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Immune system

- Dental Relevance of the Immune system
    - The oral cavity is a dense microbiome, home to beneficial and pathogenic microbes and substances.
    - The immune system plays a crucial role in keeping the oral cavity in a state of health, preventing pathogenic penetration into the body.
    - By knowing and understanding the responses of the immune system, we can understand the presentation of symptoms and signs when one is sick

Introduction to the Immune system and lymphoid tissues

- Basic terms of immunity

Antigen	- Foreign body - Has ability to stimulate an immune response
Pathogen	- Agent that causes disease - Does not need to be foreign body
Antigen Presenting Cell (APC)	- Cells that recognise, process and present antigens - Allows it to mediate the cellular immune response

Antibody/ Immunoglobulin	- Humoral immunity
	- Igs are glycoproteins
	- Interacts with specific antigens, serving to
	  - Neutralize
	  - Tag/opsonize
	  - Activate

Cytokines	- Chemical messengers at the cellular level - E.g interleukin/prostacyclin is a type of cytokine

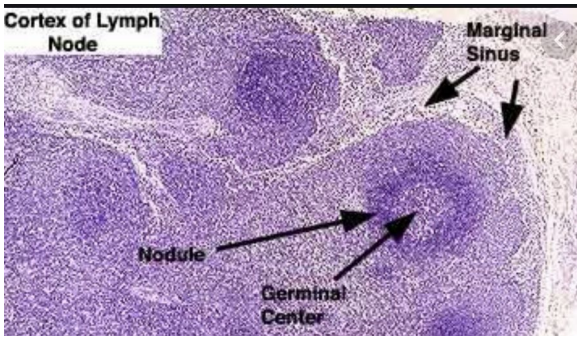
- Lymphatic system
    - Lymphatic vessels

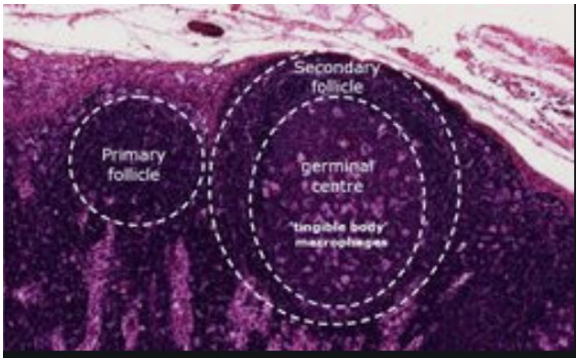
Feature	**Function**
- Thin walled - Incomplete basement membrane - Valves - Do not function as pump - Contain smooth muscle	- Return ISF to blood - Transport absorbed fat - Return Filtered plasma proteins - Lymphocyte circulation

- Primary and Secondary Lymphatic organs and their constituents

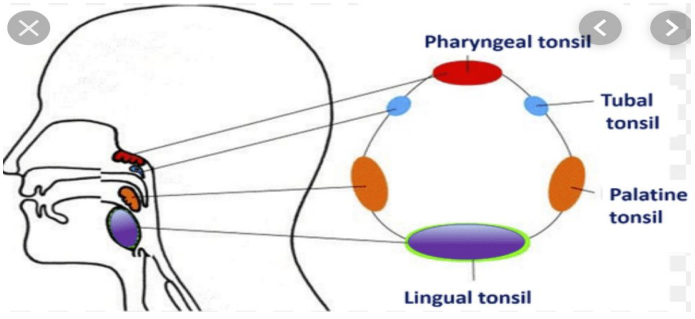
	Constituents	**Function**
Primary Lymphatic Organs	- Red bone marrow (BM) - Thymus (T)	- Sites of stem cell division and maturation - B cells develop, mature in BM - T cells develop in BM, mature in T
Secondary Lymphatic Organs	- Spleen - Lymph node	- Filters - Spleen removes old RBCs - Concentrates antigens - Immune cell activation

- Lymph Nodes
  - Site of antigen presentation to B/T lymphocytes
  - Primary follicle houses un-activated lymphocytes
  - Secondary follicle houses activated and differentiating lymphocytes
    - Occurs when a primary follicle is exposed to antigen





- Waldeyer's ring



  - First site of defence against
    - Inhaled antigen
    - Ingested antigen
  - A type of Mucosal Associated Lymphatic Tissue (MALT)

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Balance of immunity and defence: inflammation and innate immunity

Immune response

- Innate immunity
    - Surface barriers
        - Skin
        - Mucous membranes
    - Internal barriers
        - Phagocytic cells → fever
        - Neutrophils → inflammation
        - Natural Killer (NK) cells → antimicrobial substances
- Acquire immunity
    - Humoral immunity (antibody immunity)
        - B Lymphocytes
        - Plasma cells
    - Cellular immunity
        - T lymphocytes (CD4+/CD8+)
        - NK T cells

Innate	**Acquired**
Naturally occuring, present at birth	Develops over lifetime
Non-specific	Specific
Does not develop memory cells	Develops memory cells
Rapid response	Delayed response
Does not increase in potency with subsequent exposure	Secondary exposure has increased response effectiveness
Cells include neutrophils, macrophages, basophils etc	B lymphocytes, T lymphocytes

1st line of defence → external barriers

- Skin
    - Intact → impermeable → keratinized/ stratified squamous(closely packed cells)
    - Damage → breach in skin → exposure → infection risk
    - Defense of skin

- Cells are desquamated → shed from surface → removal of microbes on surface
- Secretion of sebum → inhibits growth of bacteria + fungi
- Perspiration → flush microbes from skin + low pH stops bacterial proliferation

- Mucous membranes
  - Lines surfaces of GIT, respiratory tract
  - Defense mechanism:
    - Traps microbes & foreign substances → mucocilliary escalator function → Removal of foreign bodies/bacteria
- Chemical → direct inhibiting factors
  - Defense mechanisms
    - Inhibition of bacterial growth
    - Destroying + expulsion of bacteria
  - Sweat/sebaceous secretions → Lactic acids + Low pH
  - Gastric juices → low pH
  - Tears → lysozyme
  - Nasal secretion → lysozyme
  - Saliva → lysozyme

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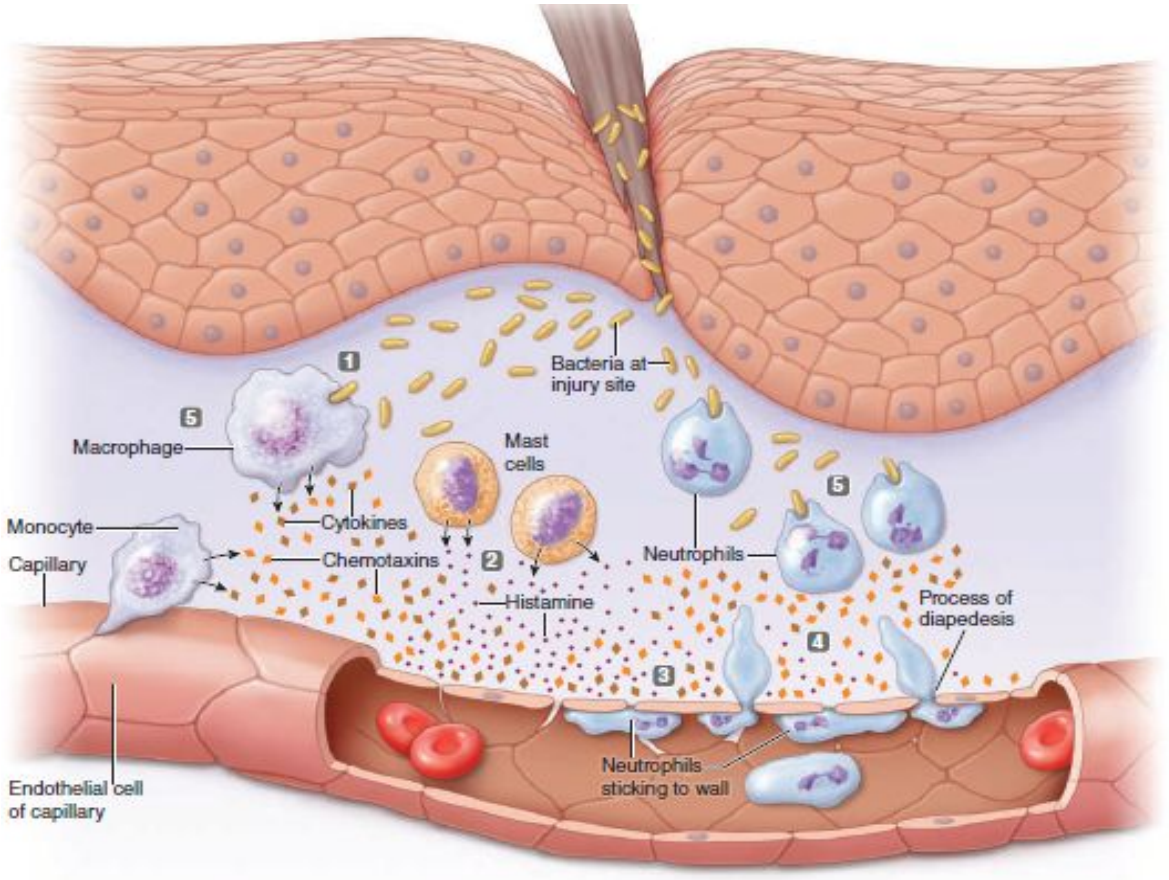
2nd line of defense → cellular response

1. Inflammation



1 A break in the skin introduces bacteria, which reproduce at the wound site. Activated resident macrophages engulf the pathogens and secrete cytokines and chemotaxins.

2 Activated mast cells release histamine.

3 Histamine dilates local blood vessels and widens the capillary pores. The cytokines cause neutrophils and monocytes to stick to the blood vessel wall.

4 Chemotaxins attract neutrophils and monocytes, which squeeze out between cells of the blood vessel wall, a process called diapedesis, and migrate to the infection site.

5 Monocytes enlarge into macrophages. Newly arriving macrophages and neutrophils engulf the pathogens and destroy them.

   a. 3 Goals of inflammation
      i. Isolate, destroy, and inactivate invaders
      ii. Remove debris
      iii. Prepare for healing repair
   b. 5 cardinal signs
      i. Redness
         1. Vasodilation and increased blood flow, bringing RBC and oxyhaemoglobin to supply energy for inflammatory process
      ii. Swelling
         1. Increase of permeability of endothelium → more plasma proteins in tissue → higher plasma colloid oncotic pressure → movement of water into tissue → oedema
      iii. Heat
         1. Vasodilation and increased blood flow bringing heat to surface of circulation

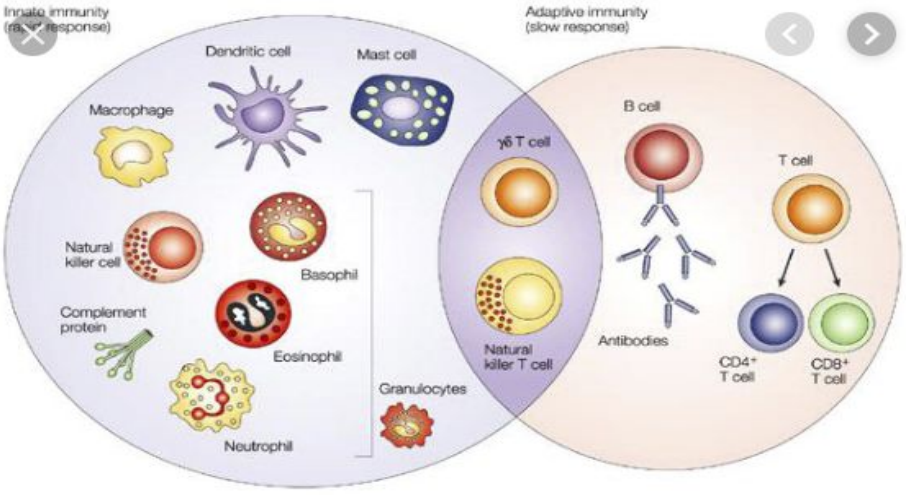
iv. Pain
    1. increase in interstitial pressure and release inflammatory mediators results in activation of nociceptors → helps prevent further agitation
    2. Bradykinins also reduce threshold of nociceptors
v. Loss of function
    1. In severe cases of prolonged inflammation

c. Process of inflammation
    i. Defense by tissue macrophage + transient vasoconstriction
        1. Break in skin → introduction of bacteria
        2. Activated macrophages phagocytose pathogen → secrete cytokines + chemotaxins
    ii. Localised vasodilation
        1. Mast cells in damaged region release histamine + heparin → vasodilation of arterioles → Increase in blood flow to site of injury → delivery of more phagocytic leukocytes and plasma proteins
    iii. Increased capillary permeability
        1. Histamine also enlarges capillary pores → increase in capillary permeability → Plasma proteins can now enter affected site (e.g complement system proteins)
    iv. Localised oedema
        1. Increased amount of plasma proteins in tissue → increase in plasma colloid osmotic pressure → plasma water enters tissue → swelling/oedema
    v. Walling off of inflamed area
        1. Fibrinogen is converted into fibrin → clotting process occurs → Walls off injured region → prevents spread of bacteria
    vi. Migration of leukocytes
        1. Cytokines secreted by macrophages cause neutrophils + monocytes Stick to blood vessel wall (due to increase in amt of integrins)
        2. Chemotaxins attract them → undergo diapedesis → undergo chemotaxis to site of infection
        3. Monocytes differentiate into macrophages → professional phagocytic cells phagocytose pathogens

2. Fever
    a. Function
        i. An abnormally high body temperature, due to resetting of hypothalamic thermostat
    b. Caused by
        i. Bacteria & viruses release exogenous pyrogens [fever-producing molecules] → Neutrophils & macrophages attack exogenous pyrogens → Secrete endogenous pyrogens → Stimulate secretion of prostaglandins a Rise in hypothalamic set point for body temperature

c. 3 effects of fever
    i. Intensifies effects of interferons
    ii. Inhibits growth of microbes
    iii. Elevates metabolic rate + rate of tissue repair
d. Shivering → body shivers to generate more heat → rise in hypothalamic set point for body temperature

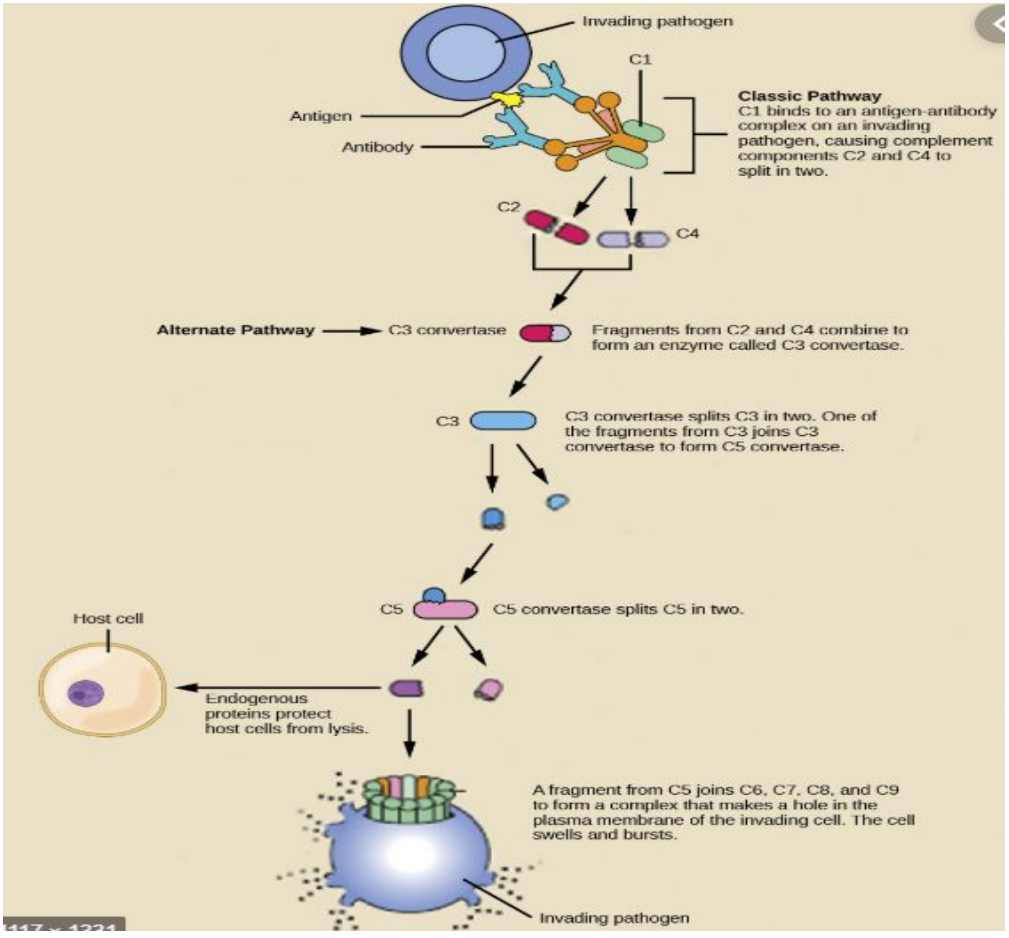
3. Leukocytes (white blood cells)



a. Macrophage
    i. Migrate to inflammation site & phagocytose pathogens
    ii. Originate from monocytes in the bone marrow
    iii. Professional phagocytic cell, Agranulocyte, Antigen presenting cell
b. Neutrophil
    i. Bactericidal
    ii. Migrate to inflammation site + phagocytose pathogens
    iii. Produce lysozyme + defensins
    iv. Most abundant in body
    v. Professional phagocytic cell, granulocyte, PMN
c. Eosinophil
    i. Parasites + bacteria
    ii. Release toxins from granules to kill pathogens
    iii. Involved in allergic reactions
    iv. Granulocyte, Bilobed nucleus
d. Basophil/mast cells
    i. Allergic reactions
    ii. Contain histamine (vasodilator + increase permeability) and heparin (anticoagulant)
    iii. Granulocyte, Bilobed nucleus
    iv. Mast cells are tissue basophils
e. Natural killer cells
    i. Large granular lymphocyte

ii. Serve as immune surveillance cells → patrol for pathogens or diseased host cells
iii. NK cells → recognise antibodies bound to antigens on virus infected host cells/bacteria/cancer → activated → release perforin & granzymes → apoptosis of infected cell
iv. Produces cytokines that cause infected cell/bacteria to undergo apoptosis/lysis

f. Phagocytosis
i. Chemotaxis towards the foreign bodies
ii. Ingestion of microbe by pseudopodia of phagocyte
iii. Foreign body ingested → formation of phagosome
iv. Phagosome fuses with lysosome → formation of Phagolysosome, contains lysozyme + proteolytic enzymes
v. Microbe/Foreign body broken down
vi. Residual body formed → contains indigestible material + epitopes
vii. Epitopes presented on cell surface by MHC Class 2 molecules and residual body is discharged/exocytosed

4. Antimicrobial factors
- Complement system
  - 

  - Upon activation → amplification of response → through an amplifying cascade of protein cleavage → cell killing complex (MAC) forms on pathogen → Pathogen dies

    - Lysis of cell
    - Opsonization of cells and cell fragments
    - Triggers inflammation
    - Immune clearance → removes complexes and deposits in spleen + liver for breakdown
  - Interferons
    - Host cell → infected by virus → Produces interferons → killed by virus
    - A type of cytokine that signals NK cells to kill virus infected cells, also activates macrophages
    - Surrounding cells → produce antiviral proteins to resist viral infection
- Defensins
    - Proteins kill bacteria by disrupting cell walls and inserting pores → killing Cell
    - Produced by PMN, in their granules
- Lysozyme
    - Enzyme that hydrolyses bacterial cell wall → killing cell
    - Produced by neutrophil/PMN
- Toll like receptors (PAMP- Pathogen Associated Molecular Patterns)
    - Involved in inflammatory response
    - Functions as a pattern recognition receptor → recognises fixed patterns on microbes → ligands bind → signal cascade in cell → triggering inflammatory response

Balance of immunity and defence: Acquired immunity

Branches of Acquired Immunity

- Humoral → B lymphocytes + Plasma cells
    - Derived from haematopoietic stem cells in bone marrow
    - Differentiate in Bone marrow
    - Enter Lymph node for maturation
    - Contain B cell Receptors on cell membrane
    - Upon activation → differentiate and proliferate into Plasma cells, Effector B cells, and memory Cells (10% memory, 90% effector)
    - Cells produce antigen specific antibodies
- Cellular → CD4+/CD8+ T lymphocytes + NK T cells
    - Derived from haematopoietic stem cells in bone marrow
    - Undeveloped/undifferentiated lymphocytes leave and goes to the thymus and differentiate into T cells there
    - Enter lymph node for activation
    - Contain T cell Receptors on cell membrane
    - CD4+ Helper and CD8+ Cytotoxic T lymphocytes

Antigen

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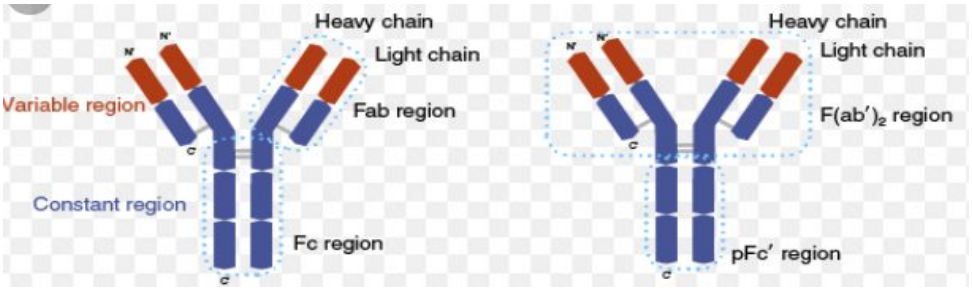
- Foreign, Nonself molecule (pathogenic or non-pathogenic) that is recognised by cells of the acquired immune system
- Epitopes → small molecular domain of an antigen where antibodies recognize and bind to via Fab Receptors (Fc receptor bound to cell membrane)
- 

- Antigen presentation via Major Histocompatibility Complex (MHC)
    - Specialised integral membrane protein complexes on cell surfaces to which antigens/epitopes bind
    - Class 1
        - All nucleated cells express on cell membrane
        - Presents Intracellular/endogenous epitopes
        - Presents and recognised by CD8+ cytotoxic T lymphocyte
        - Results in apoptosis of cell
    - Class 2
        - Only found on Antigen Presenting Cells (APC)
        - Presents extracellular/exogenous epitopes
        - Presents and recognised by CD4+ Helper T lymphocyte
        - Results in activation of naive T helper cell

Antigen Presenting Cell (APC)

- Heterogenous group of cells that mediate cellular immune response
- Stimulates acquired immunity and is necessary for Acquired immunity
- Express MHC II molecules
- Presents Epitopes to CD4+ Helper T lymphocytes
- Cells
    - Macrophages
    - Dendritic cells
    - Langerhans cells
    - B lymphocytes

Antibodies

- GLycoprotein molecules Produced by plasma cells and B lymphocytes That interact to their respective antigens.
- B lymphocytes present Antigen on membrane
- Plasma cells secrete antibodies
- Variable region → determines binding specificity → Antibody's antigen binding site (Fab receptor)
- Constant region → determine immunological mechanism of action

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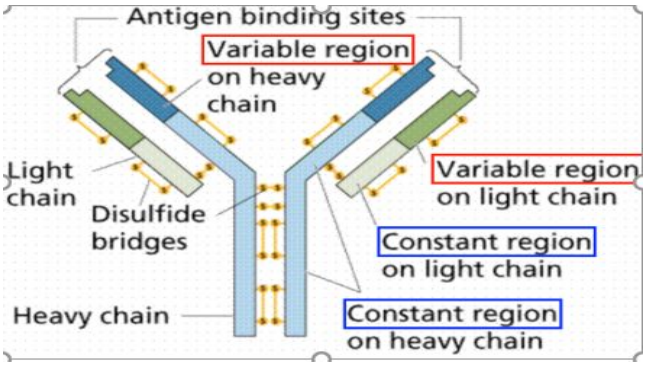
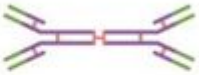
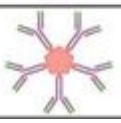
- 

- Classes of Antibodies
  - IgG → most common → passive immunity in newborns
  - IgM → Activates complement system when bound to antigen
  - IgA → Found in mucus, saliva, tears, Breast milk
  - IgD → Least abundant
  - IgE → Allergic reactions
Name	Properties	Structure
IgA	Found in mucous, saliva, tears, and breast milk. Protects against pathogens.	
IgD	Part of the B cell receptor. Activates basophils and mast cells.	
IgE	Protects against parasitic worms. Responsible for allergic reactions.	
IgG	Secreted by plasma cells in the blood. Able to cross the placenta into the fetus.	
IgM	May be attached to the surface of a B cell or secreted into the blood. Responsible for early stages of immunity.	
- Function of Ig in innate immunity
  - Complement system activation
  - Opsonisation → agglutination and identification of Antigens → allows receptors on Professional phagocytic cells to recognize and bind to antibodies attached to antigen → increases efficiency of phagocytosis
  - NK cell activation

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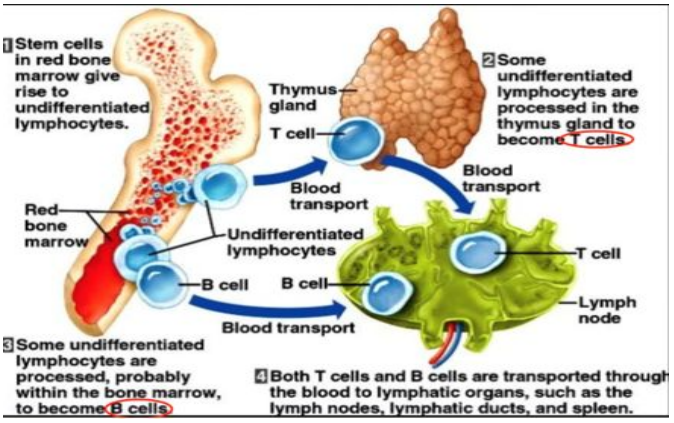
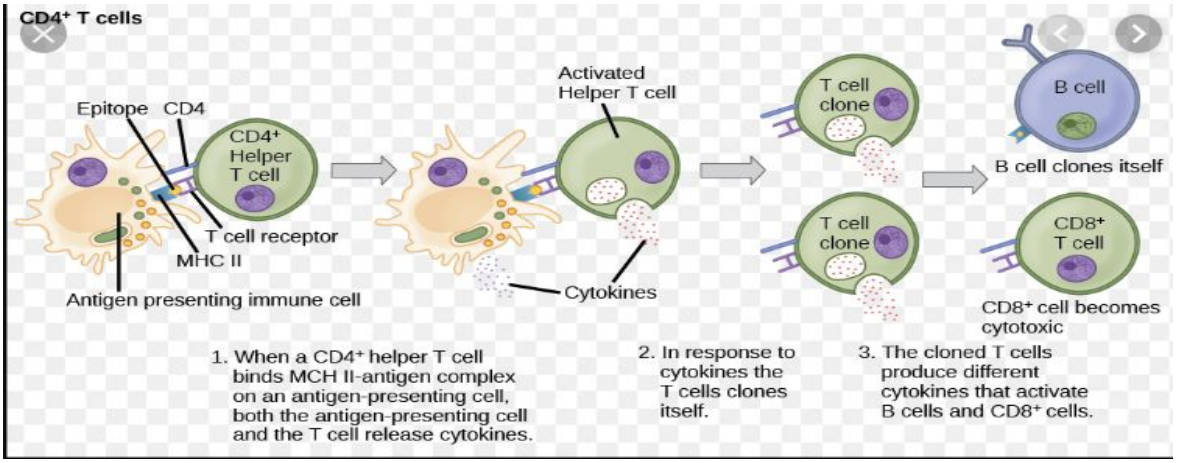
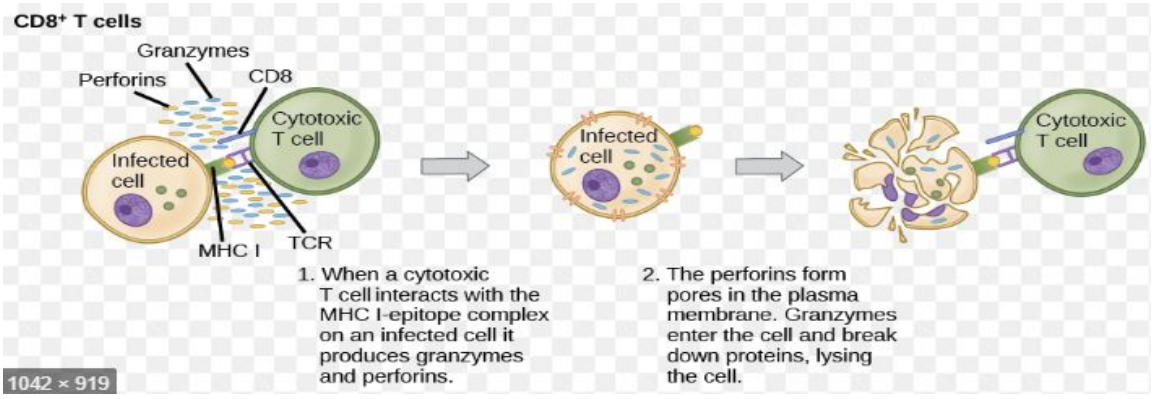
Cell Mediated immunity

- T lymphocytes
  - Must have direct contact with target for cell mediated immunity to function
  - 

  - T Cell maturation
    - Pluripotent stem cell in red bone marrow → undifferentiated Lymphocyte → Migrate to thymus → matures and differentiates into Naive T lymphocyte in thymus → become functional and immunocompetent (able to recognize antigens)
    - Induction of central tolerance → Deletion of self reactive helper and cytotoxic T lymphocytes → prevents autoimmunity → typically 99% deletion rate
  - Types of T cell
    - CD4+ Helper T Cell (need to know)
      - Majority of these (CD4/CD8 produced in clonal process)
      - Antigen filtered out of lymph, undergoes phagocytosis, degraded in lysosome → APC presents Epitope to Naive CD4+ T helper cell via MHC class II molecule → TCR of T cell binds to it → activation of T helper cell → expansion to undergo clonal process → clonal cells secrete cytokines which activate T and B cells
      - Promotes cytotoxic T cell activity via secretion of cytokines
      - Produce cytokines that promote activation of B lymphocytes



- CD8+ cytotoxic T cell (need to know)
  - Majority of these (CD4/CD8 produced in clonal process)
  - Target and destroy infected host cells → virus
  - Upon the TCR binding to MHC class I molecule with epitopes → Secrete perforins → perforins form pores in infected cell → undergoes Lysis



- Natural Killer T cell (need to know)
  - Like an NK cell but with T cell Receptors (TCR)
- Memory T cell
  - Small amount of these produced in clonal process
  - Important in immunological memory
  - Antigen binds to memory T cells → induced for rapid proliferation → allow for greater and quicker production of antibodies
- Regulatory T cell
  - Limits immune response by inhibiting multiplication
  - Responsible for stopping immune response

B lymphocytes

- Able to attack antigens at long distances via antibody and complement systems
- Development of B cells
  - Develop in red bone marrow
  - Pluripotent stem cells in red bone marrow differentiate into undifferentiated lymphocytes → differentiate and mature into B cells → become functional and immunocompetent (able to recognize antigen)
  - Undergoes clonal process when activated → expands and undergoes mitosis of clones that all recognize antigen → 90% effector (produce antibodies and some differentiate into plasma cells) and 10% memory B cells
- Mechanism of action
  - Antigen presentation to T helper cell by APC → activation of T cell → secretion of cytokines → activation of B cells → expansion and undergoes clonal process → 90% effector (produce antibodies and some differentiate into plasma cells) and 10% memory B cells

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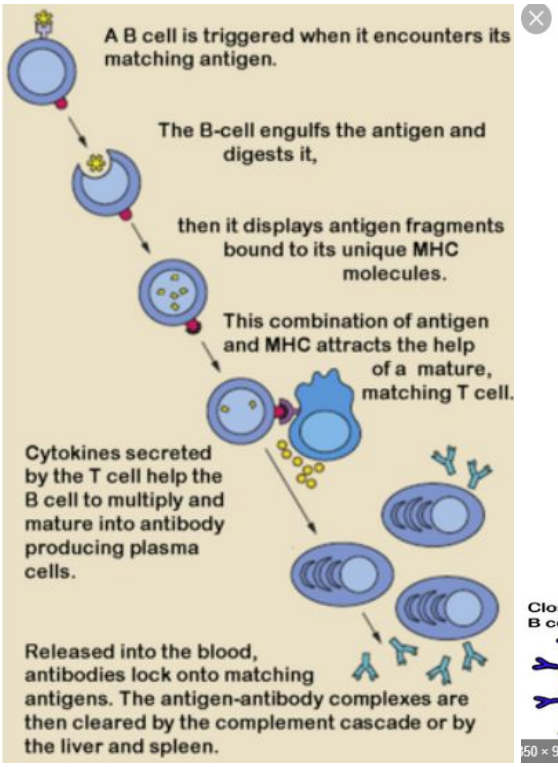

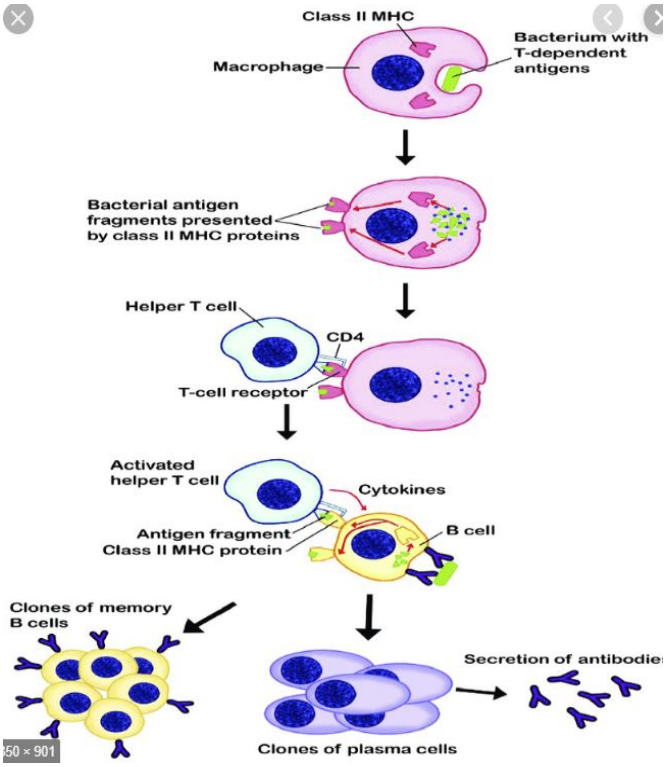

Immunological memory

- Created from primary exposure to specific antigen
- Memory T/B cells
    - Circulate around the body for long periods of time (years) → Upon exposure to specific antigen → Acquired immunological response is rapid
    - Memory cells exposed to specific antigen → Differentiation into effector cells → quick immune response (known as secondary exposure/response)

Artificial immunity

- Types
    - Live attenuated vaccines
        - Weakened versions of pathogens
        - Mimic immunity attained from live infection
        - Stronger cellular and antibody response
        - Contain adjuvants → Enhance magnitude of immune response + Modulate quality + Produces local reactions (fever/chills)
    - Subunit vaccines
        - Fragments of pathogen
        - Surface protein e.g epitope
        - Contain adjuvants → Enhance magnitude of immune response + Modulate quality + Produces local reactions (fever/chills)
- Antigen specific to infectious disease injected into body → initial exposure to pathogen, primary acquired response → production of memory cells → Secondary exposures to antigen result in quicker immune response times
- Herd immunity
    - Critical vaccinated Percentage for it to function ~90%
    - Serve to protect non-immunised individuals by preventing spread of disease

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Autoimmune diseases

- Defective immune system → central tolerance not functioning well → proliferation of self recognizing cells
- Results in damage of own tissues and organs (autoantibodies, self recognizing antibodies cause damage and disease)
- Classification
    - Type 1 → allergic reaction
    - Type 2 → transfusion reaction
    - Type 3 → immune complexes
    - Type 4 → delayed → transplant + dermatitis
- Immediate hypersensitivity
    - Allergic hypersensitive reaction
    - Excessive immune response due to harmless antigen
    - Involves → mast/B/CD4+ helper cells and IgE
    - Results in hives/urticaria, in severe cases of anaphylactic shock → mass degranulation of all mast cells → swelling → can be fatal if airways compromised