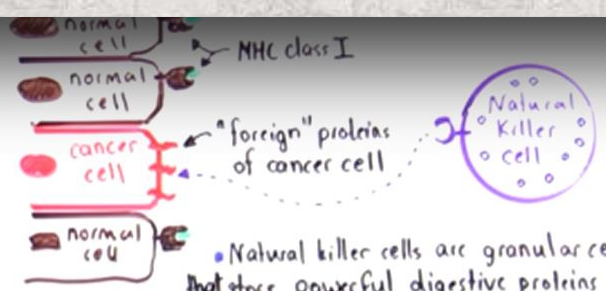
- Since these cancer cells have slightly different DNA, they will express slightly different proteins on their membrane. These different proteins can be read by certain white blood cells as foreign antigens, which can mark the cancer cell for destruction. In fact, according to the current theory, our body produces from several to thousands of cancer cells on a daily basis! So why doesn't everyone get cancer in their lifetime?

- Although our entire immune system must work together to locate and destroy cancer cells, two particular white blood cells seem to play a dominant role. These include natural killer cells and cytotoxic T cells.

1) Natural Killer Cells (NKC)

- These cells are lymphocytes that are part of our innate immunity. Majority of the white blood cells of our body can only recognize an abnormal cell if it contains an antigen attached onto an MHC membrane protein.

- However, natural killer cells are unique because they do not require the presence of the major histocompatibility complex to notice that something is wrong with the cell. Interestingly, some infected or cancer cells sometimes are missing the MHC entirely from their membrane, which makes these abnormal cells virtually invisible to all cells other that natural killer cells!

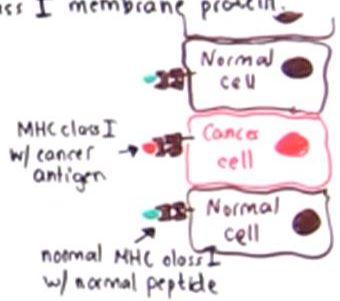


- When cells display little or no MHC proteins on their membrane, this triggers the natural killer cell to bind to and destroy the cell.

- Natural killer cells are granular cells - they contain tiny vesicles that store powerful digestive proteins such as perforin. When they bind to cancer or infected cells, they release these proteins which cause the abnormal cell to lyse.

2) Cytotoxic T-cell (killer T cells)

- These cells are part of our adaptive immunity. They contain T-cell receptors along with the CD8 glycoprotein, which means they can only bind to cells that contain the MHC class I membrane protein.



- When a healthy cell becomes cancerous, it can replace a normal peptide on its MHC class I membrane protein with a cancerous one, and this can be readily recognized by the CD8 - T cell receptor of the cytotoxic T cell. Once bound, the cytotoxic T-cell can release proteins that lyse the cancer cell.

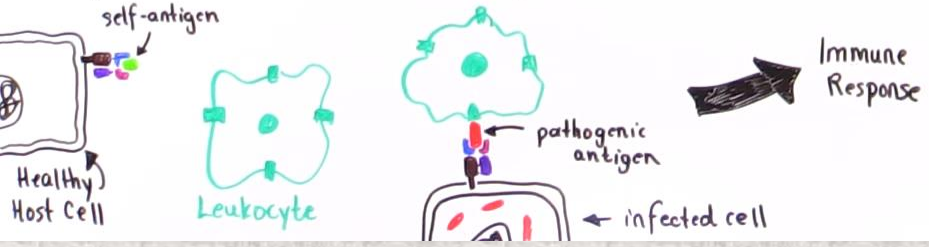
Major Histocompatibility Complex (MHC)

- The ability of our immune system to recognize its own cells and distinguish those cells from foreign pathogens depends on a group of protein markers found on cell membranes called the major histocompatibility complex. These markers are present on the surface of every cell and in humans are called the human leukocyte antigens.
- There are three types (classes) of these membrane markers - MHC class I, MHC class II and MHC class III.

MHC Class I

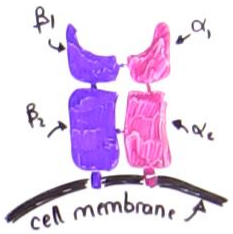
- These protein markers are found on the membrane of most nucleated cells.
  - They are used to differentiate healthy host cells from infected cells (i.e. infected by viruses).

- A healthy cell will bind one of its normal peptides (self-antigens) onto the MHC class I. When a leukocyte approaches, it can recognize the healthy cell by the self-antigen and the leukocyte will therefore leave it alone.
- In the case of an infected cell, the cell will produce a viral peptide (antigen) and will place it onto the MHC class I. Leukocytes can recognize these foreign antigens, bind to them and initiate a defensive mechanism that can destroy the infected cell.

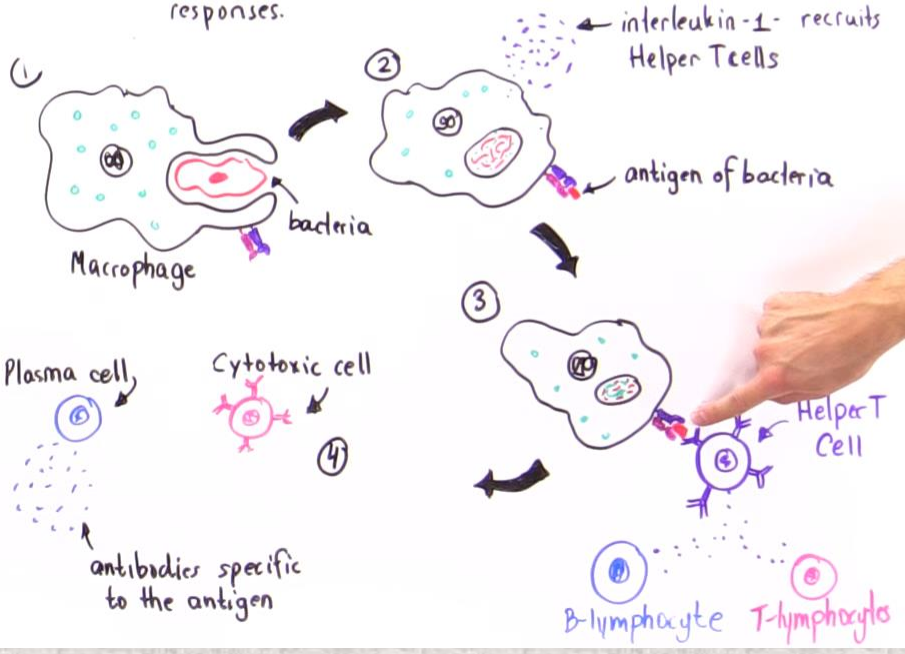


MHC Class II

- These protein complexes are found on only specific immune cells such as B lymphocytes, macrophages, dendritic cells and some T lymphocytes.



- These protein complexes function in helping immune cells to communicate with one another.
- Suppose a macrophage engulfs a bacterial cell and partially digests it. It then takes a peptide from the bacterial cell (the antigen) and places it onto the MHC class II located on its surface. This can in turn stimulate T lymphocytes such as Helper T cells to initiate a set of defensive responses.



Autoimmune Disease

- Our immune system has a natural immunological tolerance to the healthy cells of our body. This means that the white blood cells of our body do not attack the body's own proteins (self-antigens).

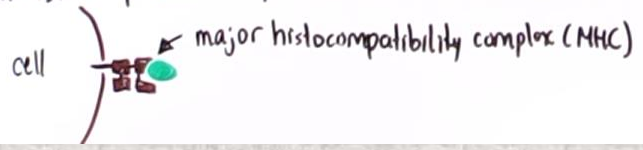
- Normally our immune system has no issues distinguishing between the body's proteins and foreign antigens that come from invading pathogens. However, in certain individuals, the immune system loses this ability to differentiate between self-antigens and pathogenic antigens. This condition is called autoimmunity or autoimmune disease.

- Some examples of autoimmune diseases include multiple sclerosis, diabetes (type I), myasthenia gravis, rheumatoid arthritis, among many others. In the case of myasthenia gravis, the body produces an antibody that circulates our blood and attaches onto acetylcholine receptors found on our motor neurons. This process can decrease the interaction between neurons of our nervous system and ultimately affects our ability to contract our skeletal muscle.

- Although this topic is heavily researched, we still do not fully understand why this takes place. Some possibilities include mutations in genes, infections by pathogens and damage to immunologically privileged sites.

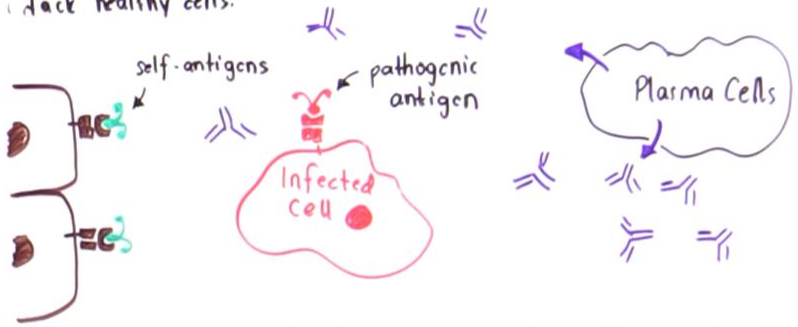
Gene Mutations

- A genetic predisposition is believed to be one possible cause of autoimmunity. Research indicates that autoimmunity runs in families and may be passed down to offspring. Genetic mutations of DNA that code for the MHC membrane proteins may lead to autoimmune disease.



Infections

- When an individual is infected by a pathogen, that pathogen may contain or produce antigens that resemble the self-antigens of the healthy cells our body. When the pathogenic antigens induce the immune system to produce antibodies, the antibodies may then attack healthy cells.



- For instance streptococcal infections can produce antigens that have similar epitopes compared to self-antigens found in our heart. This can lead to rheumatic heart disease.

Privileged Sites

- Certain places of our body are out of reach to the majority of our white blood cells because they contain virtually no blood and lymph vessels. The cornea and our brain are two examples.

- Physical damage to these "privileged" places can release self-antigens that have not yet been encountered by our immune system, leading to an autoimmune response that can destroy those areas.

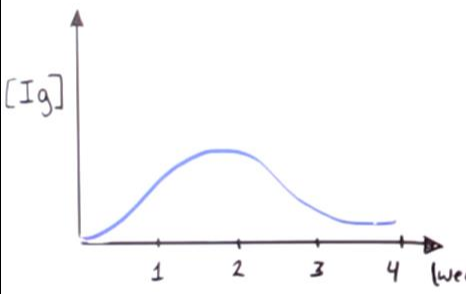
Interferons

- How exactly does our innate immune system deal with pathogens that ultimately make their way into our cells such as viruses or intracellular parasites?
- When a cell becomes infected, it responds by releasing proteins called interferons. Interferons will travel to neighboring healthy cells, bind to special receptors on those cells and initiate a response that will prepare them for viral infection. For instance, the cells begin producing anti-viral proteins that function to block viral replication. This way, when the infected cell lyses and releases more viruses, the nearby cells have already mounted a defense.
- These interferons can also bind to, stimulate and recruit specialized leukocytes.
  1. Natural Killer Cells
     Natural killer cells are mobilized after interacting with interferons. They can seek out and destroy infected cells as well as cancer cells.
  2. Macrophages
     Interferons recruit these large phagocytic cells that can engulf and break down infected cells. Macrophages themselves can release their own interferons, amplifying the immune response.
- Interferons can also stimulate cell death of the infected host cell.

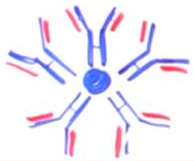
Primary and Secondary Immune Response

- The first exposure to some particular pathogenic antigen elicits a primary response. When the antigen makes their way into our body, there is a period of time called the latent period during which our adaptive immune system is being mobilized and the appropriate lymphocytes are being cloned.

- Once we have all the lymphocytes we need, they will begin to produce antibodies that are specific for that invading antigen. If we plot the concentration of antibodies that are produced versus time, we see that there is a sharp increase in concentration of antibodies following the latent period. Eventually however, the concentration reaches a peak and levels off. This period of sharp increase and the subsequent leveling off is called the logarithmic phase.

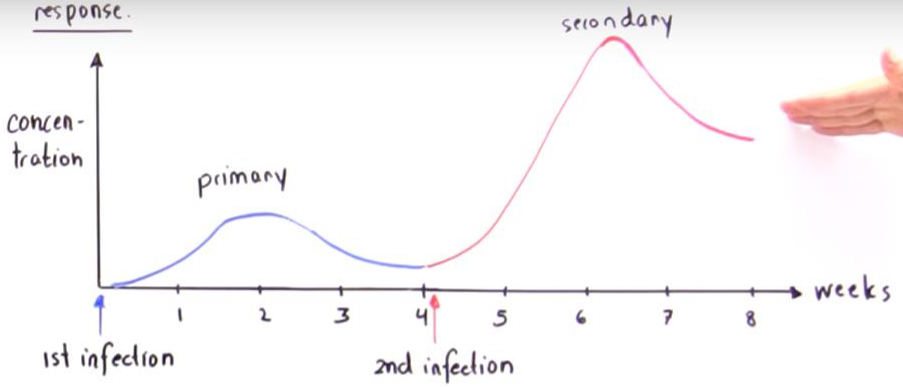


- In the primary response, the major antibody synthesized is immunoglobulin M. This antibody is usually formed in its pentamer form, which means that five individual antibodies are connected by disulfide bonds.



- Notice on the graph that the concentration of antibodies begins to decrease following the peak. This is called the decline phase. The antibody concentration drops to a very low level during this period for the primary response.

- What happens when the body is reinfected by the same type of pathogen? In this case, the immune system will elicit a secondary response.



- Following the first infection, the immune system will produce memory cells that will carry the antibody that is specific to that particular antigen. When the antigen reinfects the second time around, the immune response will be much more rapid, with a shorter latent period because of these memory cells. In addition, the amount of antibodies produced is much greater and the major antibody used is immunoglobulin G

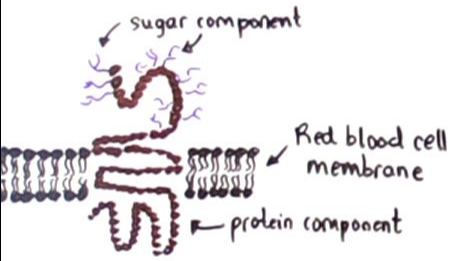
Primary Response	VS.	Secondary Response
1. Relatively long latent period		1. Relatively short latent period (quick)
2. Amount of antibodies produced is low		2. Amount of antibodies produced is much greater
3. During decline phase, the antibody level drops to a very low value.		3. During decline phase, antibody level persists at a higher value for longer.
4. Immunoglobulin M		4. Immunoglobulin G

ABO Blood Group

- Humans have four types of blood groups - A, B, AB and O.

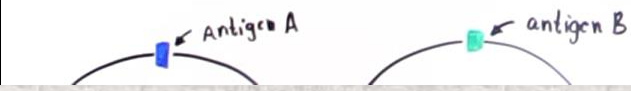
Determination of Blood Type

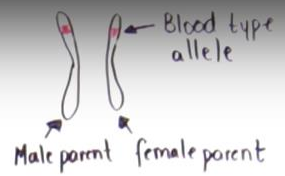
- What exactly determines blood type? Human DNA contains a gene that codes for a protein that eventually becomes a membrane protein of red blood cells. Before it is attached onto the membrane however, it is modified and becomes a glycoprotein. This glycoprotein contains a carbohydrate component and the terminal sugar determines the group type.



- These glycoproteins are sometimes called self-antigens or simply antigens. They can come in two different types - antigen A or antigen B.

- An individual with a gene that codes for antigen A will have membrane-bound antigen A glycoproteins on their red blood cells. This implies that the immune system will not produce any antibodies against these self-antigens. However since it lacks antigen B, the immune system will produce antibodies against red blood cells that contain the antigen B glycoprotein. In such a case, the individual is said to have blood type A.
- On the other hand, a person with a gene for antigen B will have red blood cells that only contain the antigen B glycoprotein, which means the immune system will produce antibodies for antigen A. In this case, the individual is said to have blood type B.





- The ABO blood group locus is found on chromosome 9. Each allele is passed down from each one of the parents.
- Blood type is a codominant trait. This means that if one parent gives the antigen A gene while the other gives an antigen B gene, then the offspring will have red blood cells with both antigen A and B glycoproteins. In such a case, that individual is said to have blood type AB. These individuals do not have antibodies for either antigens
- It is also possible to donate a chromosome that does not code for either antigens. If both parents donate such a chromosome, they will produce an offspring with blood type O. Such an individual lacks both antigens on their red blood cells and so produces both antibodies.

Blood Transfusion

- It is possible to transfer blood from one individual to another. However one must keep in mind that certain blood types cannot mix and will agglutinate (clump together). Since people carry antibodies for antigens they don't have, mixing red blood cells that have particular antigens with a complementary antibodies will cause them to stick, causing agglutination.

Recieving \ Donating	A	B	AB	O
A	Yes	No	No	Yes
B	No	Yes	No	Yes
AB	Yes	Yes	Yes	Yes
O	No	No	No	Yes

Yes = Mixing is allowed; no agglutination

No = Mixing is not allowed; agglutination occurs.

Blood type	Genotype
A	I^AI^A/I^Ai^O
B	I^BI^B/I^Bi^O
AB	I^AI^B
O	i^Oi^O

Rh Factor and Rh Incompatibility

- Aside from antigen A and antigen B that can be found on the membrane of our red blood cells, there are other antigens that can be found. One group of of such antigens is called the Rh factor. By far the most common antigen of this group is antigen D.

- An individual with a gene that codes for antigen-D is is said to be Rh-positive. This means that their red blood cells will have the antigen D protein on their membrane. On the other hand, an Rh-negative person will lack the protein on its red blood cells.

- Unlike for the ABO groups, a Rh-negative individual will not normally produce antibodies against antigen D. However, if they are ever exposed to antigen D, then their immune system kicks in and begins forming antibodies.

	R	r
R	RR(+)	Rr(+)
r	Rr(+)	rr(−)

- The gene that codes for the Rf factor (antigen D) is dominant to the gene that does not code for it. If two heterozygous individuals mate, then there is 75% chance of being Rh-positive and 25% chance of being Rh-negative.

Maternal-Fetal Blood Incompatibility

- Suppose a woman who is Rh-negative decides to have a child with a man who is Rh-positive. Then there is a chance that the fetus will be Rh-positive. If the man is homozygous dominant, then the child will be Rh-positive. If the man is heterozygous, then there is 50% chance of being Rh-positive.

	R	r
r	Rr	rr
r	Rr	rr

← Heterozygous Father

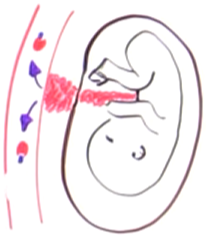
↑ Homozygous Recessive Mother

Homozygous Father ←

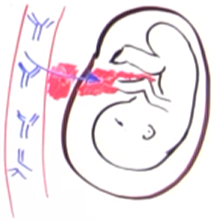
	R	R
r	Rr	Rr
r	Rr	Rr

↑ Homozygous recessive Mother

- If the fetus ends up being Rh-positive, how will this effect the pregnancy and any future pregnancy of that woman?



- During the first pregnancy, some of the red blood cells of the fetus that have the antigen D Rh factor can leak into the mother's blood.
- This will cause the mothers immune system to produce antibodies against antigen D. However, since the fetal red blood cells usually leak during child birth, this will not effect that fetus.



- When the woman becomes pregnant again, the antigen D antibodies can now cross across the placenta and enter the blood stream of the fetus. If the fetus is Rh-positive, the antibodies will bind onto the red blood cells and lyse them. The lysing rel... dangerous chemicals into the fetal blood, which ... ultimately cause damage to the organs (i.e brain).

- This is known as Rh-incompatibility.

Kontrolleri taşı / değiştir

SOURCE: AK Courses on Youtube