UNIT 11 - IMMUNITY

Immune system - the body's internal defense system
Immune response - the complete series of reactions of the body to the entry of a foreign antigen; it involves the activity of lymphocytes and phagocytes

Antigens: Self and Non-Self

Antigen - a substance foreign to the body that stimulates an immune response (e.g. by a large molecule such as a protein)

- All cells have antigens on their surface that allow for cell-to-cell recognition between the cells of the body. Pathogenic antigens allow for the pathogen to bind to and enter the body cells.
- Self-antigens are produced by the organisms' body cells – those the immune system does not flag as foreign. Self-antigens do NOT stimulate an immune response.
- Antigens can also be non-self. These antigens are not produced by the organisms' cells and are recognized by the immune system as foreign. Non-self antigens DO stimulate an immune response.

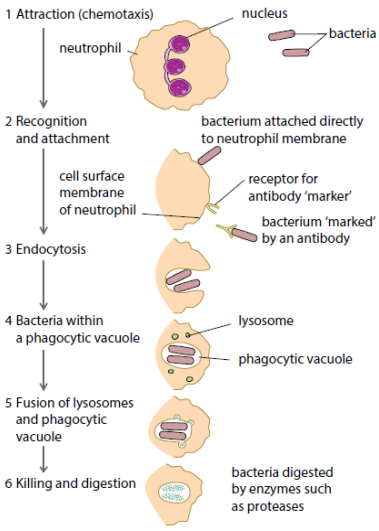
Phagocytes

Mode of action - describes a function or anatomical change resulting from the response of a living organism to a substance

- Phagocytes are white blood cells produced in the bone marrow and are also stored in the bone marrow
- They are responsible for removing dead cells and invasive organisms. They carry out NON-SPECIFIC immune responses.

There are 2 types of phagocytes:
1) Neutrophils
2) Macrophages

Phagocytes carry out phagocytosis and must recognize and engulf the pathogen. This process varies between neutrophils and macrophages.



1) Neutrophils

- They travel through the body via the bloodstream and squeeze through capillary walls to patrol tissues
- During infections, they are released in large quantities from their stores in the bone marrow
- Neutrophils have a developing period of 7-11 days and a short lifespan of 6 hours to a few days.

Mode of action:
1) Attraction (chemostasis) - chemicals released by the pathogen (e.g. toxins) and chemicals released by attacked body cells (e.g. histamine) attract neutrophils to the site of infection
2) Neutrophils move toward the pathogens. These pathogens might be covered in antibodies. Neutrophils have cell surface receptors complimentary to the antibodies, which allows them to bind to the pathogen
3) Endocytosis - once attached to the pathogen, the neutrophil membrane folds inwards and forms a phagosome with the bacteria inside.
4) Fusion of lysosomes - lysosomes fuse with the phagosome and form a phagolysosome. They release their hydrolytic enzymes and digest the pathogen.
5) The pathogen is digested into enzymes such as proteases
6) After killing and digesting pathogens, the neutrophils die. Pus is an indicator of dead neutrophils.

2) Macrophages

- Macrophages are bigger than neutrophils and longer-lived.
- Rather than traveling in the blood, they move to organs such as the lungs, liver, spleen, kidneys, and lymph nodes.
- They are produced in the bone marrow and stay in the blood as monocytes (immature)

Mode of action:
1) They still carry out phagocytosis, but they do not destroy the pathogen completely
2) Instead, they "cut up" the pathogen and display the pieces on their surface through the major histocompatibility complex.
3) The displayed antigens are then recognized by lymphocytes
   - ★ Cells that present pathogenic antigens like this are known as antigen-presenting cells (APCs)

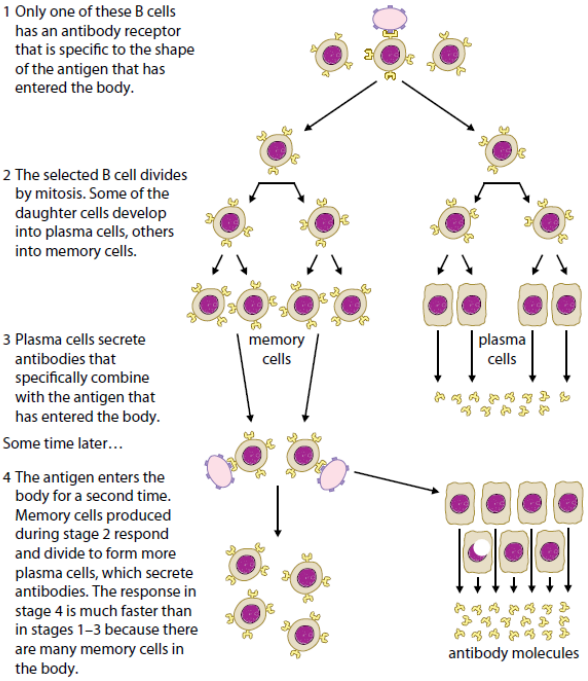
Lymphocytes

- Lymphocytes are another type of white blood cell and exhibit SPECIFIC immune responses
- They are smaller than phagocytes (5-17μm) and have a lifespan varying from hours to years, depending on their type

- They have a large nucleus that fills most of the cells and is produced by the bone marrow. There are two different types of lymphocytes, each with different modes of action:

1) B Lymphocytes
2) T Lymphocytes

1) B Lymphocytes



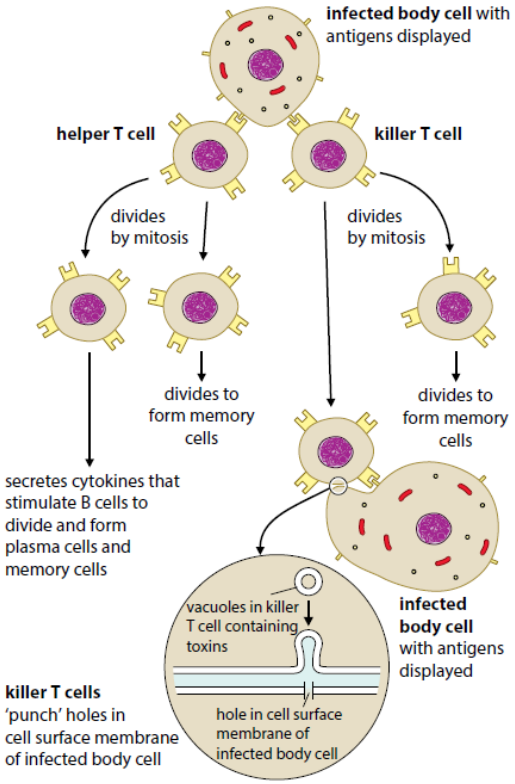
- B cells remain in the bone marrow until they mature and then spread throughout the body
- Once mature, each type of B cell can make one type of antibody molecule, and have receptors complimentary to one type of antibody
- At this stage, the antibodies remain inside the cell, on the cell surface membrane
- Part of each antibody molecule forms a glycoprotein receptor that can combine specifically with one type of antigen

Antibody - a glycoprotein (immunoglobulin) made by specialized lymphocytes in response to the presence of a specific antigen. Each antibody has a shape that is complementary to its specific antigen.

- When an antigen enters the body for the first time, the B cell with a receptor complementary to the antigen is stimulated to divide by mitosis. This is known as clonal selection.
- As the clones divide repeatedly (clonal expansion), a large number of B cells with receptors complimentary to that antigen are produced.
- During the immune response, B cells differentiate into plasma cells and memory cells.
- The primary immune response is slow and occurs over days or weeks

Both clonal expansion and the replication of memory B cells & plasma cells occur through mitosis.

2) T Lymphocytes



- T cells are produced in the bone marrow but mature in the thymus gland
- Mature T cells have specific cell surface receptors called T cell receptors
- These receptors have a similar structure to antibodies and are each specific to one antigen
- T cells are activated when they encounter and bind to their specific antigen that is being presented by APCs that have been infected or macrophages that have engulfed the specific pathogen and are displaying the antigens

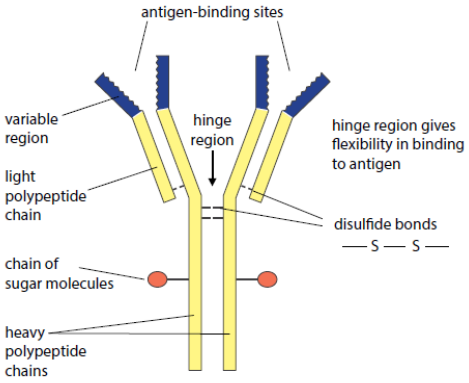
Activated T cells divide by mitosis to increase in number. These T cells differentiate into Helper T cells and Killer T cells

- Helper T cells secrete cytokines that stimulate B lymphocytes to divide and develop into plasma cells. Some Helper T cells also secrete cytokines that stimulate macrophages to increase the rate of phagocytosis.
- Killer T cells attach to the antigens on the cell surface membrane of infected cells and secrete toxic substances that kill the cell as well as the pathogens inside.

Cytokine - any signaling molecules released by cells to influence the growth and/or differentiation of the same or other cells.

Memory T helper and Memory T killer cells are also produced and remain in the body and become active very quickly during the secondary immune response.

Antibodies: Structure and Function



- Antibodies are globular proteins (glycoproteins) and are referred to as immunoglobulins.
- Antibodies have a quaternary structure represented as a Y-shape, with 2 'heavy' (long) polypeptide chains, and 2 'light' (short) polypeptide chains.
- Each polypeptide chain has a constant and variable region
- The constant regions do not vary within a class (isotype) but DO vary between classes.
- The constant region determines the mechanism used to destroy antigens (there are 5 classes of mammalian antibodies)
- The amino acid sequence in the variable region of the antibody is different for each antibody. The variable region is where the antibody attaches to the antigen to form an antigen-antibody complex.
- At the end of the region is the antigen-binding site which is composed of 110-130 amino acids, and includes both ends of the light and heavy chains.
- The antigen-binding sites vary greatly, giving the antibody its specificity for building to the antigen
- A pathogen may express multiple different antigens so multiple different antibodies will be required.

Functions of antibodies

- Antibodies can combine with viruses and toxins of pathogens to block them from entering or damaging cells
- Antibodies can act as anti-toxins by binding to toxins produced by pathogens which neutralize them, making them harmless
- Antibodies can attach to bacteria, making them readily identifiable to phagocytes. This is known as opsonization.
- Antibodies can attach to the flagella of bacteria, making them less mobile and making it easier to carry out phagocytosis.
- Antibodies can also act as agglutins, causing pathogens carrying antigen-antibody complexes to clump together. This reduces the chances of the pathogen spreading around the body and makes phagocytes more efficient.
- Antibodies, together with other molecules, can create holes in the cell walls of pathogens, causing them to burst (lysis) when they absorb water.

Monoclonal antibodies

Monoclonal antibody (mAb) - is an antibody made by a single clone of hybridoma cells; all the antibodies are made by the clone and have identical variable regions specific to one antigen

Hybridoma - a cell formed by the fusion of a plasma cell and a cancer cell; it can both secrete antibodies and divide to form clones

Monoclonal antibodies are artificially produced from a single B cell. Monoclonal antibodies bind to antigens in the same way as naturally produced antibodies.
The hybridoma method is used.

The hybridoma method enables large quantities of identical antibodies to be produced
The hybridoma method solves the problem of having B cells that can divide by do not produce antibodies and plasma cells that can produce antibodies but cannot divide. The hybridoma method was established in the 1970s. The method involves:

1) Injecting mice with an antigen that stimulates the production of antibody-producing plasma cells
2) Isolating the plasma cells and fusing them with tumor cells, resulting in the creation of hybridoma cells
3) These hybrid cells are grown and screened for the desired antibodies
4) They are then cultured to produce large amounts of monoclonal antibodies

It is important to note that monoclonal antibodies must be humanized before being administered to patients (to prevent an immune response). This is done by genetically modifying the amino acid sequence so that it is human and compatible, and by altering the type and position of the sugar chain on the antibodies.

Uses of monoclonal antibodies

Monoclonal antibodies can be used diagnostically for:

- Pregnancy tests
- Diagnosing HIV
- Detecting the presence of pathogens e.g. streptococcus
- Distinguishing between Herpes I and Herpes II
- Blood typing before transfusions and tissue typing before transplants
- Detecting antibiotics in milk
- Detecting cancer cells

Monoclonal antibodies can also be used to locate blood clots in patients with deep vein thrombosis. This is done by:

1) Injecting a mouse with human fibrin (a protein in blood clots)
2) This activates plasma cells to produce antibodies against fibrin
3) The cells are then collected from the mouse's spleen
4) The plasma cells are then fused with tumor cells, forming hybridomas that produce anti-fibrin antibodies
5) To detect where the antibodies are binding to fibrin molecules, a radioactive chemical is attached to the antibodies, making them radioactively labeled and visible in scans. A gamma ray camera is used to detect where these radioactively labeled antibodies have attached to a fibrin molecule.

Therapeutically, monoclonal antibodies are used to:

- Tret rabies virus by injecting purified antibodies
- Prevent transplanted organ rejection, achieved by intervening with the T cells involved in the rejection process
- Help with autoimmune therapies for allergic asthma and rheumatoid arthritis; here, monoclonal antibodies help relieve inflammation
- Treat diseases caused by the over or underproduction of B-cells e.g. leukemia, multiple sclerosis, and myasthenia
- Treat breast cancer (Herceptin)
- Treat melanoma (skin cancer) (ipilimumab)

Vaccines

- Vaccines work by injecting dead or weakened pathogens into the body to stimulate an immune response and provide long-term artificial active immunity

Some vaccinations are highly effective and provide lifetime immunity. Others are not as potent and so require booster injection to stimulate a secondary immune response.

- Vaccines provide 2 types of immunity: herd immunity and ring immunity

Herd immunity - vaccinates a large proportion of the population; protects those not immunized as the transmission of the pathogen is reduced

Ring immunity - vaccinating all those in contact with an infected person to prevent transmission in the immediate area.

One of the most successful vaccination programs was the smallpox vaccination program, which has since eradicated smallpox from every country due to global cooperation in ending disease transmission.

However, some diseases like the flu cannot be fully eradicated because of how often they mutate and change their antigens.