

BIO 359: IMMUNOLOGY

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INTRODUCTION

Course

- **Types of Immunity**
 - Innate: Non-specific physiological and cellular barriers
 - Adaptive Immunity - Characteristics
- **Cells & Organs of Immune System**
- **Immune Response**
 - Primary and Secondary Immune response
 - Humoral Immune response
 - B cell development and function
 - Cell-mediated immune response
 - T cell development and function

INTRODUCTION

- **Antigens and Antibodies**
 - Antibody types, structure and function
 - Antigen-antibody interactions: Affinity, avidity, cross reactivity, Precipitation reaction
- **Recognition and killing mechanisms**
 - Immune cell receptors/recognition of targets
 - APC and MHC structure and function
 - Complement system
 - Immune Evasion/Tolerance

INTRODUCTION

- **Dynamics of Immune responses**
 - Immunity to bacteria
 - Immunity to viruses
 - Immunity to fungus
 - Immunity with parasites

INTRODUCTION

- **Malfunction of Immune Response**
 - Immunodeficiencies
 - Hypersensitivity
 - Autoimmunity
 - Transplant
 - Immunology of cancer
 - HIV Immunology

INTRODUCTION

- **Immuno-techniques**
 - Radial immune diffusion, Ouchterlony double diffusion
 - Agglutination reaction, agglutination titer, incomplete agglutin
 - Complement fixation
 - ELISA
 - Immunocytochemistry

INTRODUCTION

- **Clinical Immunology**
 - Vaccines-Types and application
 - Polyclonal antibodies and monoclonal antibodies
 - Alloantigens-Immunohaematology, Blood groups and blood grouping.A, B, Rh antigens and antibodies, Rh typing Bombay group.

COURSE OUTCOMES



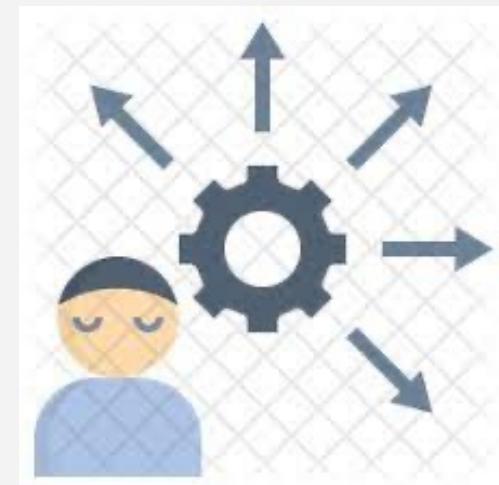
At the end of the course, you will be required to:

- Understand the basic concepts of immunology
- To appreciate the types and how components of the immune system work to protect against development of clinical disease.
- The basic systems and cells involved in immune responses.



COURSE OUTCOMES

- Know the various components of the immune systems to allow an understanding of the concepts of innate and adaptive responses, and how these responses interact with one another to form the basis for protection against disease
- Explain the concept of immune response and abnormalities of the immune system
- Know some of the applications of the concept of immunology



ATTENDANCE AT LECTURES

- Attendance at lectures is an integral part of the requirements of assessment for the course
- However, if any student absents herself/himself for a cumulative total of three (3) lecture periods before mid-semester, she/he will not be eligible to write both the mid-semester and end of semester examinations or will not be eligible to write the end of semester examination if this occurs after the mid-semester examination



Attendance
Tracking

EVALUATION AND GRADING

Evaluation

1. Attendance and Participation in Lectures ---- 5%
2. Assignment/presentation/Termpaper ---- 5%
3. Mid-semester examination ---- 20%
4. Final Examination ---- 70%



EVALUATION AND GRADING

GRADING

70–100%

A

Excellent

60–69%

B

Very Good

50–59

C

Good

40–49

D

Pass

0–39

F

Fail

I / I*

Incomplete

- Pass mark for the course is 40%.

READING OR REFERENCE MATERIALS

BIO359: IMMUNOLOGY

BACKGROUND

BACKGROUND

- Immunology may be described as physiologic processes that provide the host with the capacity to recognize materials as foreign to itself and to neutralize, eliminate, or metabolize them with or without injury to its own tissue(s)

BACKGROUND

- The immune system is made up of cells, tissues and their soluble products that recognizes, attacks and destroys agents that could be harmful to the health of an individual or organism.
- The Latin term **immunitas**, meaning “exempt,” gave rise to the English word immunity, which refers to all the mechanisms used by the body as protection against environmental agents that are foreign to the body.
 - microorganisms or their products, foods, chemicals, drugs, pollen, or animal hair etc.

BACKGROUND

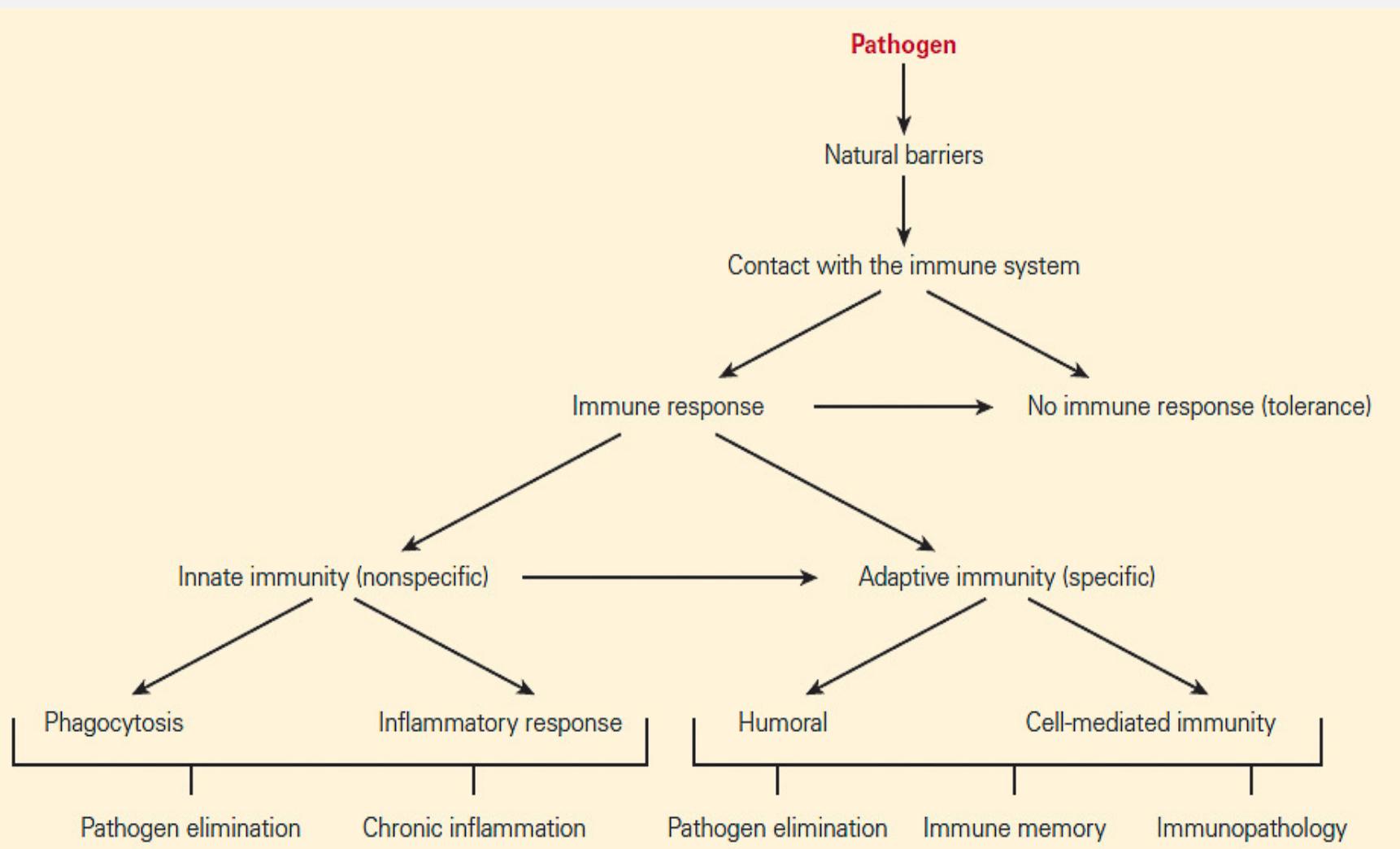
- Some foreign agents, such as the allergens found in house dust, mite, cat litter, grass or flower pollen can cause a disease as a consequence of inducing an immune response
- Likewise some individuals mount immune responses to their own tissues as if they were foreign agents. Thus, the immune response can cause the autoimmune diseases common to man such as multiple sclerosis, diabetes
- Most individuals do not suffer from autoimmune disease because they have developed tolerance towards their own (self) tissues.

BACKGROUND

Immune Response

- A normal healthy person's body always strives to maintain homeostasis, a natural state of balance of all its organs and the nervous and circulatory systems
- When this homeostasis is disturbed by trauma, pathogens, or the deregulation of body cells (as in cancer), the immune system responds in an attempt to restore balance.

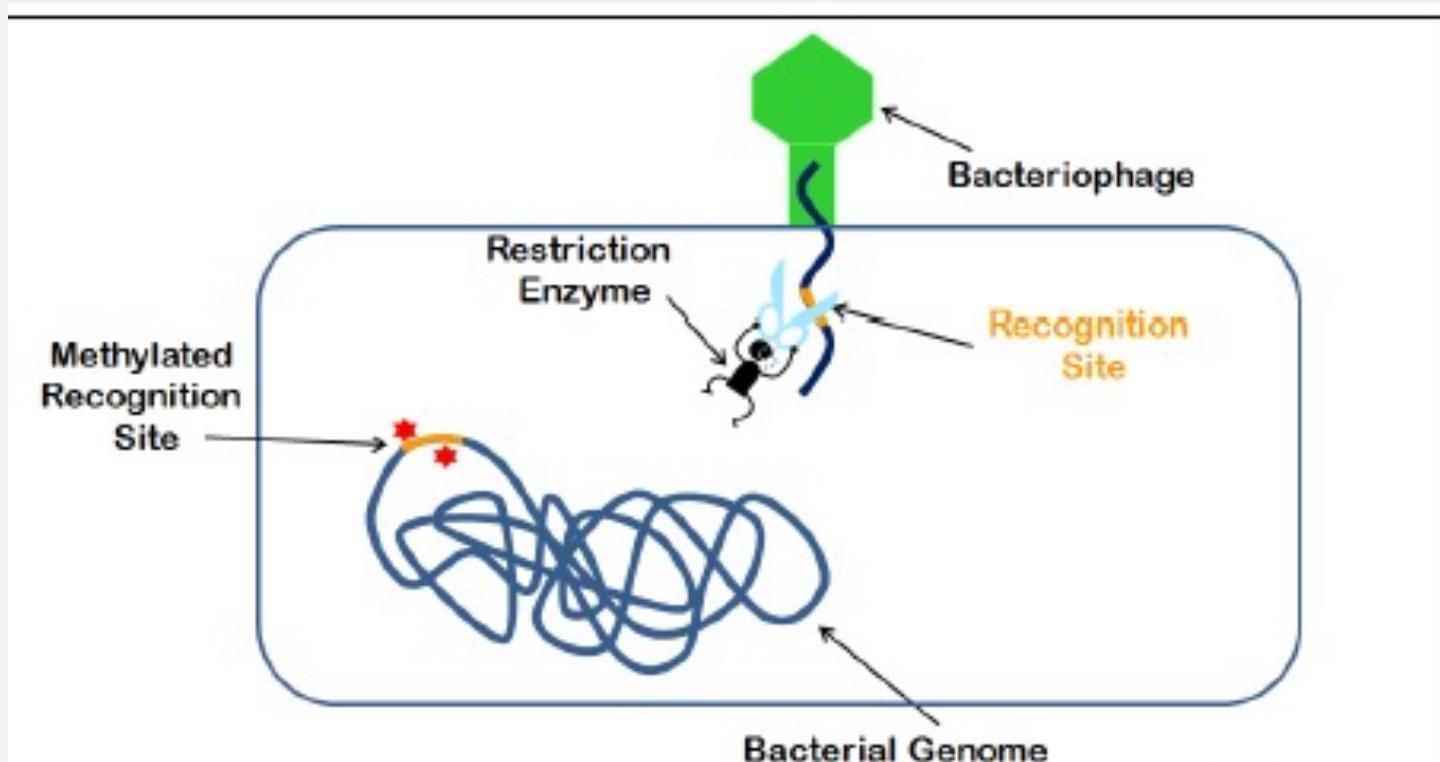
BACKGROUND



IMMUNOLOGY & Evolution

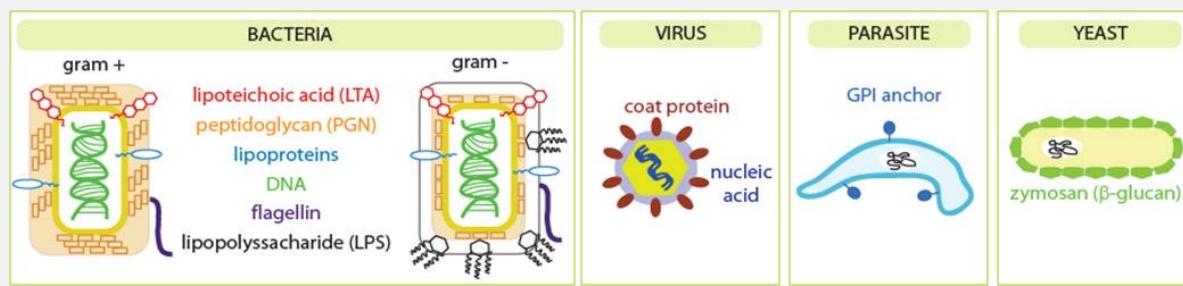
- Immune systems appear in the structurally most simple forms of life
 - eg. bacteria using restriction modification system to protect themselves from bacteriophages
- Some prokaryotes are able to have adaptive immunity, using CRISPR sequences.
 - They are able to retain genetic fragments of phages, this allows them to block virus replication through a form of RNA interference.
- Unicellular eukaryotes secrete offensive elements that form their immune systems, prevent invasion

IMMUNOLOGY & Evolution



IMMUNOLOGY & Evolution

- Defensins, the complement proteins and phagocytic cells are used by most **invertebrates**
- **Insect defence mechanisms:** hard exoskeleton, antimicrobial peptides, haemocytes (including granulocytes, plasmacytocytes, spherulocytes etc.)
- All organisms use “pattern recognition receptors” (PRR’s) to identify molecules associated with pathogens



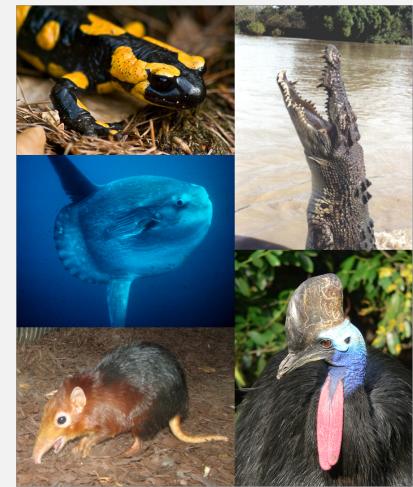
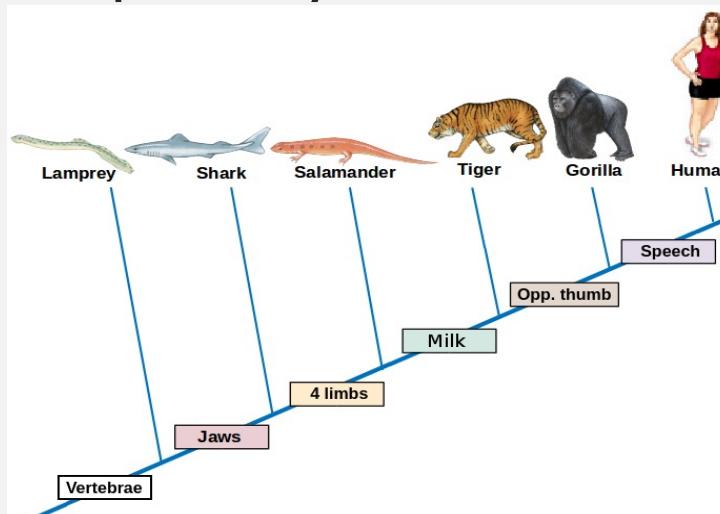
IMMUNOLOGY & Evolution

- Classical molecules of the adaptive immune system (eg. immunoglobulins and T-cell receptors) exist only in jawed vertebrates.
 - However, jawless vertebrates (eg. lamprey and hagfish) have primitive distinct lymphocyte-derived molecules; **variable lymphocyte receptors (VLRs)**



IMMUNOLOGY & Evolution

- Adaptive immune system occurred in ancestors of the jawed vertebrates.
- These molecules are believed to have evolved into antibodies, since they bind pathogenic antigens in a similar way and with the same degree of specificity



HISTORY

HISTORY

- The concept of immunity dates back at least as far as 430 BCE where the plague of Athens was described as being responsible for the death of more than a quarter of the Athenian population

HISTORY

- Explanation for why some developed disease and others did not:
 1. Moralistic or religious view or the seed theory
 2. The seed theory (Girolamo Fracastoro (1478 to 1553)): disease was caused by seminaria ("seeds") that could be transmitted by three ways:
 - direct contact from one person to another;
 - through "fomites," or articles of clothing or dirty linen;
 - and through the air.

HISTORY

Koch's Postulates:

Robert Koch established 4 criteria to identify the causative agent of a particular disease:

- The microorganism or other pathogen must be present in all cases of the disease.
- The pathogen can be isolated from the diseased host and grown in pure culture
- The specific disease must be reproduced when a pure culture of the bacteria is inoculated into a healthy susceptible host
- The pathogen must be re-isolated from the new host and shown to be the same as the originally inoculated pathogen

HISTORY

Louis Pasteur

- 1880, Worked on chicken cholera, where weakened bacteria had caused the chickens to become immune to the disease, though they had caused only mild symptoms.
- 1882, he applied this immunization method to anthrax, which affected cattle
- 1883, Pasteur obtained a vaccine for swine erysipelas, by identifying the bacillus that caused the disease, passed it through pigeons, and further passing the bacillus through rabbits, to weaken it
- 1885, produced the first vaccine for rabies by growing the virus in rabbits, and then weakening it by drying the affected nerve tissue

HISTORY

Vaccination was also carried out for centuries without any fundamental understanding of its basis in the 10th century

- Smallpox was endemic in China.
- “Variolation” was practiced by exposing healthy people to material from the lesions caused by the disease, either by putting it under the skin, or inserting powdered scabs from smallpox pustules into the nose.
 - Unfortunately, because there was no standardization of the inoculum, variolation occasionally resulted in death or disfigurement from smallpox, thus limiting its acceptance.

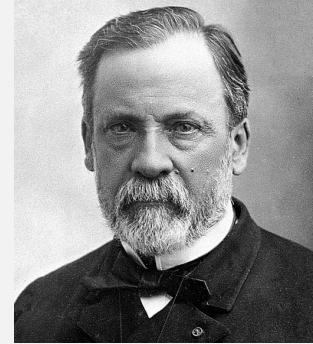


HISTORY

- Benjamin Jesty, an English farmer, first inoculated his wife and two sons with material taken from the cowpox lesion of the udder of a cow in his neighbour's herd
- 1840, Edward Jenner (physician) performed a scientific experiment by an 8-year-old boy, with material obtained from a cowpox lesion that appeared on the hand of a dairymaid . Six weeks later, he inoculated the experimental subject with smallpox without producing disease
- He publish the efficacy of his vaccination procedure and use of a safe alternative to variolation (public health)



HISTORY



Louis Pasteur:

- Infectious microbial diseases could be both prevented and treated via immunology
- Introduced the **concept that vaccination** could be applied to any microbial disease
 - reported methods as to how the virulence of microbes could be attenuated so that live microbes could be used to make prophylactic vaccines that could be made in the laboratory and manufactured in unlimited quantities for use worldwide.
- Introduced the concept of therapeutic vaccines, where post-infection prophylaxis could be used to treat individuals who were exposed to a virulent organism, and if applied soon enough after infection, clinical disease and death could be averted

HISTORY

- Pasteur and Koch led the establishment of research institutes that bore their names, out of which was born many scientist
 - 1880, Elie Metchnikoff established the “phagocytosis theory” and inflammation
 - **innate immunity.**
 - Addison and Waller also discovered pus cells are leukocyte and they migrate through capillaries in response to local injury

HISTORY

- Other discoveries showed that toxins alone derived from diphtheria bacilli could reproduce the symptoms of diphtheria;
 - 1890: Behring & Kitasato: Discovered that antibodies prepared against diphtheria toxin could neutralize its toxicity
 - humoral immunity to diphtheria and tetanus and the passive transfer of immunity to diphtheria in animals
- Alexin which was renamed "complement" by **Ehrlich**, as it "complemented the activity of antibodies (1900)
 - the ability of humoral components alone to lyse bacteria or erythrocytes in the absence of phagocytosis

HISTORY

- **Paul Ehrlich** histochemical investigations led to the identification of mast cells, neutrophils, eosinophils and basophils as well as the diagnosis of *his own case* of pulmonary tuberculosis
- His research on how antibody is formed and "selected for" by antigen brought the 'side chain theory'
 - The relationship between toxin and antitoxin are *strictly specific*
 - Thus enter into a *chemical bond* fitting each other like lock and key

TYPES IMMUNITY

IMMUNE RESPONSE

Types of Immune Response

- The mammalian immune system can mount two types of responses:
 - Innate response is triggered by disruptions to homeostasis caused by either non-infectious or infectious means
 - Adaptive response that is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogen growth

IMMUNE RESPONSE

Mechanisms Underlay Immune Responses:

Immune responses involve:

- I. The actions of cells that destroy or remove unwanted material from the body.
 - **cell-mediated immunity**
 - The cells responsible for cell-mediated immunity are collectively called leukocytes or white blood cells.

IMMUNE RESPONSE

2. Soluble molecules in the serum of the blood that directly eliminate foreign entities without the need for cellular involvement.
 - **humoral immunity**, a term derived from the historical description of body fluids as “humors.”
 - The soluble molecules responsible for humoral immunity are proteins called antibodies, and antibodies are secreted by a particular type of leukocyte. In this case a B cell (plasma cell).

IMMUNITY

The principles of immune response include:

- Elimination of many microbial agents through the nonspecific protective mechanisms of the innate immune system
- Cues from the innate immune system inform the cells of the adaptive immune system as to whether it is appropriate to make a response and what type of response to make

IMMUNITY

The principles of immune response include:

- Cells of the adaptive immune system display exquisitely specific recognition of foreign antigens and mobilize
- Potent mechanisms for elimination of microbes bearing such antigens
- The immune system displays memory of its previous responses
- Tolerance of self-antigens.

INNATE IMMUNE RESPONSE

**(NON-SPECIFIC PHYSIOLOGICAL
AND CELLULAR BARRIERS)**

BCHEM 471

CHARACTERISTICS OF THE INNATE IMMUNE RESPONSE

- Barrier Defense
- Complement Activation
- Pattern Recognition
- Inflammation
- Phagocytosis

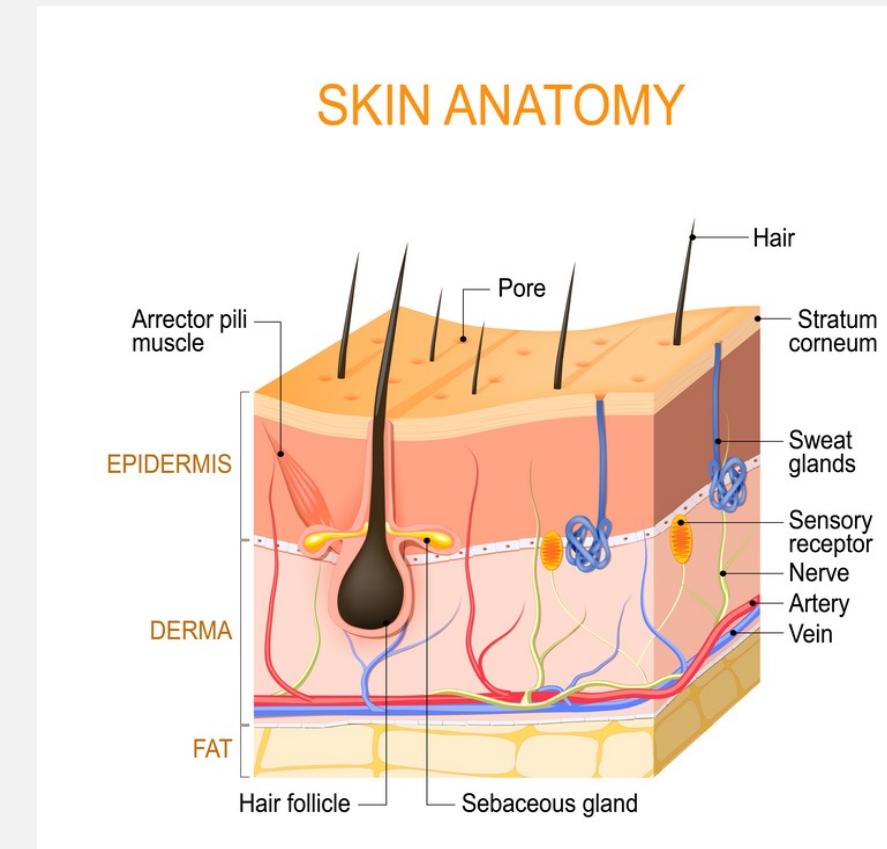
ANATOMICAL BARRIERS

- Physical barriers prevent pathogens from entering the body, have characteristics that destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues.
- Barrier defences are part of the body's most basic defence mechanisms that are not a response specifically to infections, but they are continuously working to protect against a broad range of pathogens.

ANATOMICAL BARRIERS

Skin (Intact, unbroken)

- The skin usually bars invading microorganisms unless it is physically disrupted (eg, injury)
- The skin is covered with a layer of dead, keratinized epithelium that is too dry for bacteria to grow

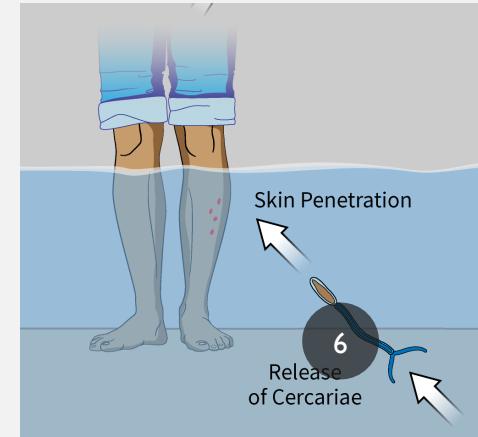
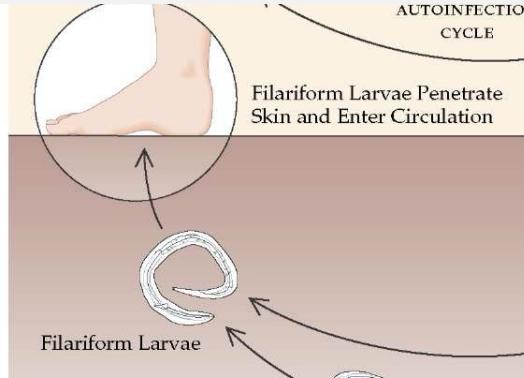


ANATOMICAL BARRIERS

- Skin cells continuously wear off from the skin, they carry away bacteria and other pathogens attached with them
- Sweat and other skin secretions may lower pH, contain toxic lipids and physically wash microbes away

ANATOMICAL BARRIERS

- Exceptions include the following:
 - Human papillomavirus, which can invade normal skin, causing warts
 - Some parasites (eg, *Schistosoma mansoni*, *Strongyloides stercoralis*)
 - Staphylococcus epidermidis* (normal flora of the skin)



ANATOMICAL BARRIERS

Mucous membranes

- Layers of mucosal cells line body cavities that open to the outside (digestive, genitourinary and respiratory tracts)
- The mucus layer covering the mucosal epithelium acts as a first physical and biochemical barrier
- Is made up of tightly interlaced cell-to-cell network of epithelial cells and intraepithelial lymphocytes

ANATOMICAL BARRIERS

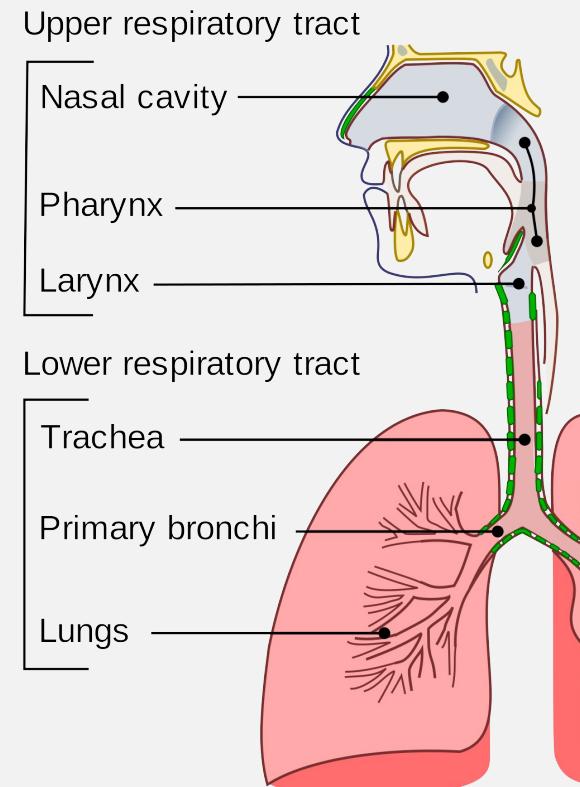
- Mucosal cells produce mucus : contains antimicrobial substance such as lysozymes, lactoferrin (sequester iron)
 - Mucosal cells are rapidly dividing → flush out of body along with attached bacteria
- Local secretions also contain immunoglobulins, principally IgE and secretory IgA, which prevent microorganisms from attaching to host cells.

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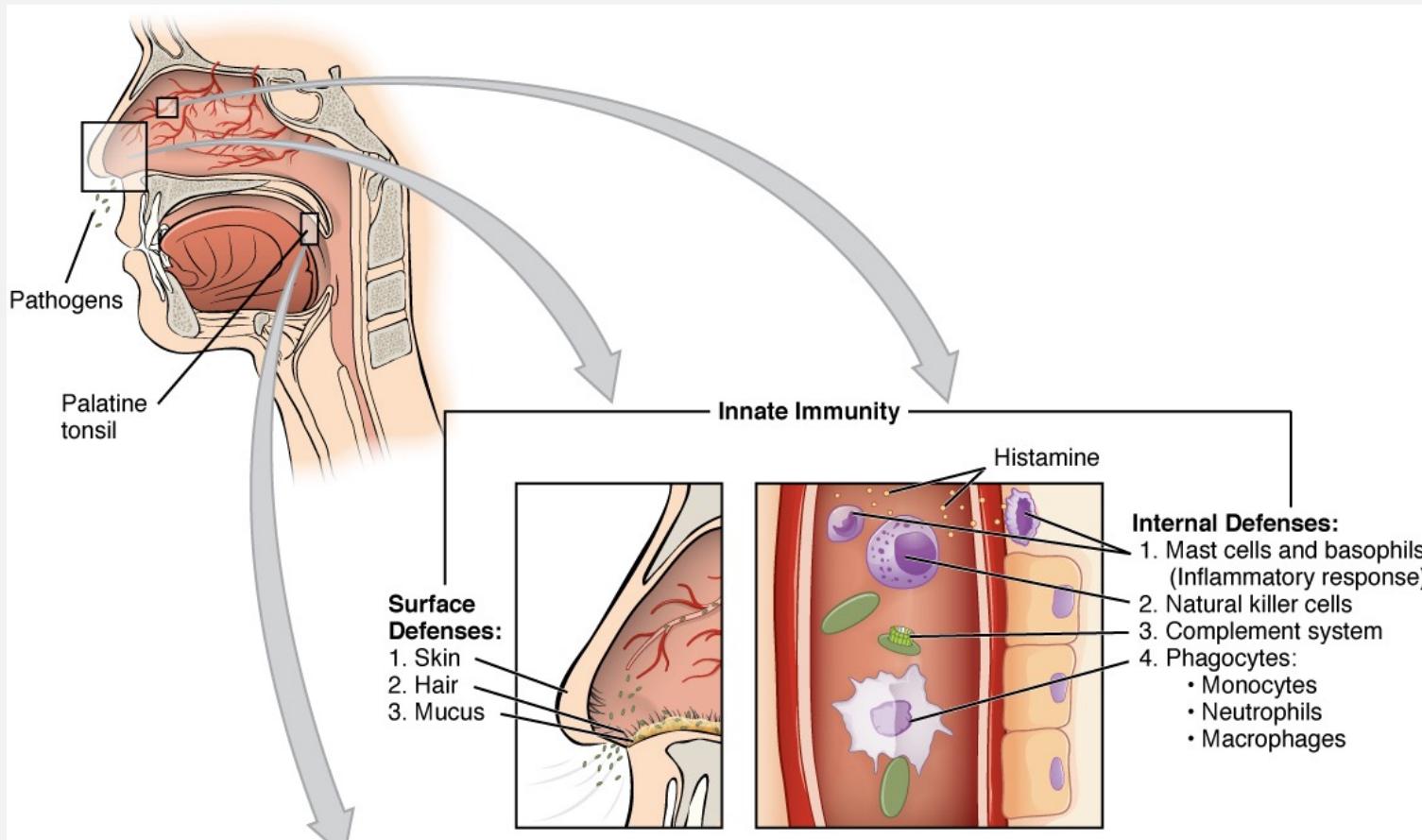
ANATOMICAL BARRIERS

Respiratory tract

- Nose - nasal hair, mucus secretions (phagocytes and antibacterial enzymes), irregular chambers
- The respiratory tract has upper airway filters. Mucociliary epithelium transports pathogens away from the nasal cavity, sinuses, bronchi and trachea
- Coughing also helps remove organisms.

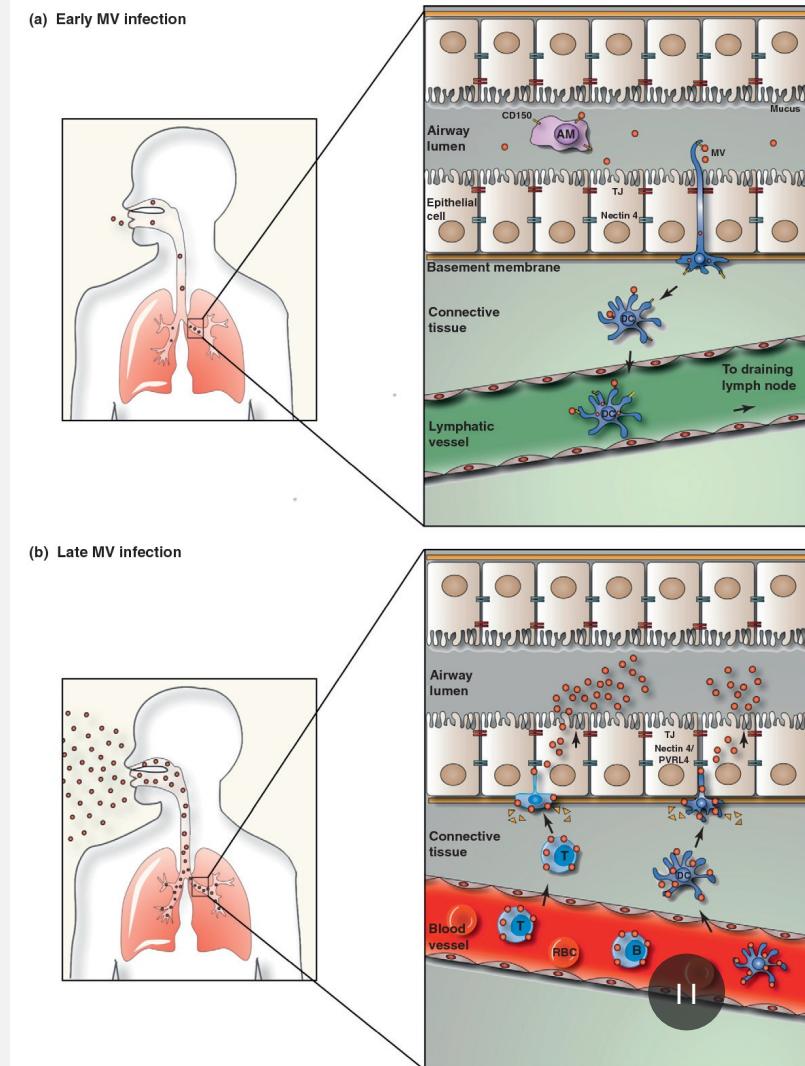


RESPIRATORY SYSTEM



ANATOMICAL BARRIERS

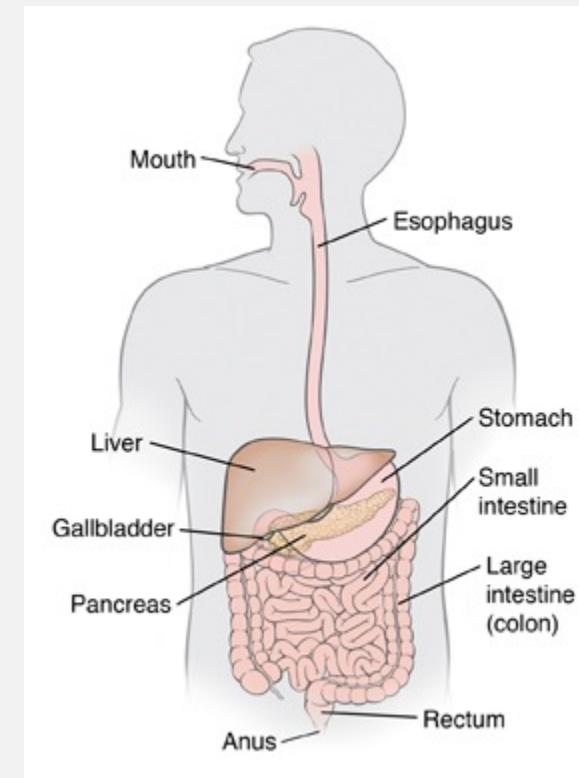
- If the organisms reach the alveoli, alveolar macrophages and tissue histiocytes engulf them
- However, these defenses can be overwhelmed by large numbers of organisms or by compromised effectiveness resulting from air pollutants (eg, cigarette smoke)



ANATOMICAL BARRIERS

Gastrointestinal tract (Digestive tract)

- Saliva from the mouth contains lysozyme
- Stomach acids and antibacterial activity of pancreatic enzymes, bile(alkaline) and intestinal secretions
- Peristalsis and the normal loss of epithelial cells remove microorganisms.
 - If peristalsis is slowed (eg, because of drugs), this removal is delayed and prolongs some infections such as symptomatic shigellosis.

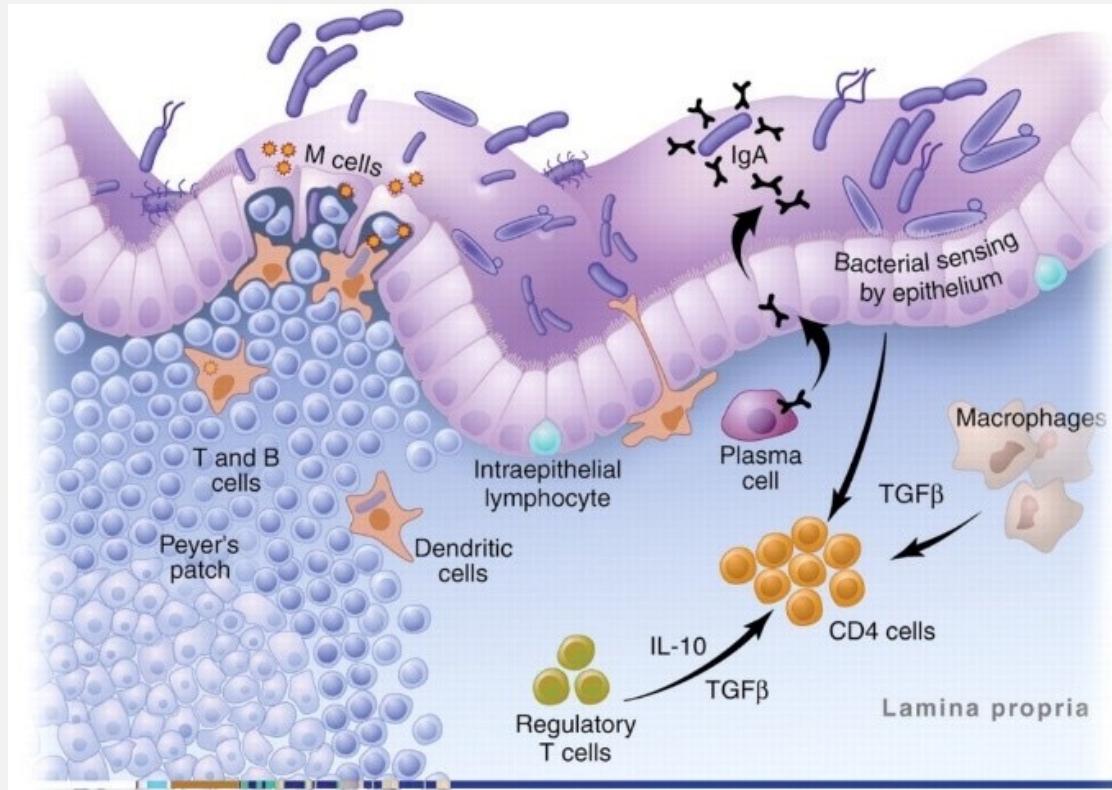


ANATOMICAL BARRIERS

- Compromised GI defense mechanisms may predispose patients to particular infections (eg. achlorhydria predisposes to salmonellosis).
- Normal bowel flora can inhibit pathogens; alteration of this flora with antibiotics can allow overgrowth of inherently pathogenic microorganisms (eg, *Salmonella Typhimurium*) or superinfection with ordinarily commensal organisms (eg, *Candida albicans*).
- Defecation (feces contains up to 50% bacteria)
- Mucus contain antibacterial agents, antibodies and immune cells called phagocytes

ANATOMICAL BARRIERS

Gastrointestinal tract



ANATOMICAL BARRIERS

Genitourinary tract

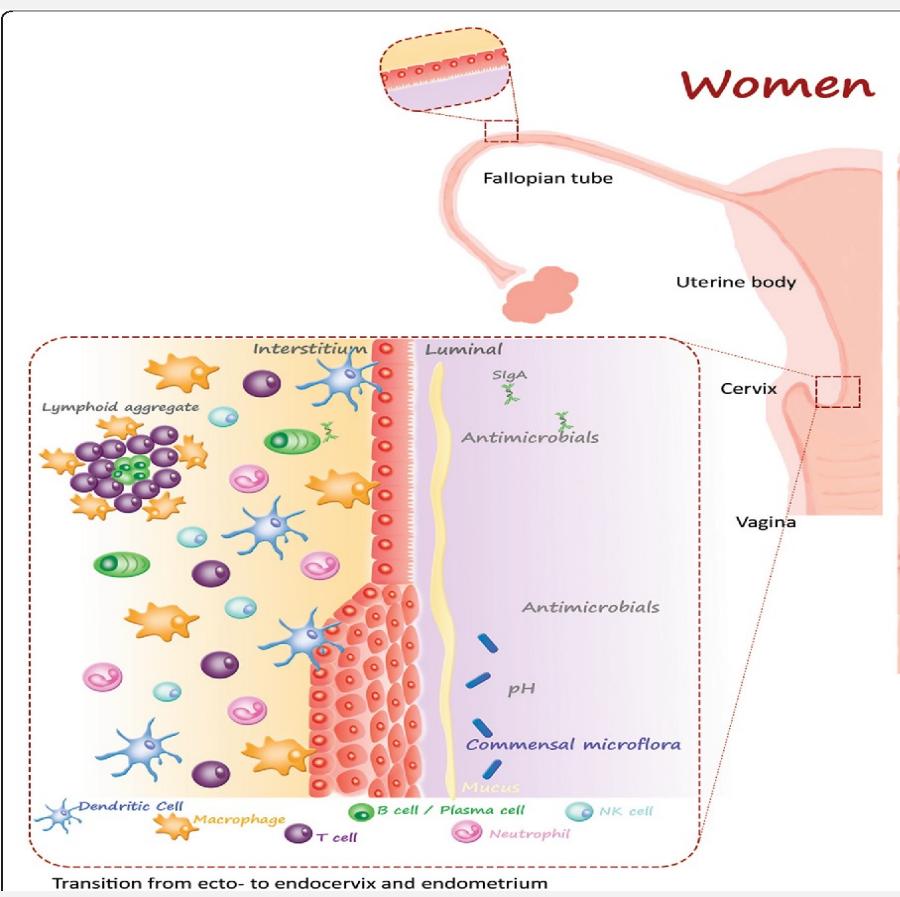
- Flushing mechanisms of sterile urine and the acidity of urine maintain the bladder and most of the urethra free of microorganisms
- Secretions of both female and male genital tracts contain more IgG and secretory IgA
- GU tract barriers include the length of the urethra (20 cm) in men.

ANATOMICAL BARRIERS

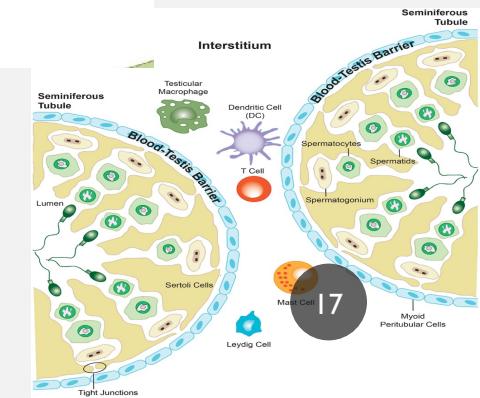
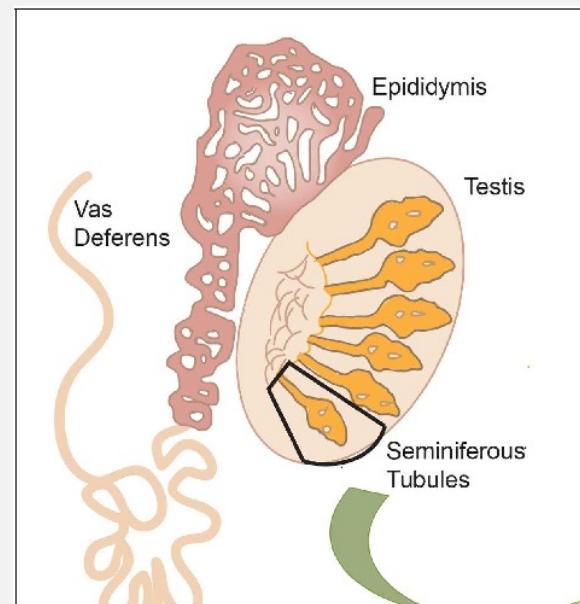
- The vaginal epithelium of the female maintains a high acidic pH.
- *Lactobacillus acidophilus* whose acidic end products of metabolism (lactic acid) prevent colonization by most other types of microorganisms including pathogenic yeast (*Candida albicans*)

ANATOMICAL BARRIERS

The genitalia



MEN



ANATOMICAL BARRIERS

Eyes

- Blinking of eyelids through the corneal nerves sensory relay remarkably free of most microorganisms, mechanically removes microbes
- Tears flush foreign particles from the ocular surface, and transport antimicrobial proteins (lactoferrin, lysozyme, lipocalin, and beta-lysin) and immunoglobulins to the ocular surface to prevent infections

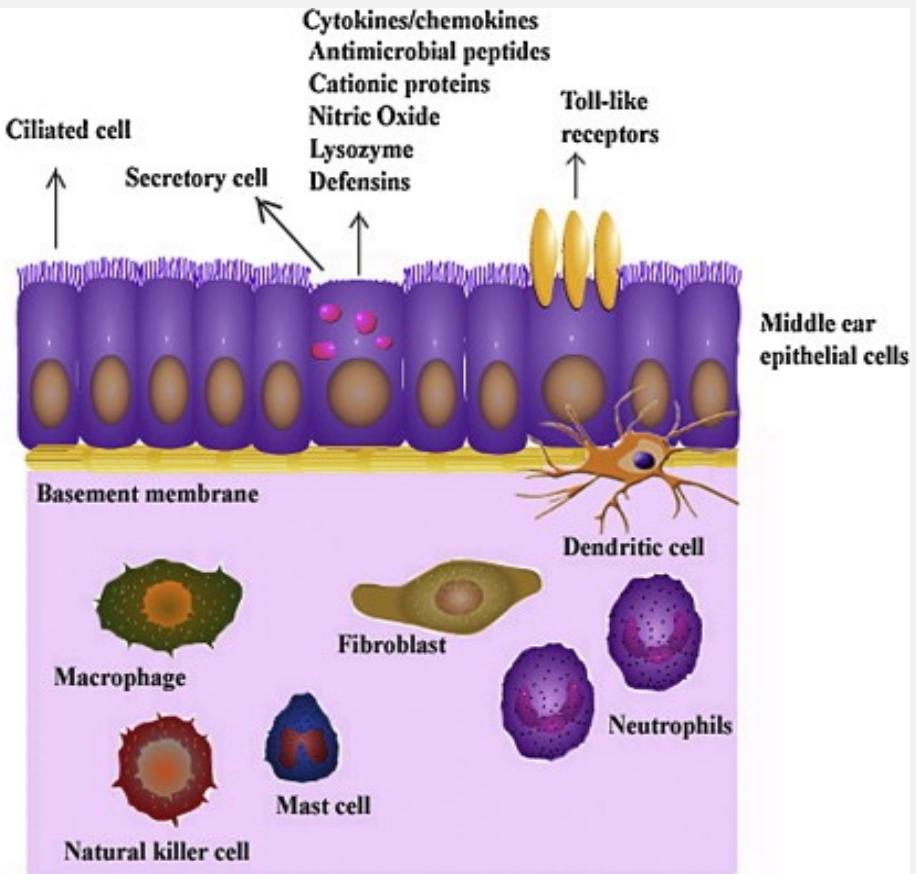
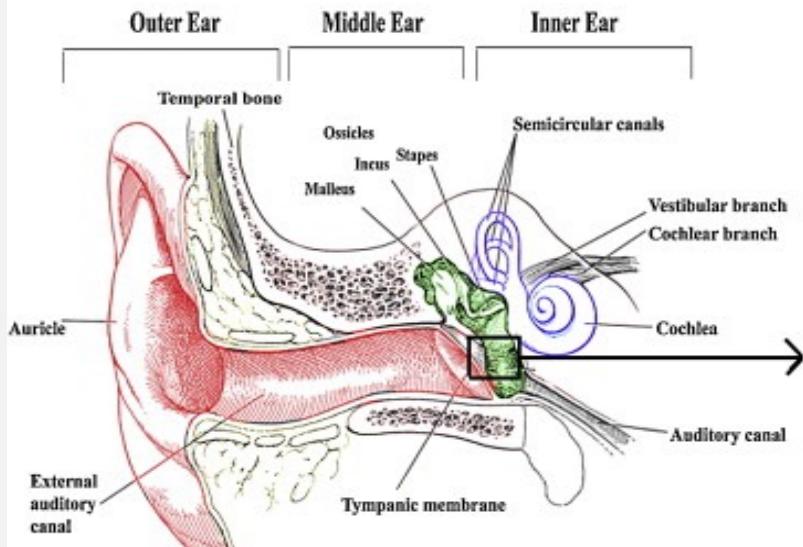
ANATOMICAL BARRIERS

- Immunoglobulins in tears, Ig A binds to bacteria and prevents bacterial adherence to epithelium.
- Corneal epithelial cells secrete cytokines to activate immune defenses to protect against microbial invasion

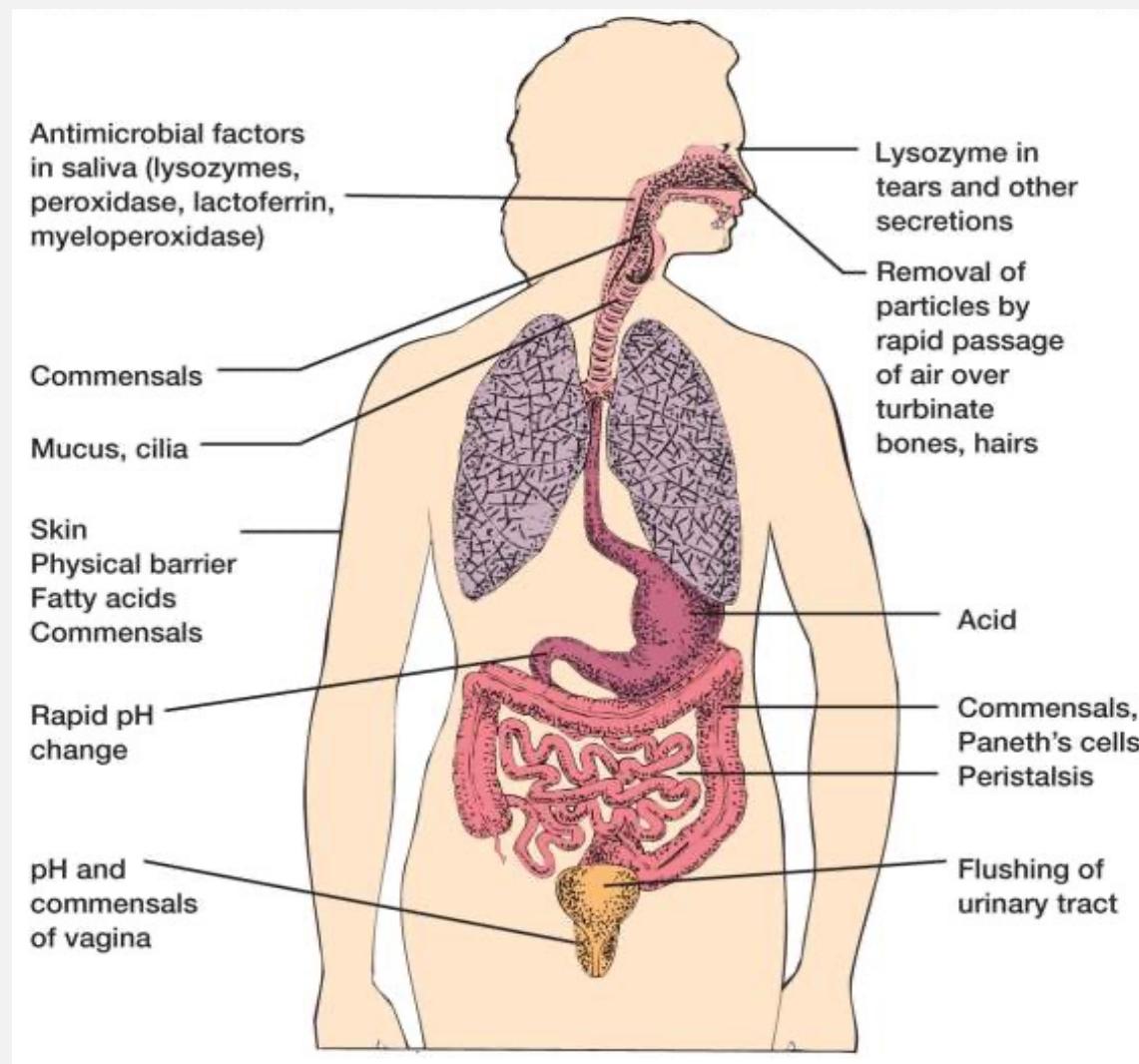
Outer ear canal

- Wax contains antibacterial components
- Inner ear contain tissue Monocytes and macrophages

ANATOMICAL BARRIERS



SUMMARY



ANATOMICAL BARRIERS

Microbial antagonism

- **Competition with non-indigenous species for binding (colonization) sites.** The **normal flora** are highly-adapted to the tissues of their host.
 - That is why they are there
- **Specific antagonism against non-indigenous species.** Members of the normal flora may produce very specific proteins called **bacteriocins** which kill or inhibit other (usually closely-related) species of bacteria

ANATOMICAL BARRIERS

- **Nonspecific antagonism against non-indigenous species.** The normal flora produce a variety of metabolites and end products that inhibit other microorganisms. These include fatty acids (lactate, propionate, etc.), peroxides and antibiotics.

PHYSIOLOGICAL & CHEMICAL BARRIERS

- Once beyond the protective outer barrier of the body, the invading microorganisms encounter a series of **nonspecific chemical and cellular defense mechanisms**

Mechanisms:

- Inflammation** – a series of events that removes or contain the offending agent and repair the damage tissues
- Chemotaxis** – movement of cells toward a chemical influence (chemokines or chemotactic agents)

PHYSIOLOGICAL & CHEMICAL BARRIERS

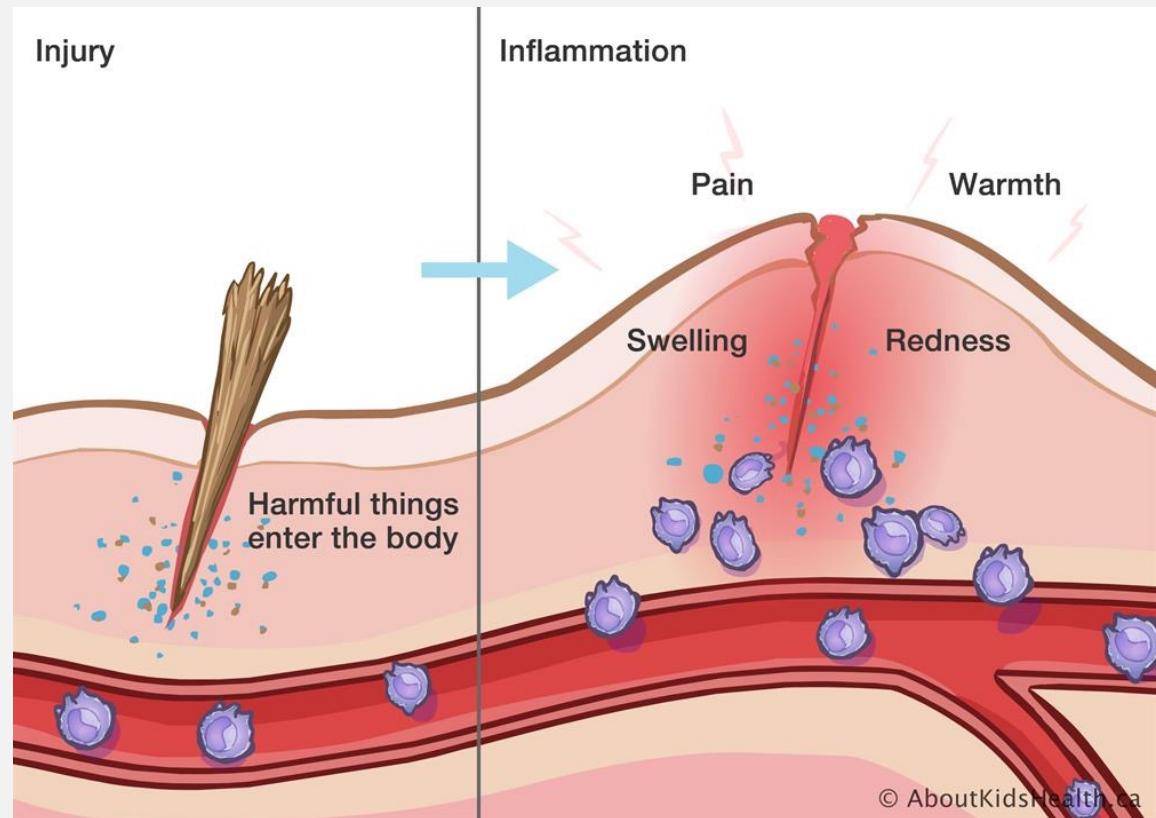
- **Phagocytosis** – process in which cell ingest foreign particulate matter e.g. microbes
- Many are carried out by the white blood cells in blood

PHYSIOLOGICAL & CHEMICAL BARRIERS

- Inflammatory response directs immune system components to injury or infection sites

Four main signs:

- Redness
- Heat
- Swelling
- Pain

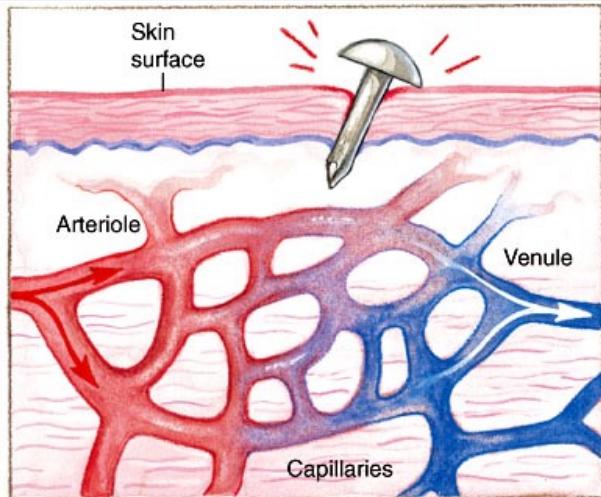


INFLAMMATION

- **Major events:**
 - Vasodilation
 - Increase permeability of capillaries
 - Mobilization of chemotactic peptides, neutrophils and mononuclear cells to site of injury (chemotaxis & emigration)
 - Phagocytosis
- Primary functions:
 - Localize infection
 - Neutralize toxins at injury site
 - Repair damage tissue

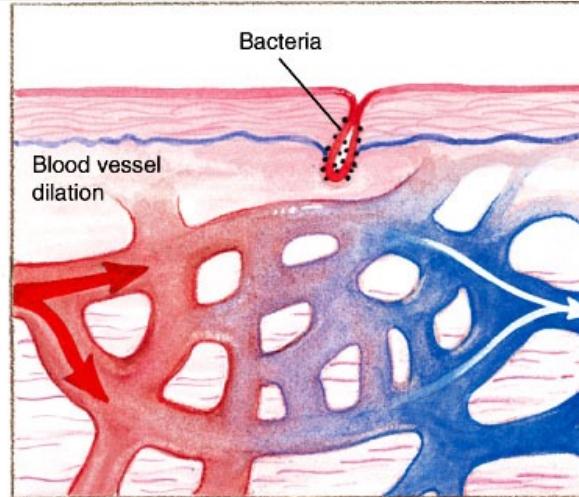
Inflammation process

trauma or infection

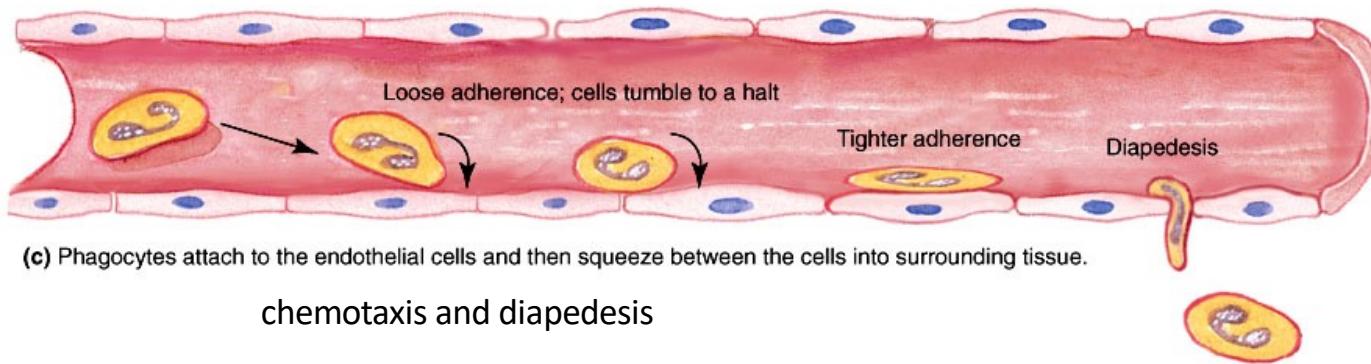


(a) Normal blood flow in the tissues as injury occurs.

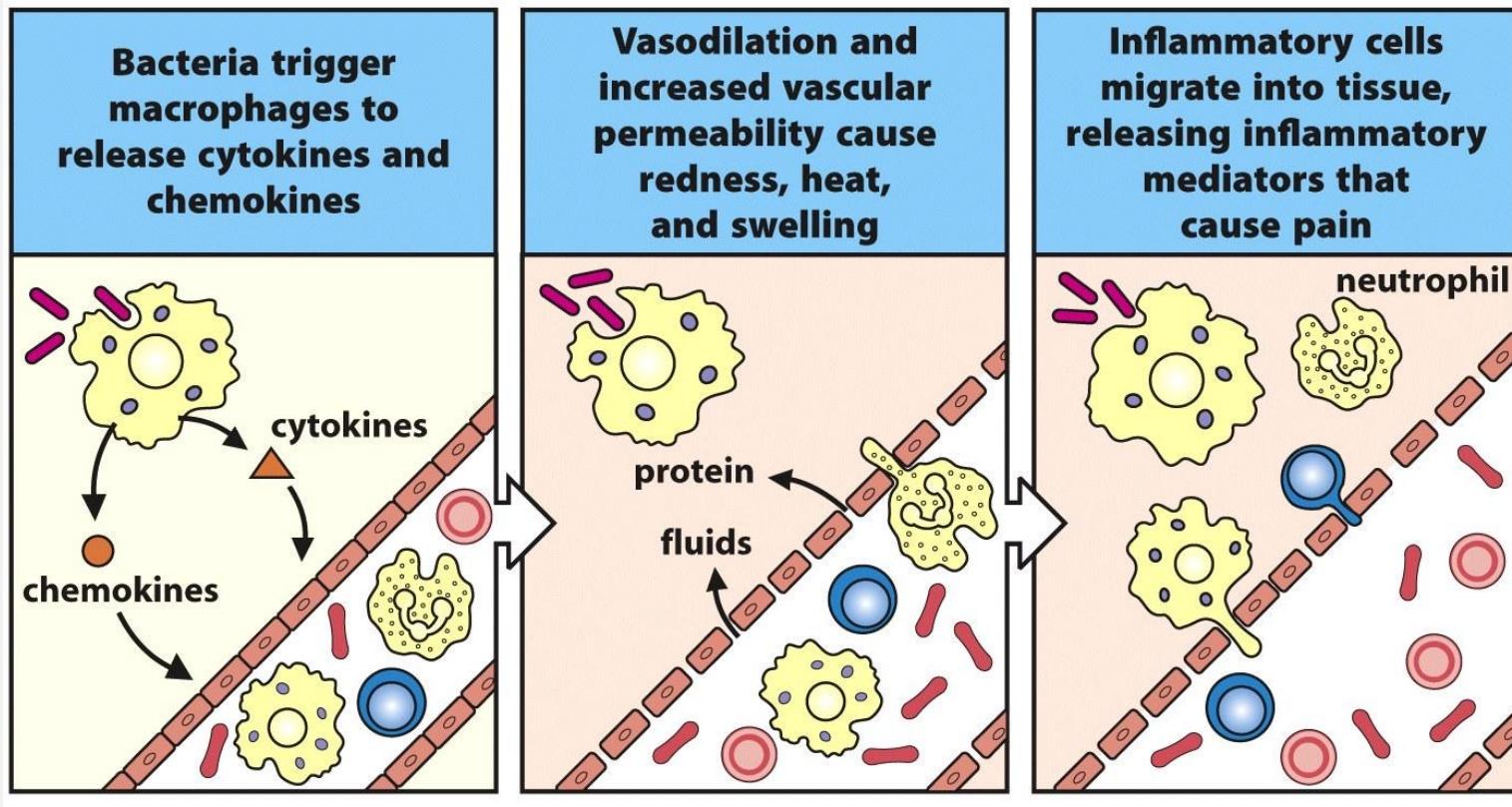
vasodilation



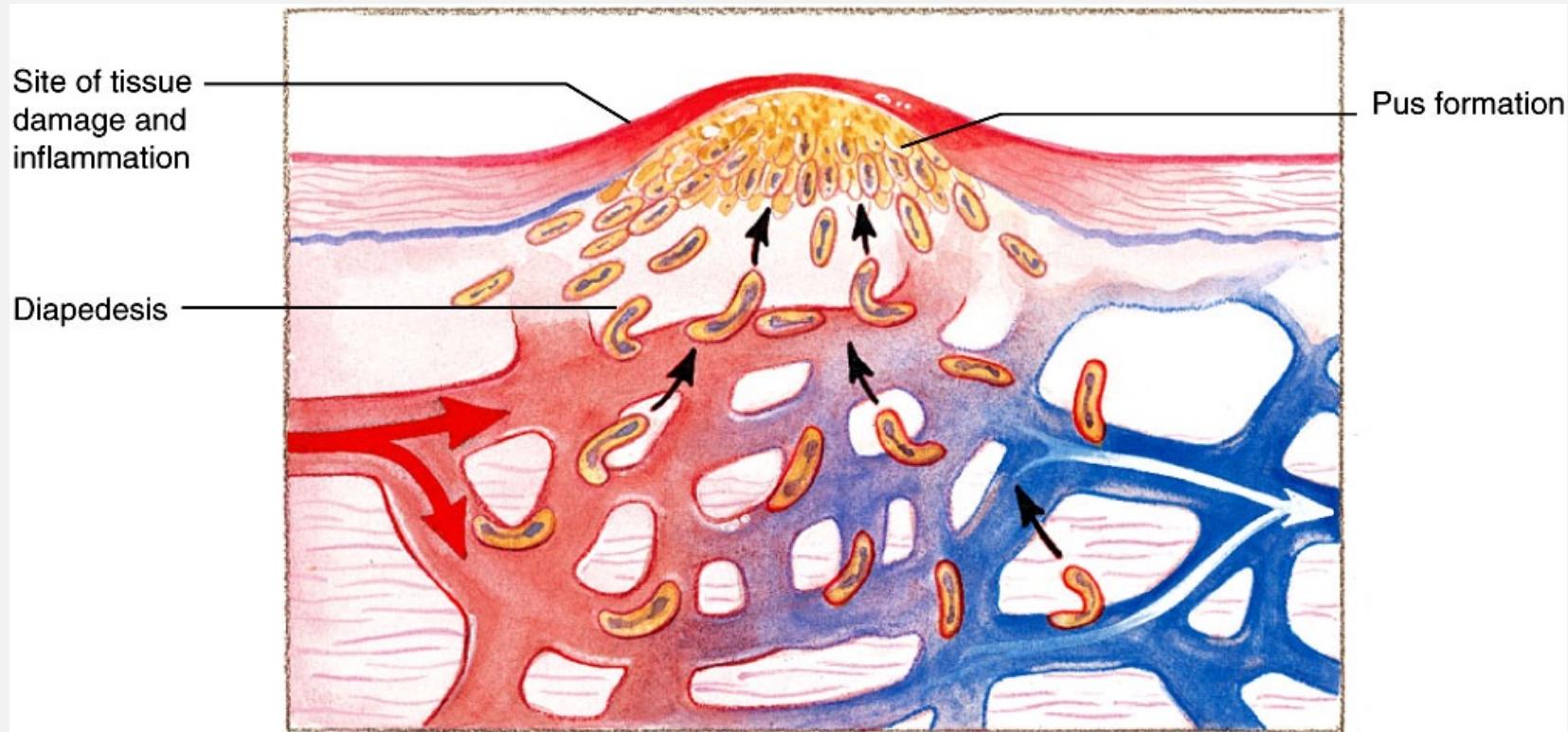
(b) Substances released cause dilation of small blood vessels and increased blood flow in the immediate area.



Inflammation process



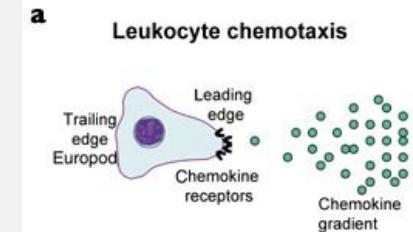
INFLAMMATION (PUS FORMATION)



(d) The attraction of phagocytes causes them to move to the site of damage and inflammation. Collections of dead phagocytes and tissue debris make up the pus often found at sites of an active inflammatory response.

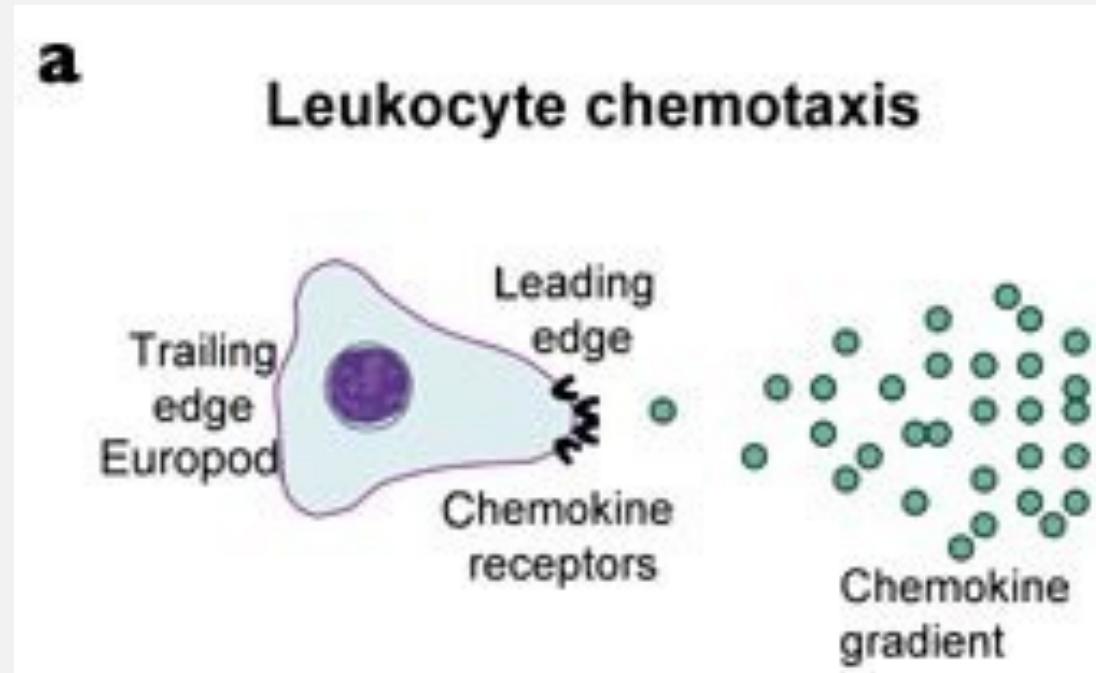
PHAGOCYTOSIS

- Ingestion of microorganisms or other matter by a cell.
- Microbial spread is limited by engulfment of microorganisms by phagocytes (eg. **macrophages, dendritic cells, granulocytes, monocytes**).
- Phagocytes are drawn to microbes via chemotaxis and engulf them, releasing phagocytic lysosomal contents that help destroy microbes.
 - **Chemotaxis** is the process by which phagocytes are attracted to microorganisms.



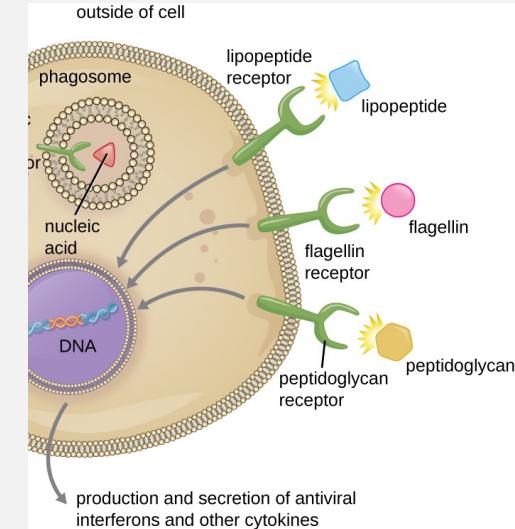
PHAGOCYTOSIS

- **Chemotaxis** is the process by which phagocytes are attracted to microorganisms.



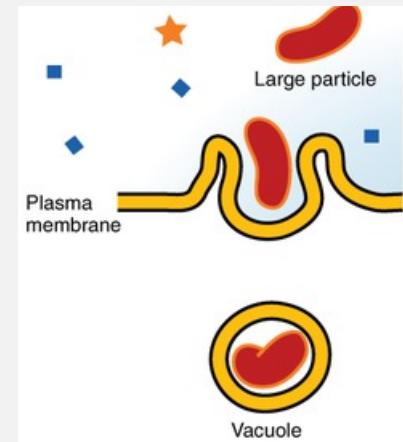
PHAGOCYTOSIS

- **Attachment:** The phagocyte then adheres to the microbial cell. This adherence may be facilitated by **opsonization** – coating the microbe with plasma proteins
 - Pathogens are recognized by **pathogen-associated molecular patterns (PAMPs)** on the pathogen surface, which interact with complementary **pattern-recognition receptors (PRRs)** on the immune cells' surfaces
- **Ingestion:** Pseudopods of phagocytes engulf the microorganism and enclose it in a phagosome to complete ingestion

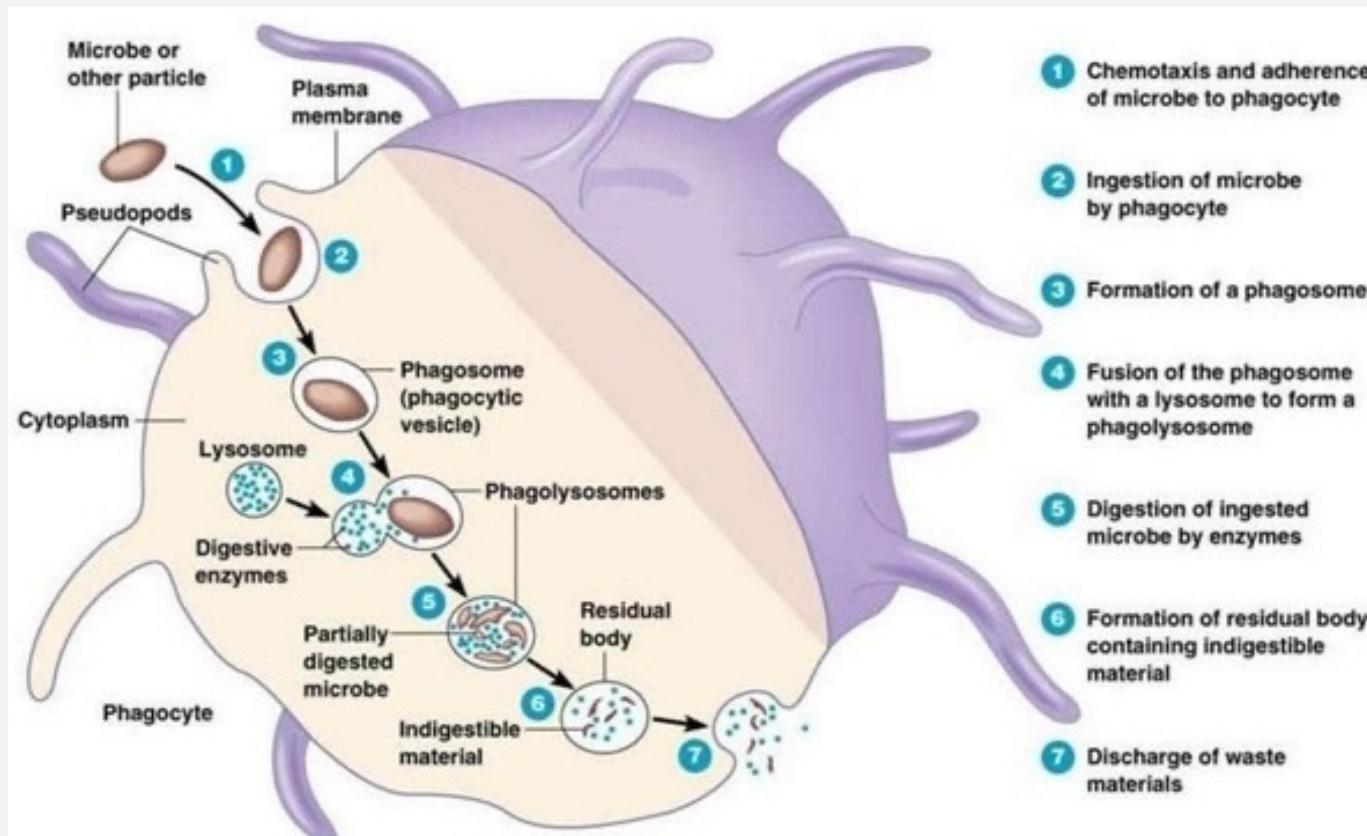


PHAGOCYTOSIS

- **Digestion:** Lysosomes fuse with the phagosome to form a digestive vacuole.
 - The microbe is killed and digested.
- Oxidative products such as hydrogen peroxide are generated by the phagocytes to kill ingested microbes
- When **quantitative or qualitative defects** in neutrophils result in infection, the infection is usually prolonged and recurrent and responds slowly to antimicrobial drugs
 - Eg: Staphylococci, gram-negative organisms and fungi.



PHAGOCYTOSIS



Dorcas Owusu

COMPLEMENT ACTIVATION

- The complement system which is made up of plasma proteins, synthesized in the liver
- “complements” the removal of pathogens or mark them for destruction by other cells.

They:

- trigger the recruitment of inflammatory cells
- "tag" pathogens for destruction by other cells by **opsonizing**, or coating, the surface of the pathogen
- Kill pathogens by forming holes in their plasma membrane, resulting in cytolysis/death of the pathogen cell
- Destroy/breakdown neutralised antigen-antibody complexes.
.....will be continued later!

IMMUNE CELLS, PROTEINS AND CHEMICALS

CHEMOKINES

- Chemokines are signaling proteins secreted by cells of the immune system that stimulate the movement of other cells.
 - **pro-inflammatory chemokines** are produced to recruit leukocytes to the sites of infection or injury.
 - Their name is suggestive of their function since it is derived from chemotaxis, or **movement in response to a chemical stimulus and cytokines**

CHEMOKINES

- Leukocytes travel along chemotactic gradients that guide them to sites of injury, infection, or inflammation
 - eg. Chemokine ligand (CCL2) which causes monocyte chemotaxis and stimulates its differentiation into macrophages inside of tissues
 - Eg. lymphocyte-specific chemotactic peptide XCLI (lymphotactin)

CHEMOKINES

- Chemokines are very small, between 8 and 12 kDa.
- There are different types, most of which share the presence of cysteine amino acids,
 - Eg.
 - CCR5 plays crucial role in HIV infection
 - XCL-XCR makes pathogens attractive molecule for specific targeting of cDC1

ACUTE PHASE PROTEINS

- Plasma proteins whose level increases during infection to enhance host defense mechanisms
- E.g. complement proteins, coagulating factors, C-reactive proteins, fibrinogen, plasminogen and transferrin

CYTOKINES

- Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system
- Cytokines are a category of signalling molecules that mediate and regulate immunity, inflammation and haematopoiesis
- Low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers to regulate the innate and adaptive immune system

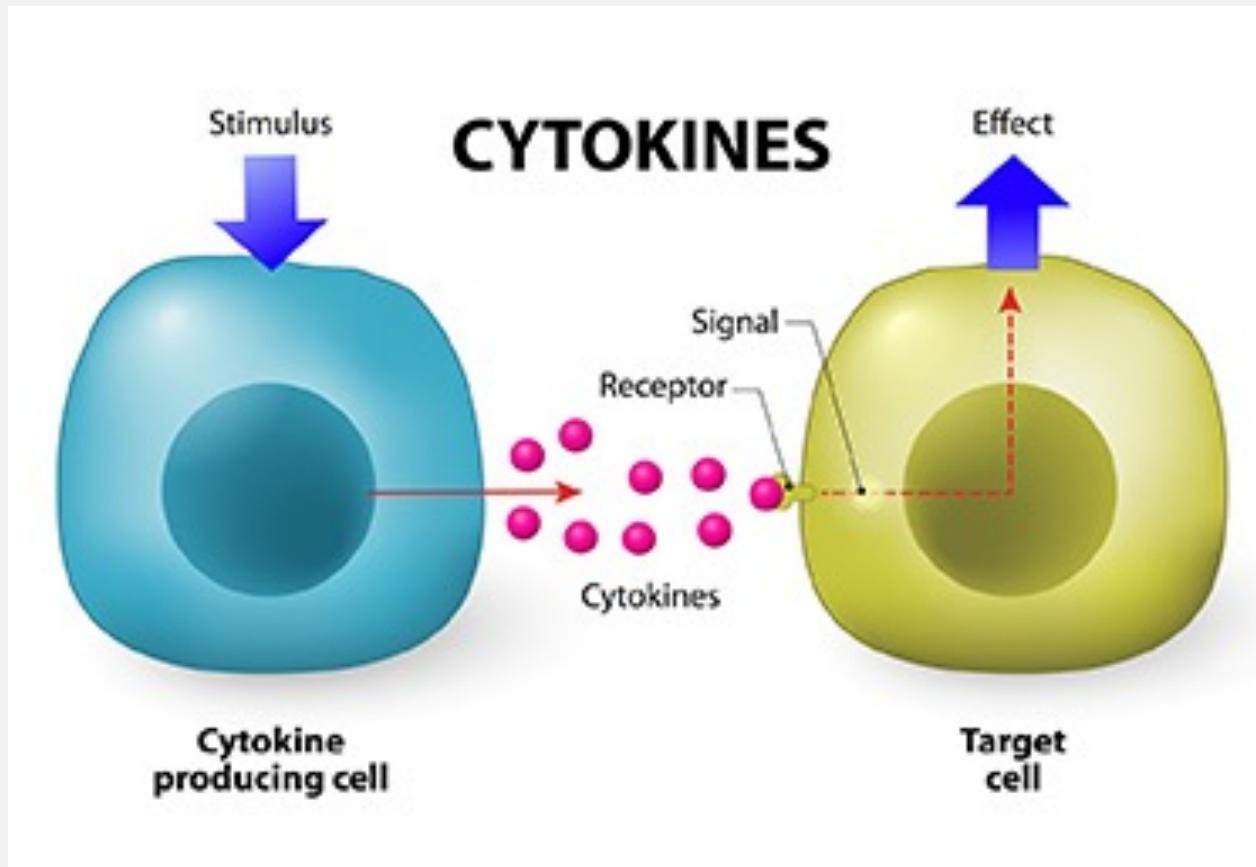
CYTOKINES

- Has matching cell-surface receptors which in turn activates cascades of intracellular signalling then alter cell functions by (increased expression) and/or downregulation (decreased expression)
- Cytokines and their receptors exhibit very high affinity for each other

CYTOKINES

- can regulate cellular activity in a coordinated interactive way due to the following attributes:
 - Pleiotropy - one cytokine has many different functions
 - Redundancy - several different cytokines can mediate the same or similar functions
 - Synergism - occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of individual cytokines
 - Antagonism - the effects of one cytokine inhibits or offsets the effects of another cytokine

CYTOKINES



CYTOKINES

- Eg. interleukins, interferons



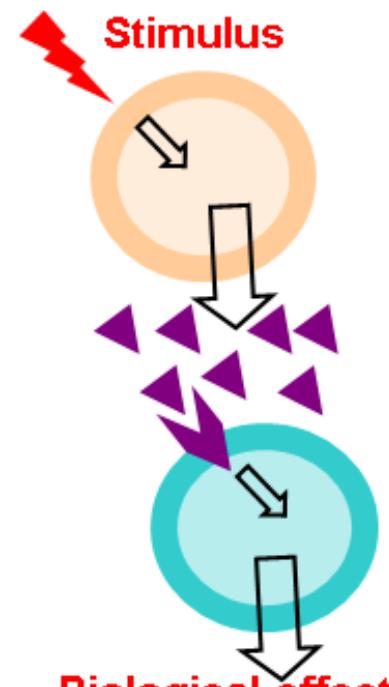
Stimulated cell produces cytokine

Cytokine secreted

Specific cytokine receptor on target cell bound and activated

Cell activation

Biological effect



CYTOKINES

Interleukins

- The interleukins are a major class of biologically active protein mediators – cytokines
- Following release from activated cells, they bind to specific cell surface receptors to induce growth and differentiating functions in target cells
- Majority of interleukins are synthesized by helper CD4 T lymphocytes as well as through monocytes, macrophages, and endothelial cells.
- They promote the development and differentiation of T and B lymphocytes and hematopoietic cells.

CYTOKINES

- **Interleukins** are not stored within cells but are instead secreted rapidly, and briefly, in response to a stimulus, such as an infectious agent
- Eg. IL 1 -> 36

CHEMOTAXIS

Pyrogens - Fever

- Pyrogens are substances that stimulate fever
 - External, e.g. bacterial endotoxin
 - Internal (endogenous) e.g. Chemokines / interleukins (IL-1)

- Body temperature increases in response to pyrogens to:
 - Stimulate eukocytes to deploy & destroy microbes
 - increase in immunological response (e.g. proliferation and activation of lymphocytes)
 - Slow down growth or kill pathogens

INTERFERONS

- Interferons are categorized as cytokines, small proteins that are involved in intercellular signalling
- Interferon is secreted by cells in response to stimulation by a virus or other foreign substance, but it does not directly inhibit the virus's multiplication
- Alert system to prevent virus from infecting other cells and to stimulate certain lymphocytes

INTERFERONS

- They can activate macrophages and natural killer (NK) cells to attack and lyse virus-infected cells.
- IFN-gamma, a pyrogen is involved in inflammatory response and macrophage and NK cell activation.
- IFN-gamma is produced by T cells (both CD4 and CD8) and NK cells.

INTERFERONS

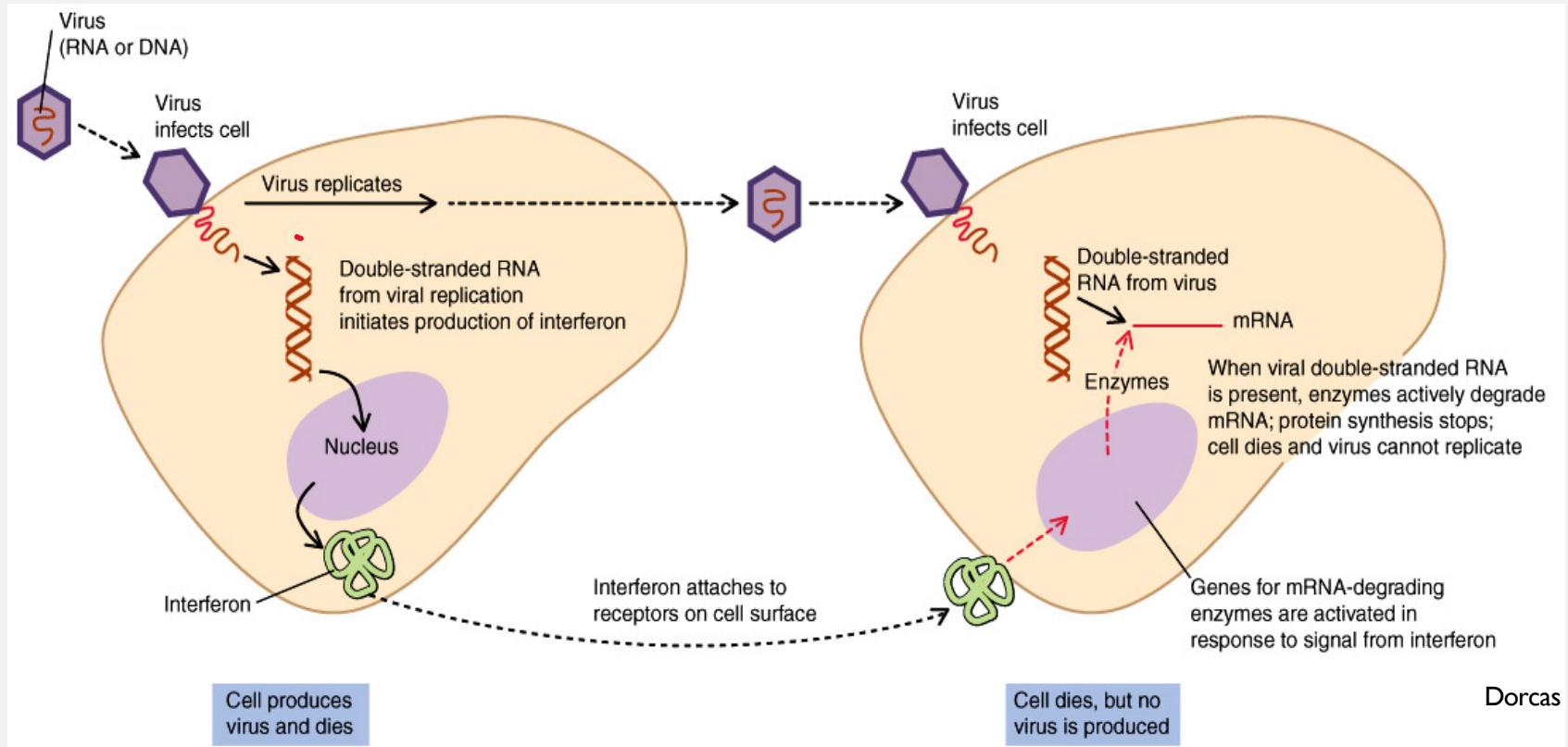
- Stimulates the infected cells and those nearby to produce proteins that prevent the virus from replicating within them.
 - Further production of the virus is thereby inhibited and the infection is controlled.
- Inhibit B-lymphocyte activation, enhance T-lymphocyte (T-cell) activity, and increase the cellular-destruction capability of natural killer cells.

INTERFERONS

Classified into two types:

- Classification is based on the type of cell that produces the interferon and the functional characteristics of the protein.
- **Type I** includes the alpha and beta forms: produced by almost any cell upon stimulation by a virus; their primary function is to induce viral resistance in cells
- **Type II** consists of the gamma form: secreted only by natural killer cells and T lymphocytes; its main purpose is to signal the immune system to respond to infectious agents or cancerous growth.

INTERFERON AND VIRAL INFECTIONS: A PROTECTIVE ALERTING SYSTEM



TUMOUR NECROSIS FACTOR (TNF)

- Cytokines that induce apoptosis in abnormal cells such as tumour cells.
- Proteins released by NK cells, macrophages, and helper T cells
- Serves as inflammatory mediator and pyrogen to cause fever and inflammation for up to 24 hours.
- It also stimulates acute phase reaction in the liver, a component of systemic immune system activation where the liver makes proteins involved in immune system response such as complement proteins.
- TNF-alpha is released in very high amounts in response to lipopolysaccharide (infection with gram negative bacteria)

PERFORINS

- Perforins are protein found in the granules of cytotoxic T lymphocytes (CTLs) and Natural Killer cells (NK cells)
- They are pore forming cytolytic proteins
- Upon degranulation, perforin binds to the target cell's plasma membrane and create pores on the target cell
- The pore formed allows for the passive diffusion of a granzymes (pro-apoptotic proteases) into the target cell.

GRANZYMES

- Granzymes (Grs) are serine proteases mainly produced by cytotoxic lymphocytes and causes apoptosis in tumour cells and virally infected cells
- Grs enter the target cell with the aid of perforins and activate various pro-apoptotic pathways by cleavage of intracellular substrates
- Granzymes have additional functions such as directly interfering with viral replication and in cytokine processing, leading to amplification of the inflammatory response to pathogens.

HEPARINS

- Immunologically induced heparin are chemicals released from mast and basophil cells that aid in the inflammatory response
- They increase capillary permeability and vasodilation during the inflammatory process
 - Mobilization of innate immune cells

HISTAMINES

- Histamine is produced by basophils and by mast cells found in nearby connective tissues
- Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues during the inflammatory process
- Regulate the proliferation of antigen-presenting cells, natural killer cells, epithelial cells, and T and B lymphocytes

CHEMOTAXIS

The complement system proteins

- Consists of ~30 proteins that complement the action of the immune system

..... Mechanism?....to be continued

CHEMOTAXIS

Antibodies

- After infection, the host can produce a variety of antibodies (complex glycoproteins known as immunoglobulins) that bind to specific microbial antigenic targets.
- Antibodies help eradicate the infecting organism by attracting the host's leukocytes and activating the complement system.
- ...details?...to be continued

CHEMOTAXIS

Opsonization

- Process by which phagocytosis is facilitated by deposition of opsonins
- Opsonins can be complement proteins or antibodies
- Deficiency in complement system may lead to increase susceptibility to certain infections.
- Opsonization is important for eradication of encapsulated organisms such as pneumococci and meningococci.

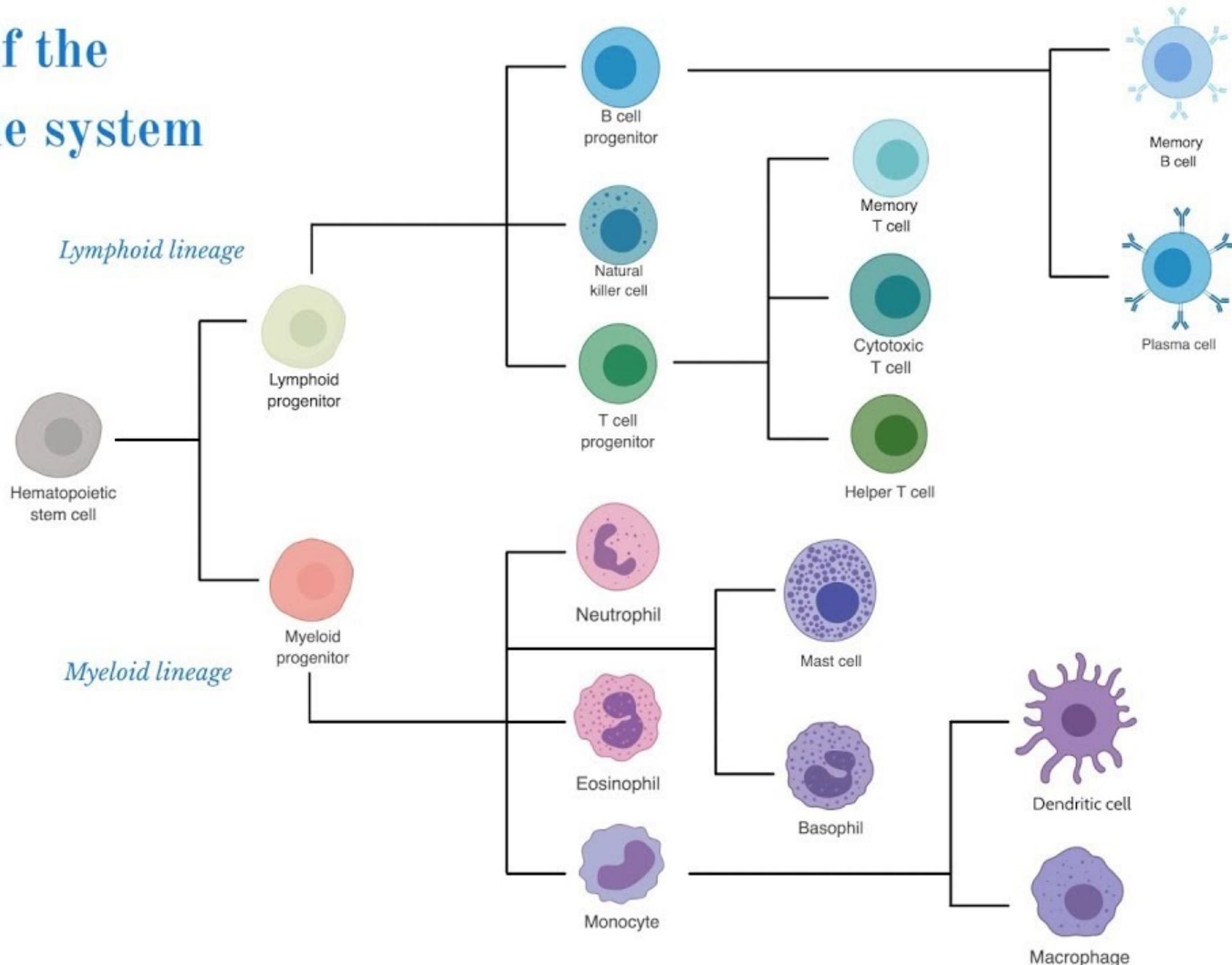
CELLS OF THE INNATE IMMUNE SYSTEM

ORIGIN OF CELLS OF THE IMMUNE SYSTEM

Leukocytes (white blood cells)

- Made up of phagocytes, mast cells, eosinophils, basophils, and natural killer cells and lymphocytes
- Produced and derived from a multipotent cell in the bone marrow known as a hematopoietic stem cell
 - Pluripotent stem cell differentiation

Cells of the immune system



IMMUNE CELLS (Innate)

- *Phagocytes or Phagocytic cells:* Phagocyte means “eating cell”
- Phagocytes circulate throughout the body, looking for potential threats, like bacteria and viruses, to engulf and destroy.
 - - security guards on patrol
- Macrophages, dendritic cells and granulocytes are the major phagocytes of the immune system

IMMUNE CELLS (Innate)

Macrophages –

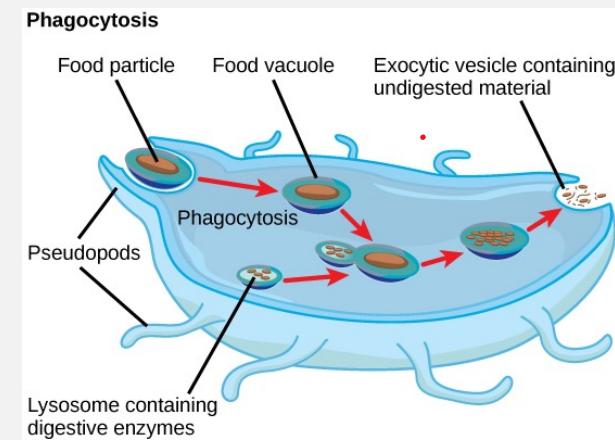
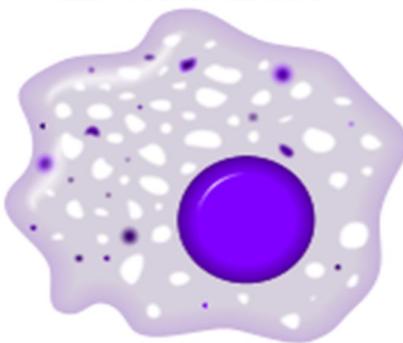
- Irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body
- Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to reticular fibres within specific tissues such as lymph nodes
- Macrophages move through tissues and squeeze through capillary walls using pseudopodia.

IMMUNE CELLS (Innate)

Macrophages –

- They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lung
 - Act as scavengers, ridding the body of worn-out cells and other debris
 - Act as antigen-presenting cells that activate the adaptive immune system.

MACROPHAGE

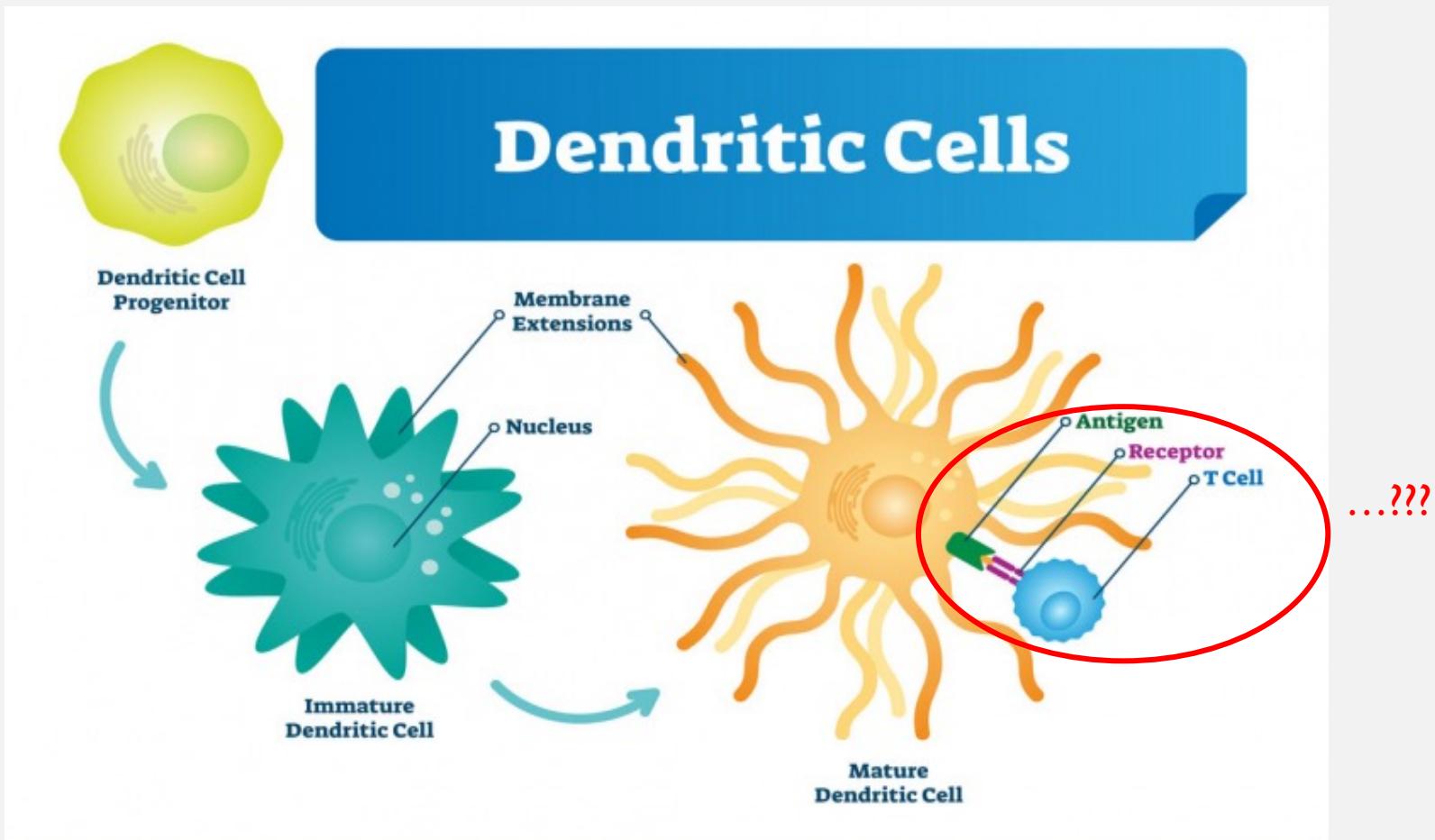


IMMUNE CELLS (Innate)

Dendritic cells -

- named for their probing, 'tree-like' or dendritic shapes
- Found in tissues that are in contact with the external environment (skin, nose, lungs, stomach, and intestines).
- These cells serve as a link between the bodily tissues, the innate and adaptive immune systems, as they present antigen to T-cells
- One of the key cell types of the adaptive immune system.

IMMUNE CELLS (Innate)



IMMUNE CELLS (Innate)

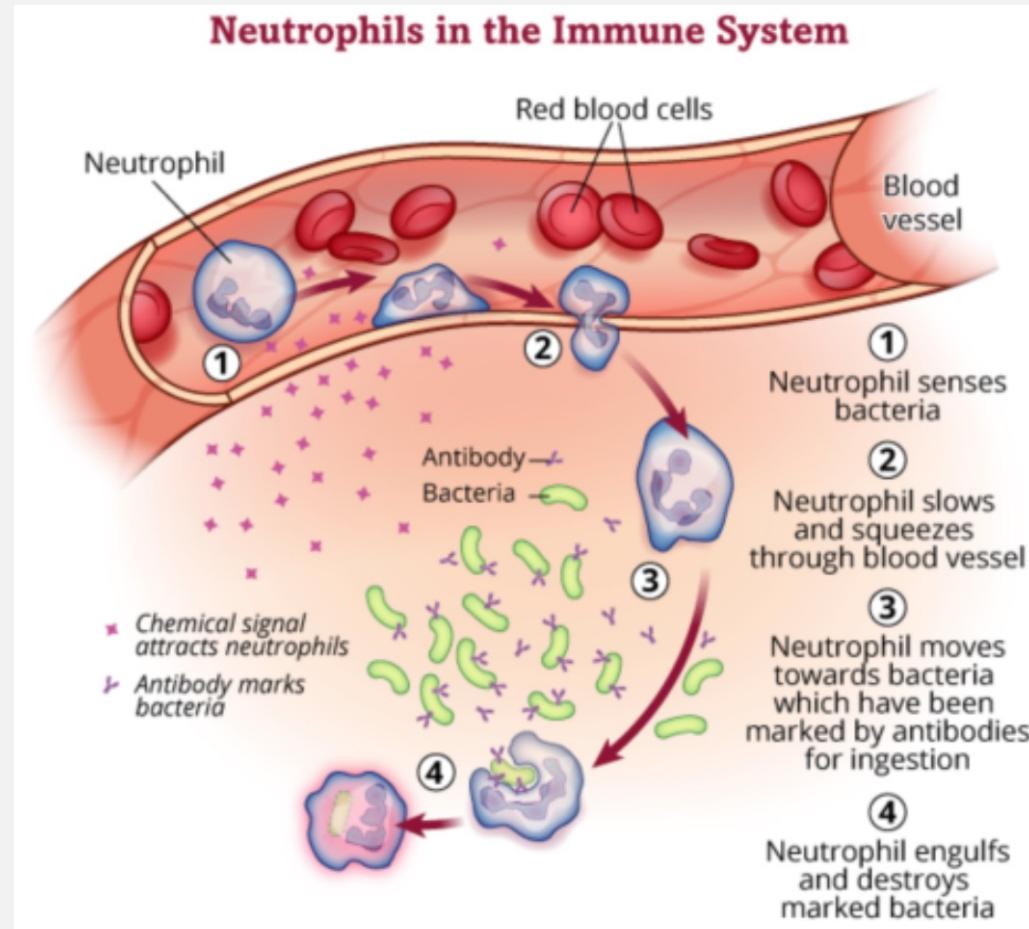


Neutrophils –

- Found in the bloodstream, most abundant type of phagocyte
- Is attracted via chemotaxis from the bloodstream to infected tissues
- Contains cytoplasmic **granules**, which in turn contain a variety of vasoactive mediators such as histamine
- First cells to arrive at the scene of infection during acute phase of inflammation, ingest microorganisms
 - *Neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy*

IMMUNE CELLS (Innate)

- The bone marrow of an average healthy adult makes approximately 100 billion new neutrophils per day
- Infection activates the bone marrow to produce more (20 million/ml of blood) through cytokine stimulation

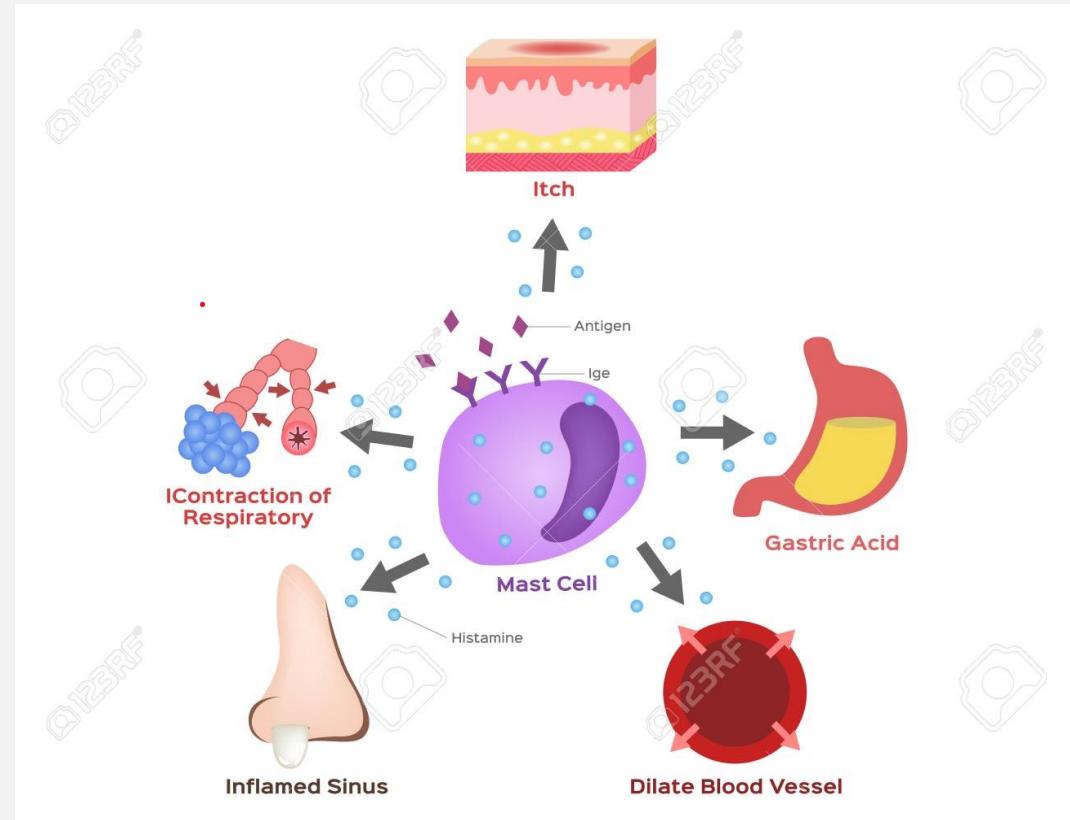
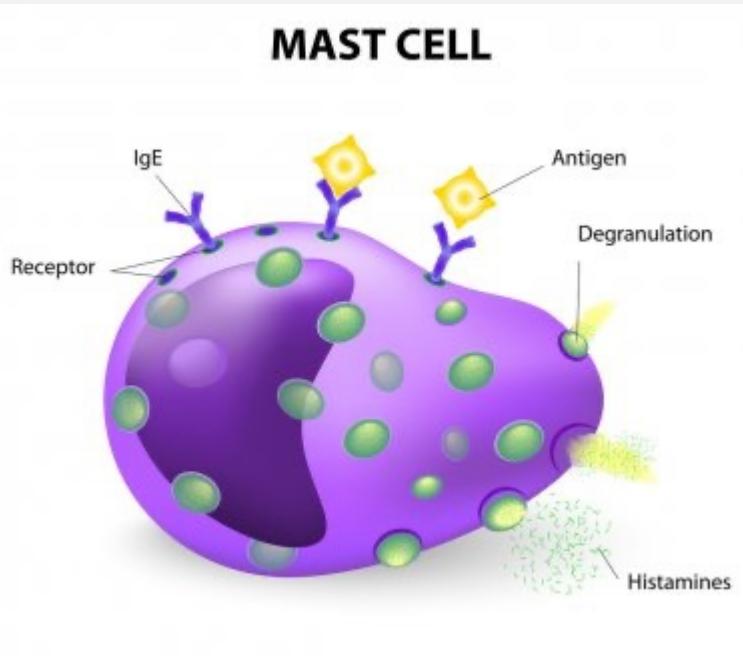


IMMUNE CELLS (Innate)

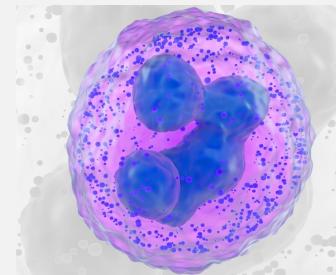
Mast cells -

- Found in connective tissues and mucous membranes
- Regulate inflammatory response. activated mast cells release cytokines and granules that contain chemical molecules to create an *inflammatory cascade*
- Mediators, such as histamine, cause blood vessels to dilate, increasing blood flow and cell trafficking to the area of infection
- Most often associated with allergy and anaphylaxis

IMMUNE CELLS (Innate)



IMMUNE CELLS (Innate)

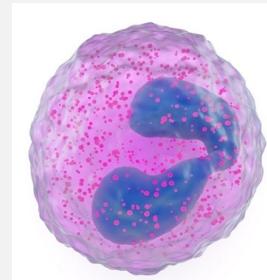


Basophils –

- Secrete chemical mediators such as histamines in allergic reactions
- Basophils express a receptor known as Fc ϵ RI that binds to IgE (a class of antibody that induces allergic reactions) and will undergo degranulation when an allergen binds to the IgE on the basophil cell surface
- Basophils are the least common type of granulocyte, representing about 0.5% to 1% of circulating white blood cells.

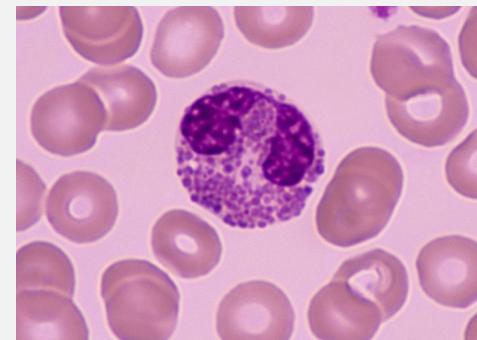


IMMUNE CELLS (Innate)



Eosinophils-

- Proinflammatory white blood cell, generally has a nucleus with two lobes (bilobed) and cytoplasm filled with approximately 200 **large granules**, release of granules with toxic substances kill microorganisms
- Modulate inflammatory responses
- Eosinophils mediate parasitic infection, an allergic reaction or cancer through the release of toxic proteins and free radicals also causes tissue damage
- Mostly found in peripheral tissue
- After activation, they Release cytokines to attract other cells

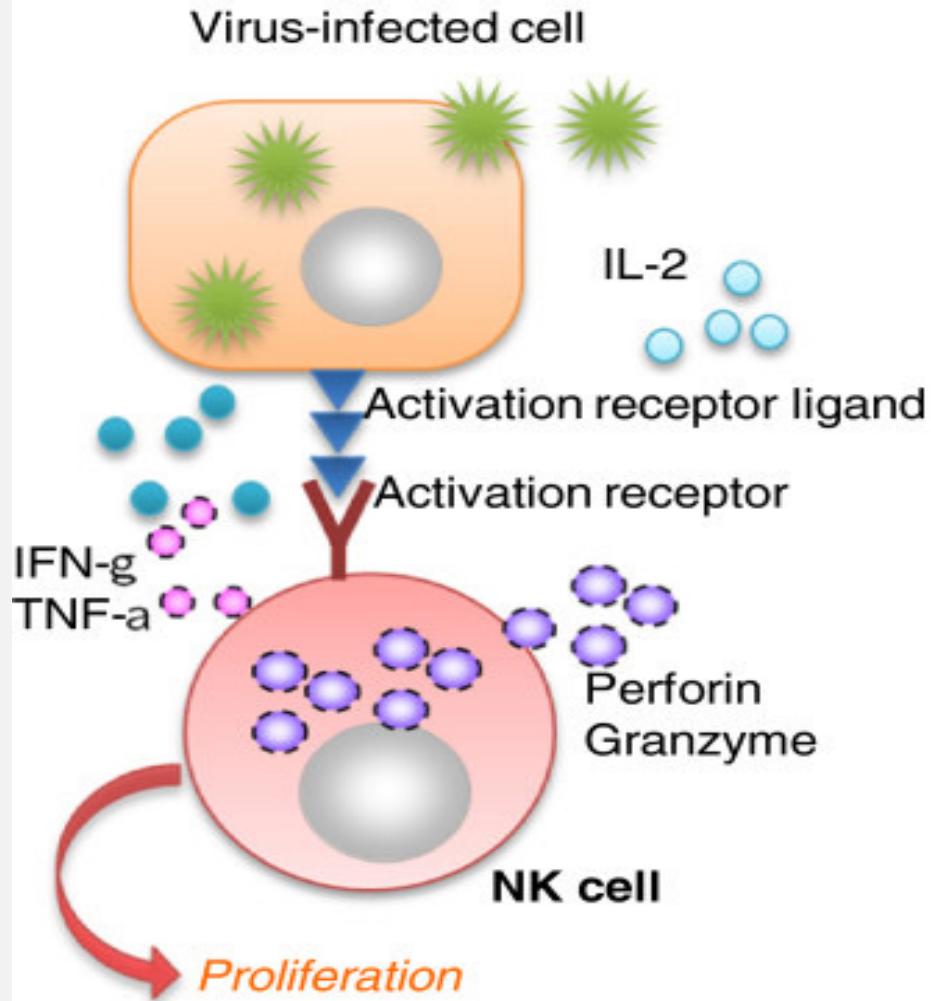


IMMUNE CELLS (Innate)

Natural killer cells (NK cells, K cells, and killer cells)

- No classical antigen receptors
- Recognise, attack and destroy tumour cells / abnormal cells that have been infected by viruses or other pathogens
- Induce apoptosis in virus infected cells by secreting proteases through pores that they make in target cells
- The role NK cells play is analogous to that of cytotoxic T cells in the vertebrate adaptive immune response

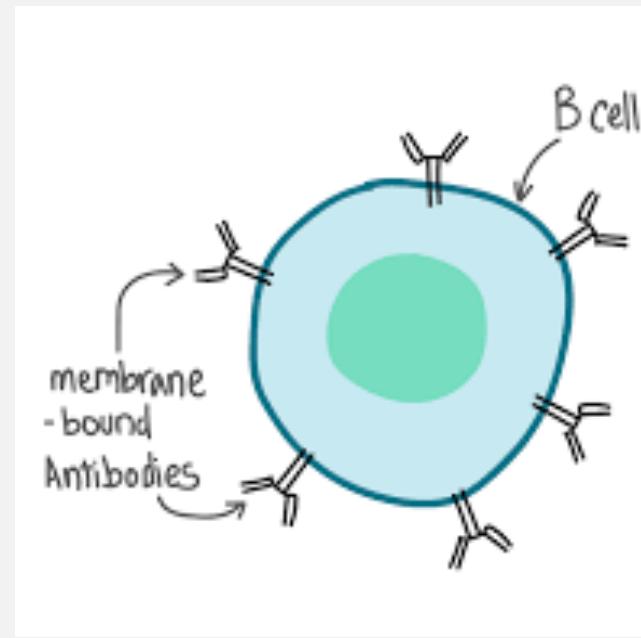
IMMUNE CELLS (Innate)



IMMUNE CELLS (Adaptive)

B cells

- B cells, also known as B lymphocytes, are a type of white blood cell
- Account for 10–15% of circulating lymphocytes (25% of white blood cells)
- They form the humoral component of the adaptive immune response system.
- B cells have membrane-bound antibodies as receptors.

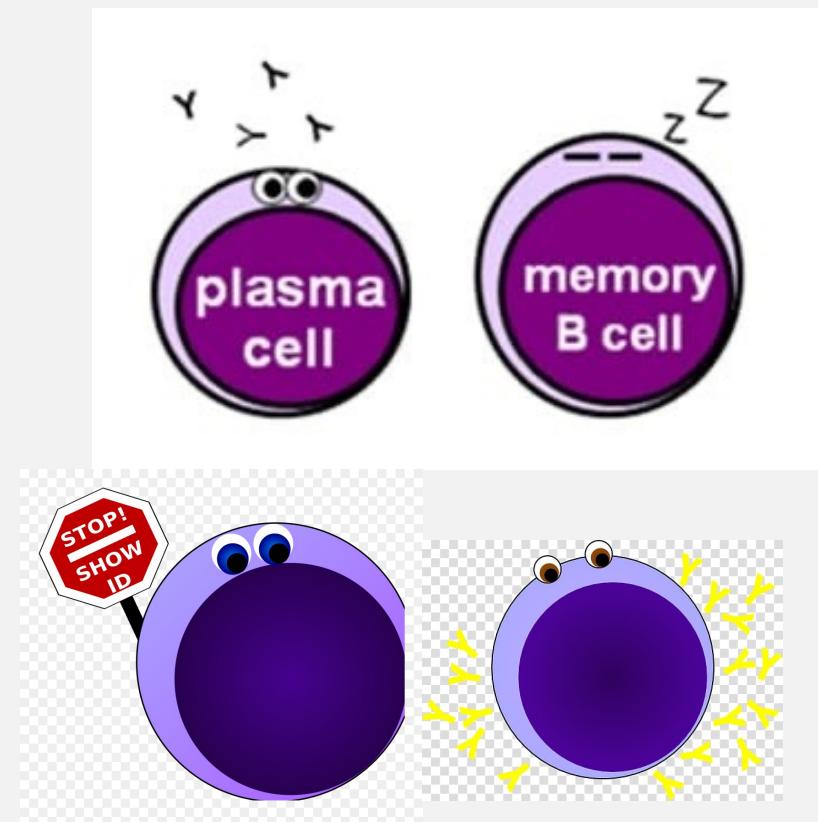


IMMUNE CELLS (Adaptive)

- They are also classified as antigen-presenting cells (APCs)

Main B cell types:

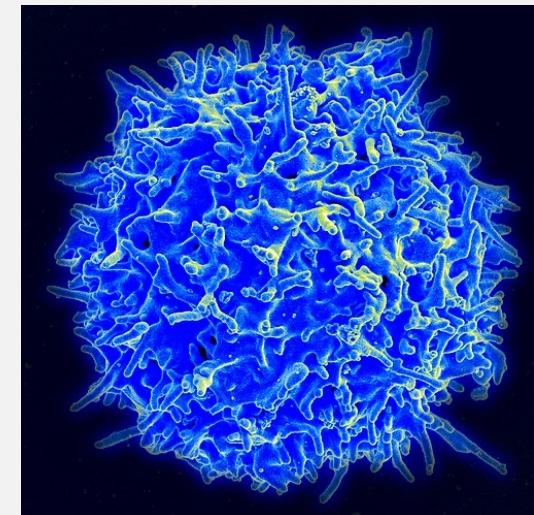
- Plasmablast
- Memory B cell
- Follicular (FO) B cell
- Regulatory B (Breg) cell



IMMUNE CELLS (Adaptive)

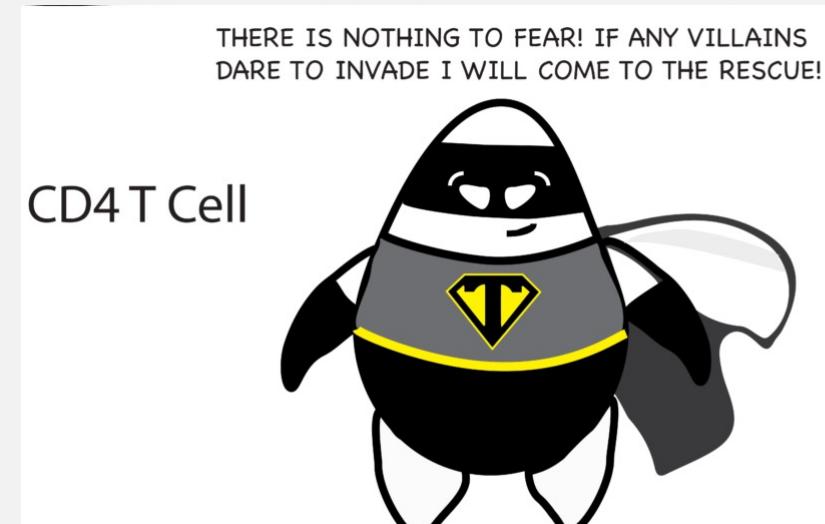
T Cells

- Cell mediated immunity is controlled mostly by T cells
- They have T-cell receptor (TCR) on their cell surface
- T cells account for about 80% of all lymphocytes
- Main types:
 - Helper T cells (Th / CD4⁺) and
 - Cytotoxic T cells (Tc / CD8⁺).



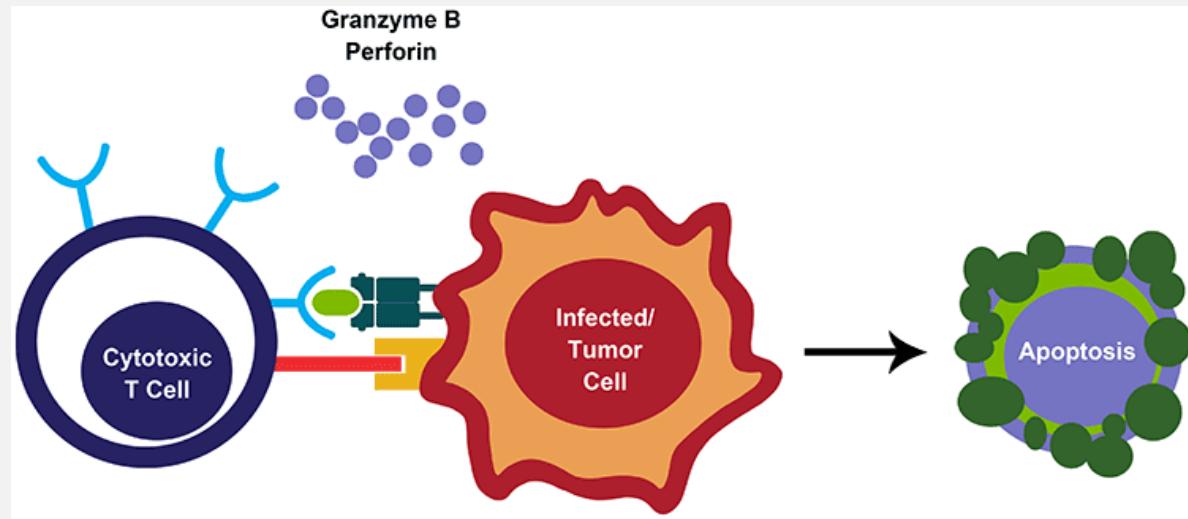
IMMUNE CELLS (Adaptive)

- **Helper T cells** also known as “CD4+ cell”, “T helper cell”, or ”helper T lymphocyte”
 - help activate B cells to secrete antibodies
 - Help macrophages to destroy ingested microbes
 - help activate cytotoxic T cells to kill infected target cells



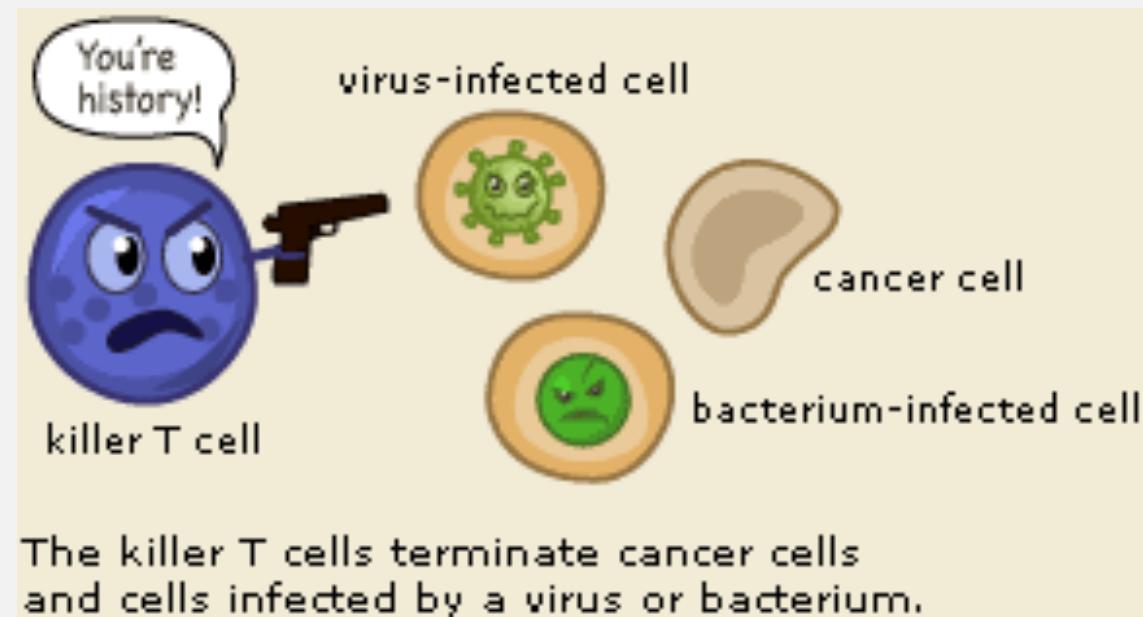
IMMUNE CELLS (Adaptive)

- **Cytotoxic T** cells also known as "TC", "cytotoxic T lymphocyte(CTL), cytolytic T cell, CD8+ T-cell



IMMUNE CELLS (Adaptive)

- Kills cancer cells, cells that are infected by intracellular pathogens (such as viruses or bacteria), or cells that are damaged



IMMUNE CELLS (Adaptive)

Cytotoxic T cells (Tc/ CD8⁺)

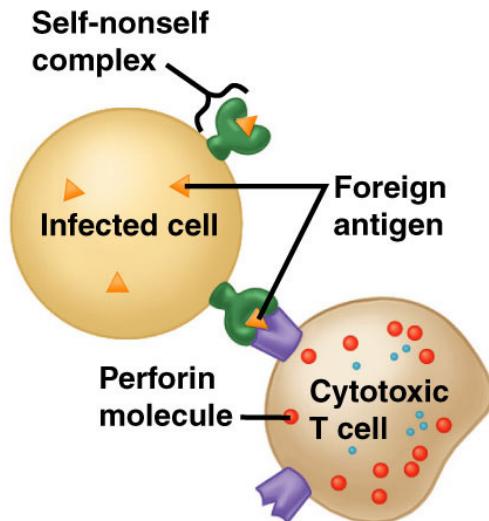
- Cytotoxic T cells are important in defending against virally infected cells, immune response to certain tumour types and the rejection of tissue grafts.
- Cytotoxic T cells require activated APCs and rely on the presence of helper T cells.
- Following activation by Th cells, cytotoxic T cells attach to infected cells and release **perforins** which perforate them by punching holes in them

IMMUNE CELLS (Adaptive)

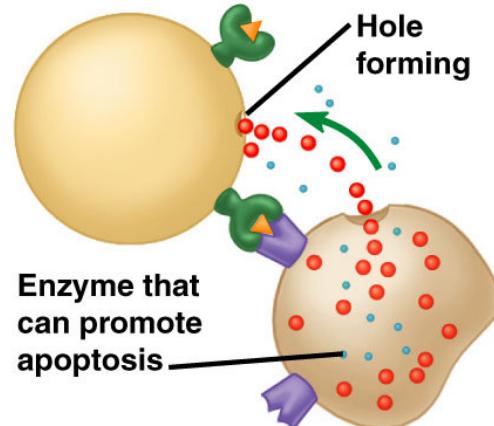
- Enzymes (oxides) are also released that destroys the cell structure
- Granzymes: serine proteases which activate apoptosis
- Granulysin: antimicrobial action which induce apoptosis
- Only the infected cell is destroyed, the cytotoxic T cell can detach itself and leave to destroy other infected or otherwise damaged cells.

CYTOTOXIC T CELL

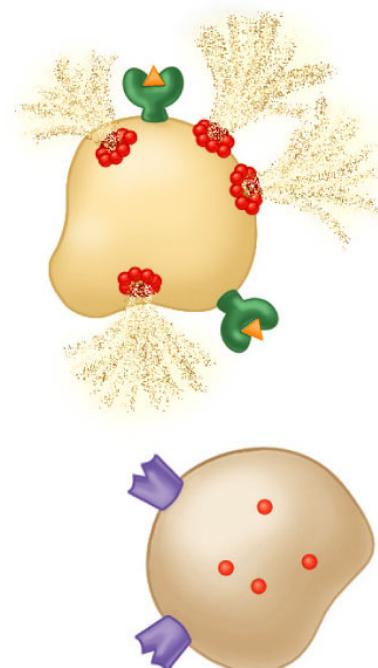
- 1 Cytotoxic T cell binds to infected cell



- 2 Perforin makes holes in infected cell's membrane and enzyme enters

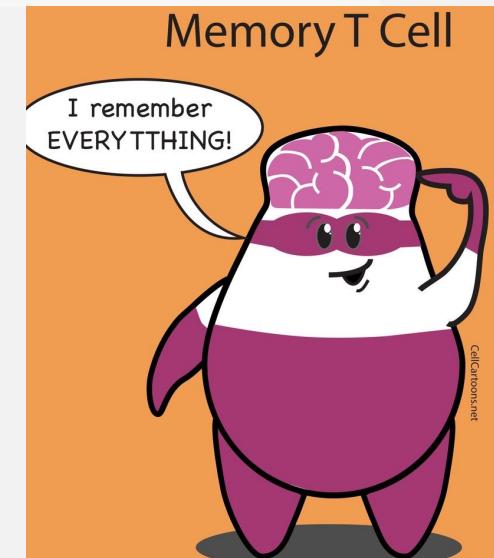
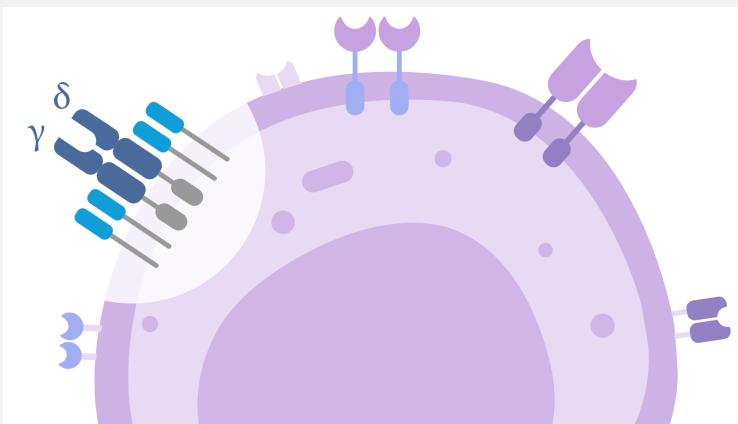
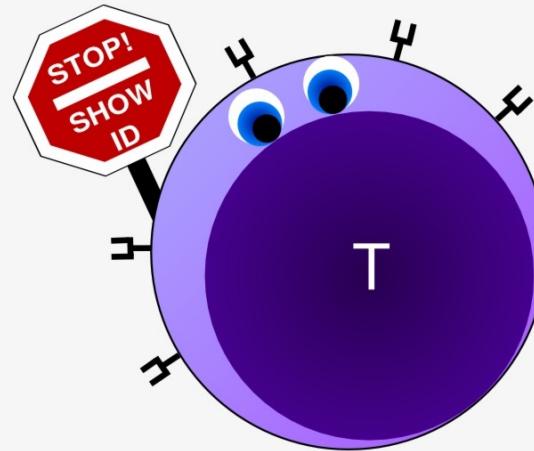


- 3 Infected cell is destroyed



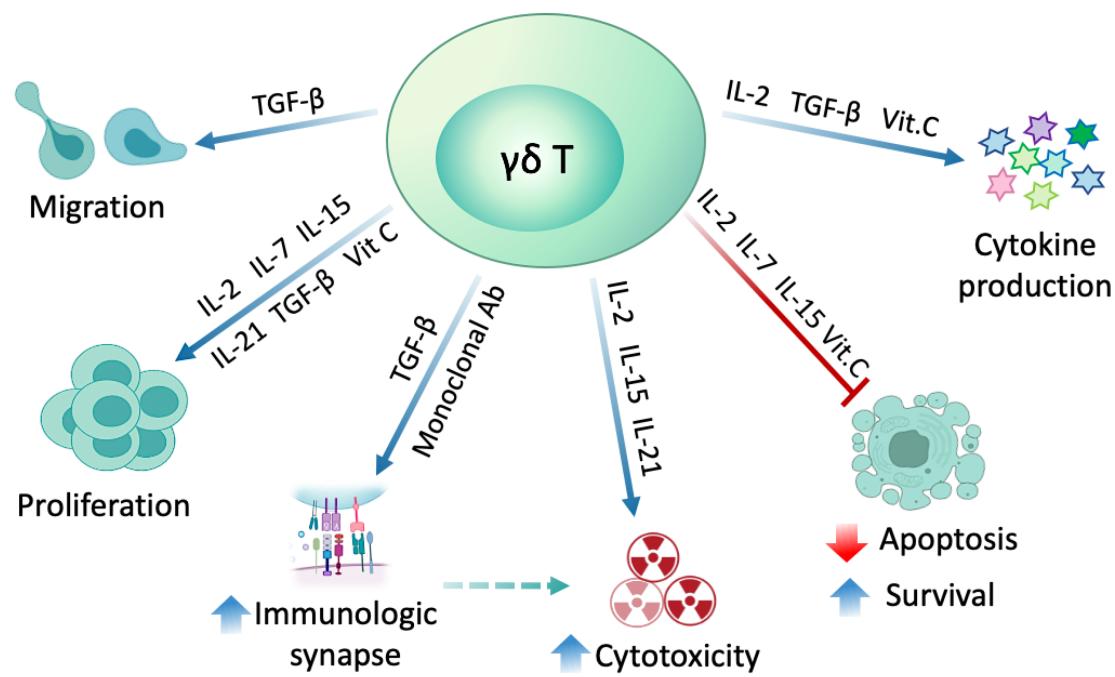
IMMUNE CELLS (Adaptive)

- Other T cell types include:
 - Memory T cells
 - Regulatory (suppressor) T cells
 - Natural killer T cell and
 - Gamma delta T cells ($\gamma\Delta$ T cells)



IMMUNE CELLS (Adaptive)

- Other T cell types include:



IMMUNE CELLS (Adaptive)

Natural Killer (NK) T cells

- Bridge the adaptive immune system with the innate immune system
- Contain cytotoxic granules kill virus-infected cells, tumor cells and Antibody-coated target cells
- Employed by both specific and non-specific immune response
- Activated to cytokine production and release of cytolytic/cell killing molecules

IMMUNE CELLS (Adaptive)

Memory T cells

- T cells expand and differentiate into effector and memory T cells after they encounter their antigens on the surface of antigen presenting cells
- 'Prime' the body in case of a subsequent exposure to the antigen
- They provide the immune system with "memory" against previously encountered pathogens.
- Memory T cells may be either CD4+ or CD8+

IMMUNE CELLS (Adaptive)

Regulatory / Suppressor T cells (Tregs)

- maintenance of immunological tolerance or balance
- Tregs control the immune response to self and foreign particles (antigens) and help prevent autoimmune disease
- Terminates T cell-mediated immunity toward the end of an immune reaction by suppressing activation, proliferation and cytokine production of CD4+ T cells and CD8+ T cells as well as suppress B cells and dendritic cells

IMMUNE CELLS (Adaptive)

- Produced by a normal thymus are termed ‘natural’
- suppress autoreactive T cells that escaped the process of negative selection in the thymus
- Regulatory T cells can develop either during normal development in the thymus, and are then known as thymic Treg cells, or can be induced peripherally and are called peripherally derived Treg cells

INNATE AND ADAPTIVE IMMUNITY

Innate

- Non-Specific alarm system to pathogens, damaged or stressed cells
- First responders, clinically called acute inflammatory response, dissipates in 2 to 14 days

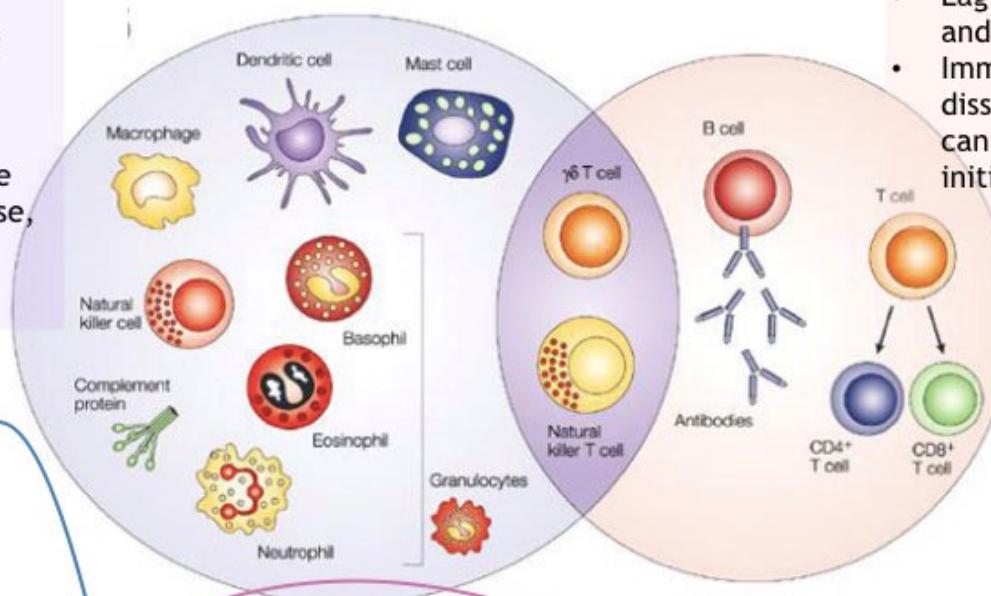
Adaptive

- Lag time, days between exposure and maximal response
- Immunological memory, response dissipates in years not days, and can vary dependent upon the initial insult



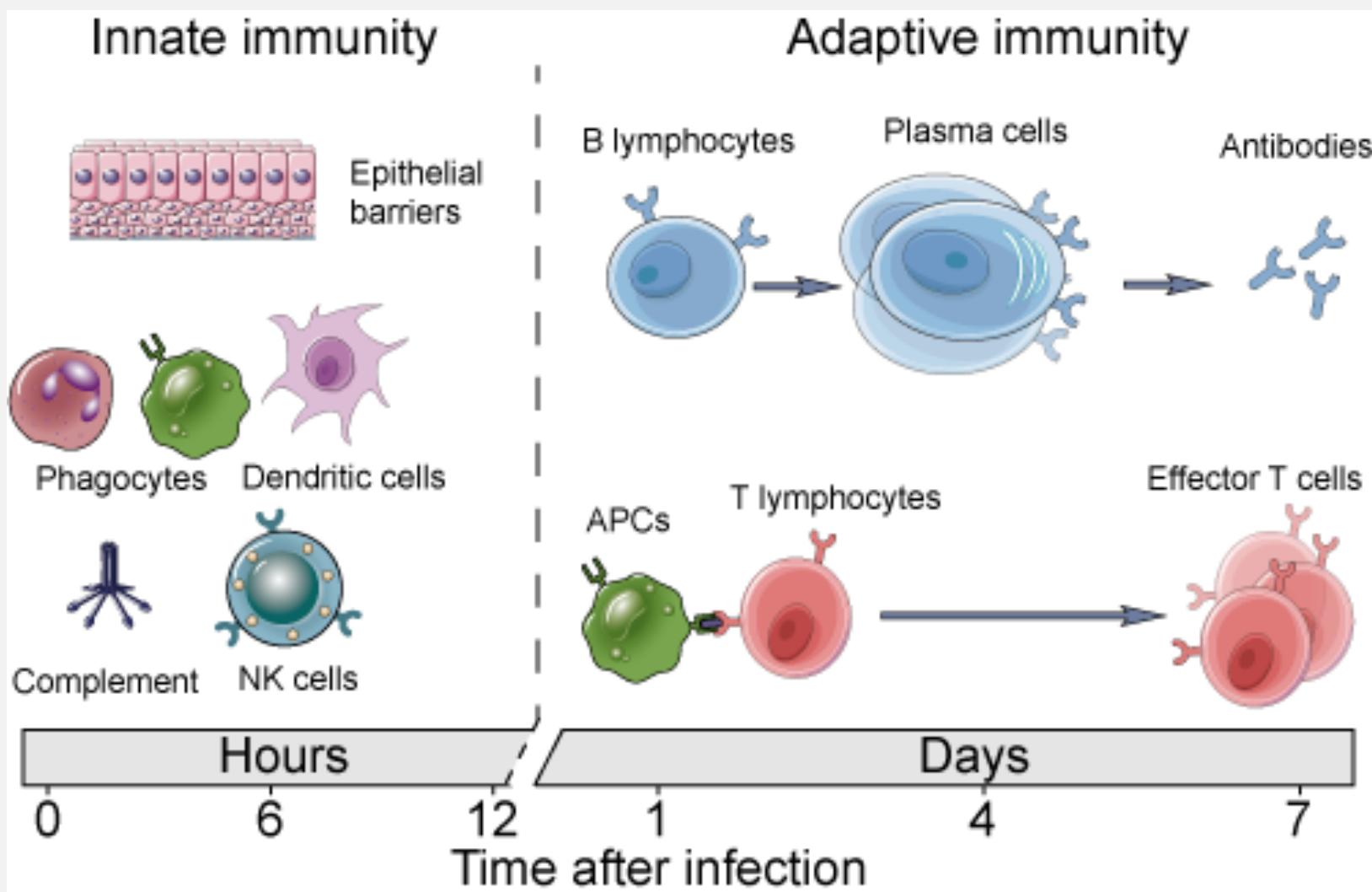
2-14 days

Time after initial inflammatory insult

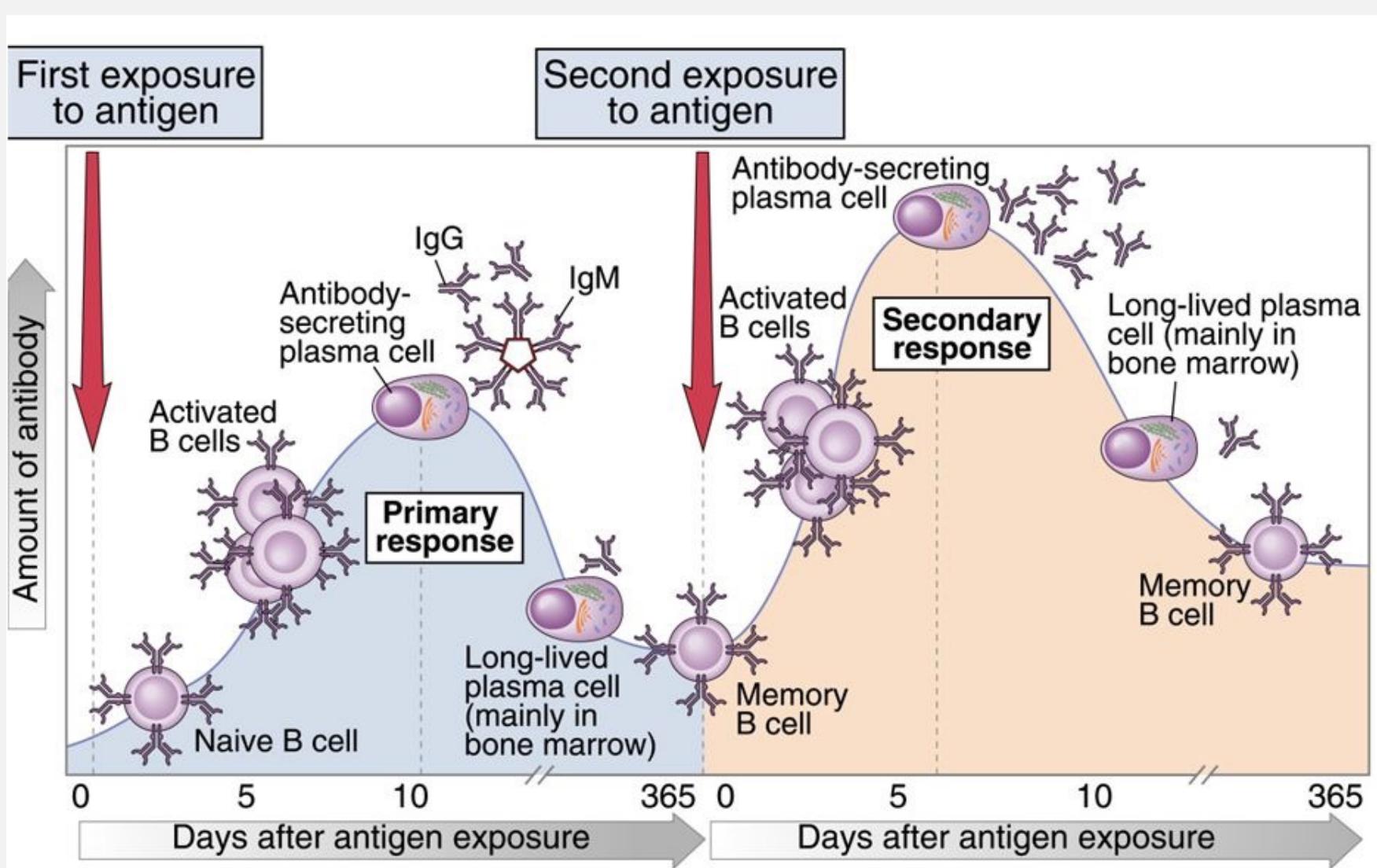


Adaptive immune responses
(T Cells, neutralizing antibodies,
seroconversion, etc.)

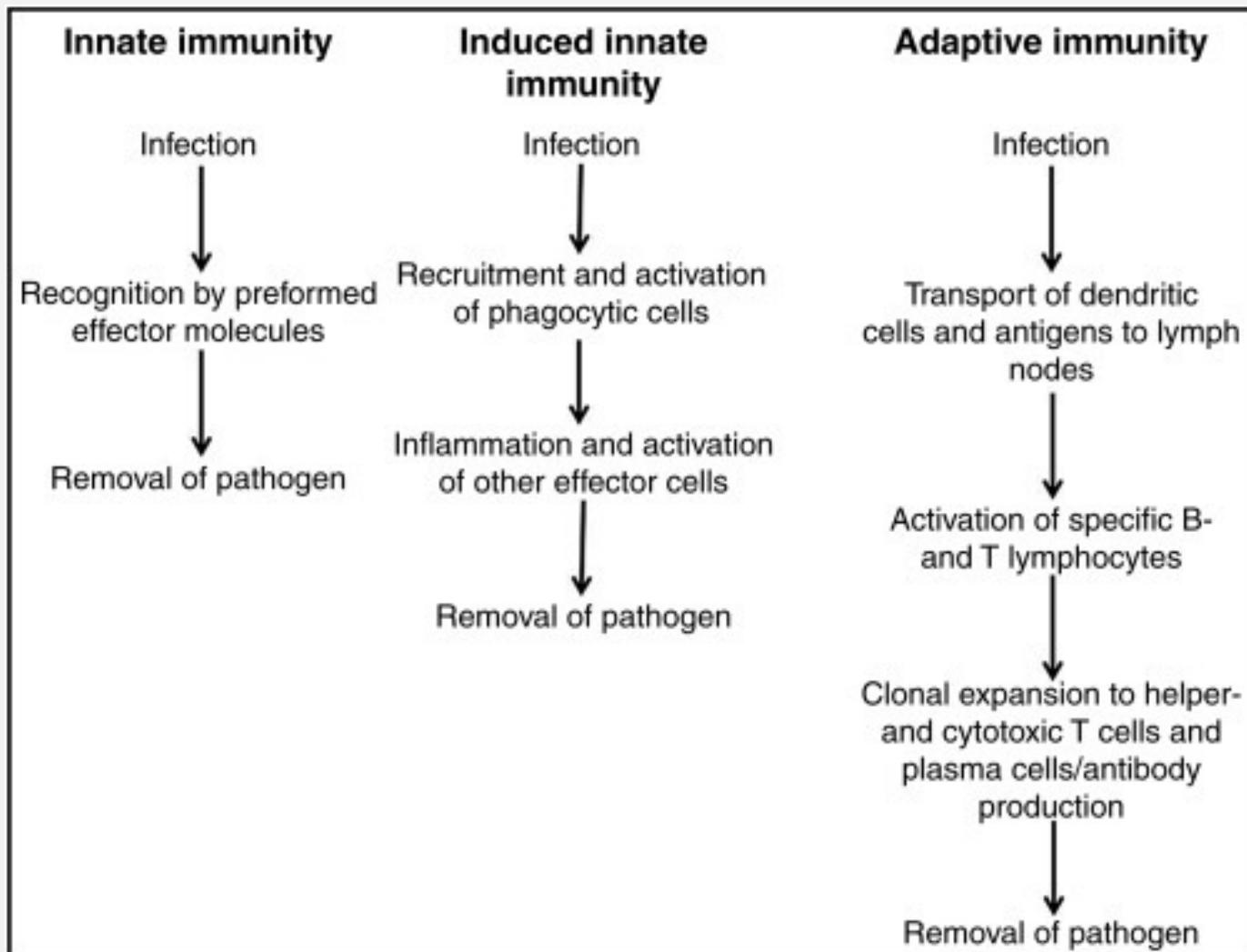
INNATE AND ADAPTIVE IMMUNITY



INNATE AND ADAPTIVE IMMUNITY



SUMMARY INNATE AND ADAPTIVE IMMUNITY

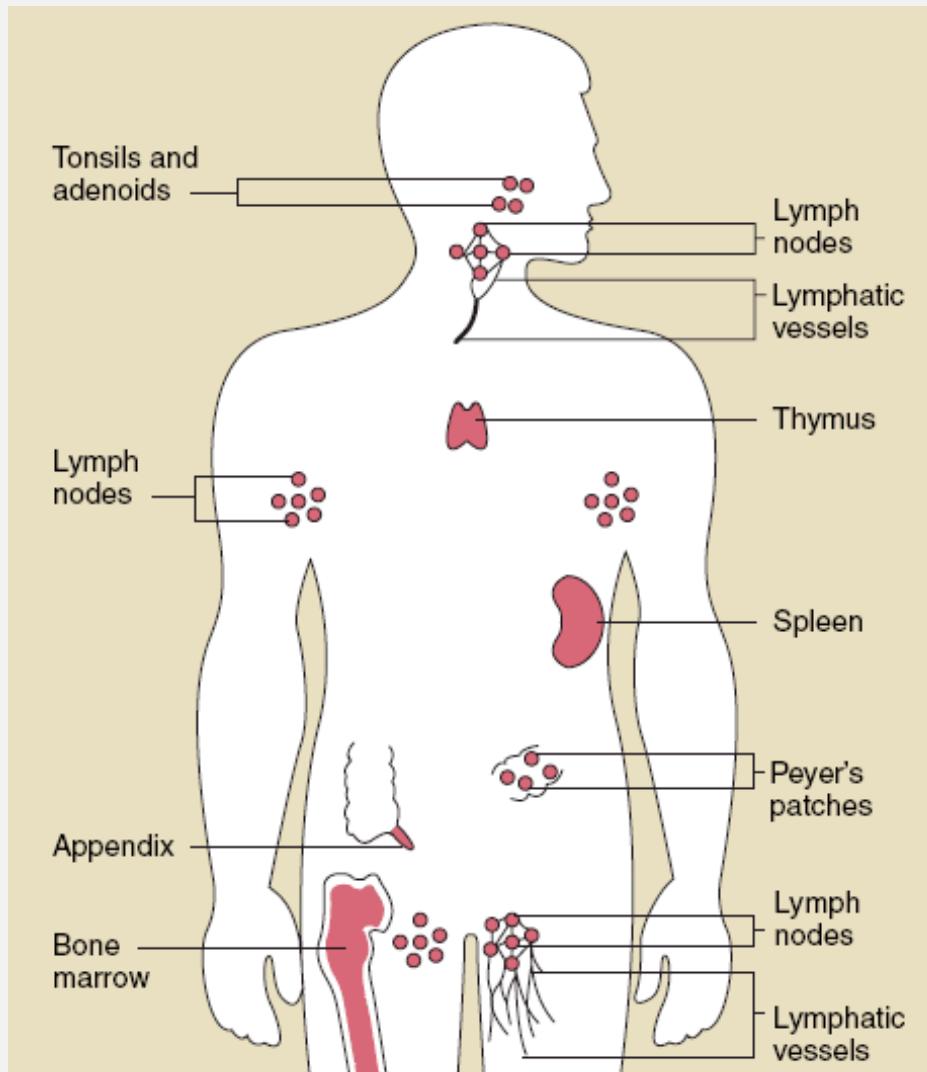


ORGANS OF THE IMMUNE SYSTEM

ORGANS OF THE IMMUNE SYSTEM

- The immune system is made up of organs that control the production and maturation of certain immune cells
- **Primary (1°) lymphoid organs** - the thymus and bone marrow
- **Secondary (2°) lymphoid organs** - spleen, tonsils, lymphatic vessels, lymph nodes, adenoids and liver
- **Lymphoid tissues** – mucous membranes (nose, throat, lungs, intestines, bladder and reproductive organs)

ORGANS OF THE IMMUNE SYSTEM



ORGANS OF THE IMMUNE SYSTEM

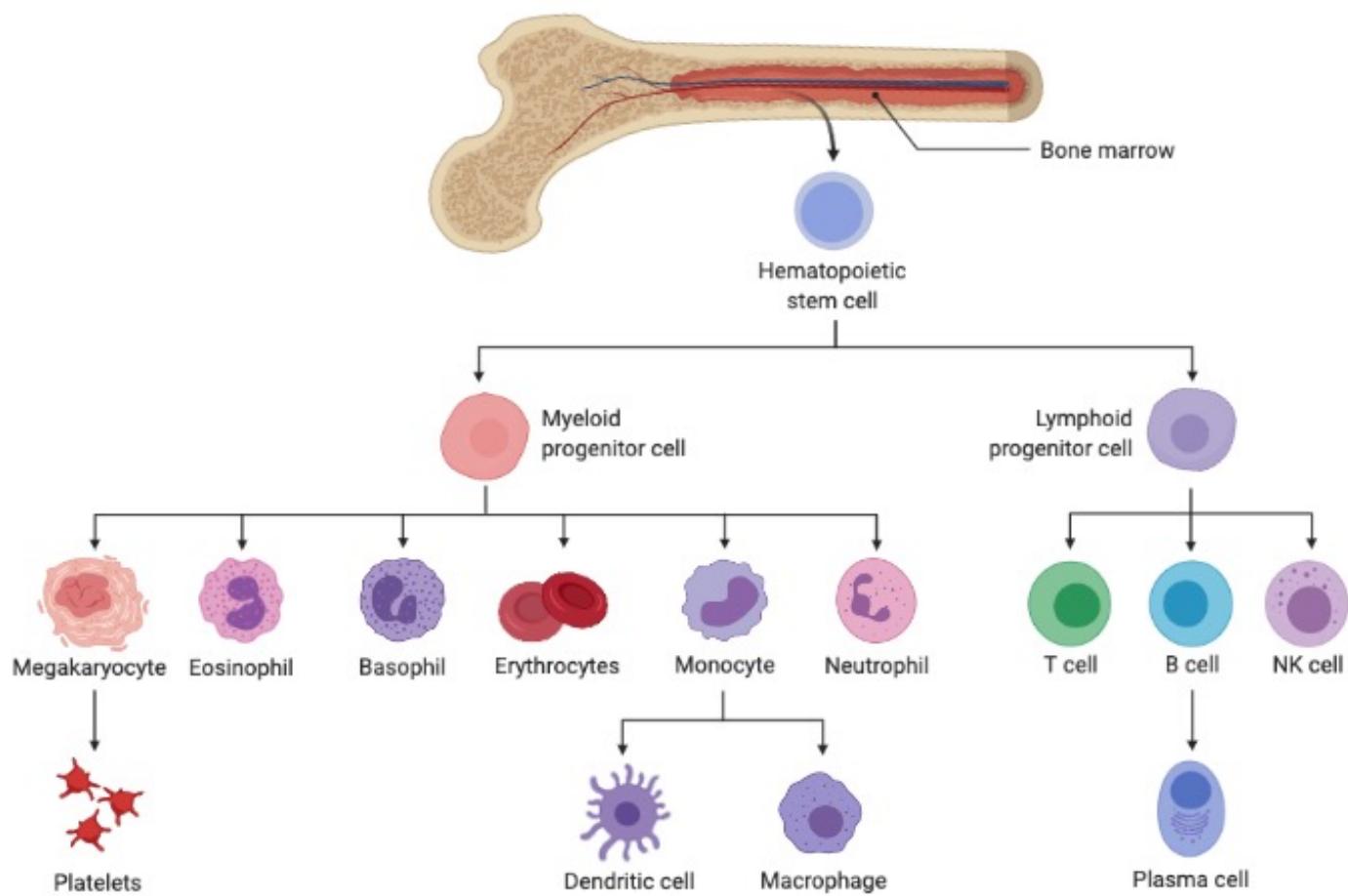
- The secondary lymphatic organs are the place where the defence cells do their actual work
- In these places, the defence cells have constant contact with non-self substances and pathogens

ORGANS OF THE IMMUNE SYSTEM

Bone marrow

- Is a key element of the lymphatic system that generate **myeloid** and **lymphocytes** from immature **hematopoietic progenitor cells** (stem cell)
- They then migrate from the bone marrow into the bloodstream and reach other organs and tissues, where the immune cells mature and specialize

ORGANS OF THE IMMUNE SYSTEM



ORGANS OF THE IMMUNE SYSTEM

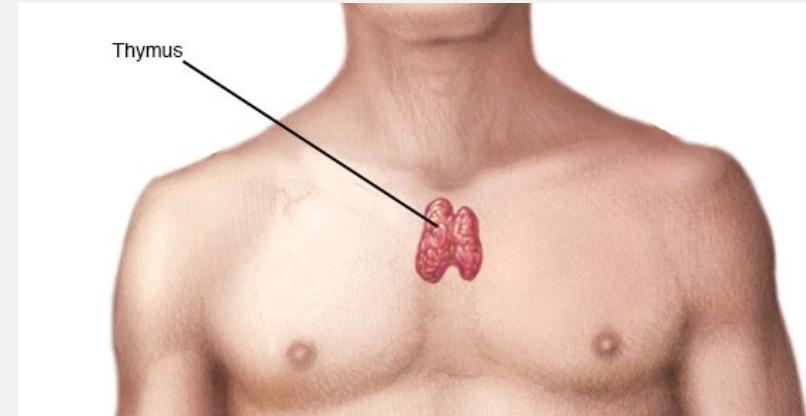
Bone marrow

- At birth, many bones contain red bone marrow, which actively produce immune cells (hematopoietic progenitor cells).
- Adults only have red bone marrow in a few bones as most marrow turns into fat tissue. Eg. ribs, in the breast bone and in the pelvic bone

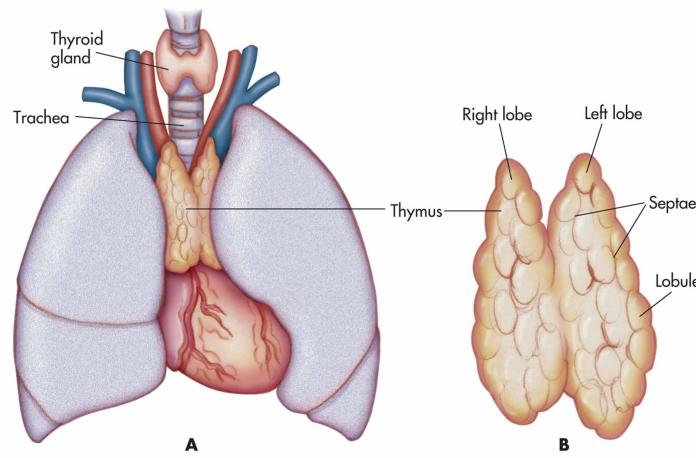
ORGANS OF THE IMMUNE SYSTEM

Thymus

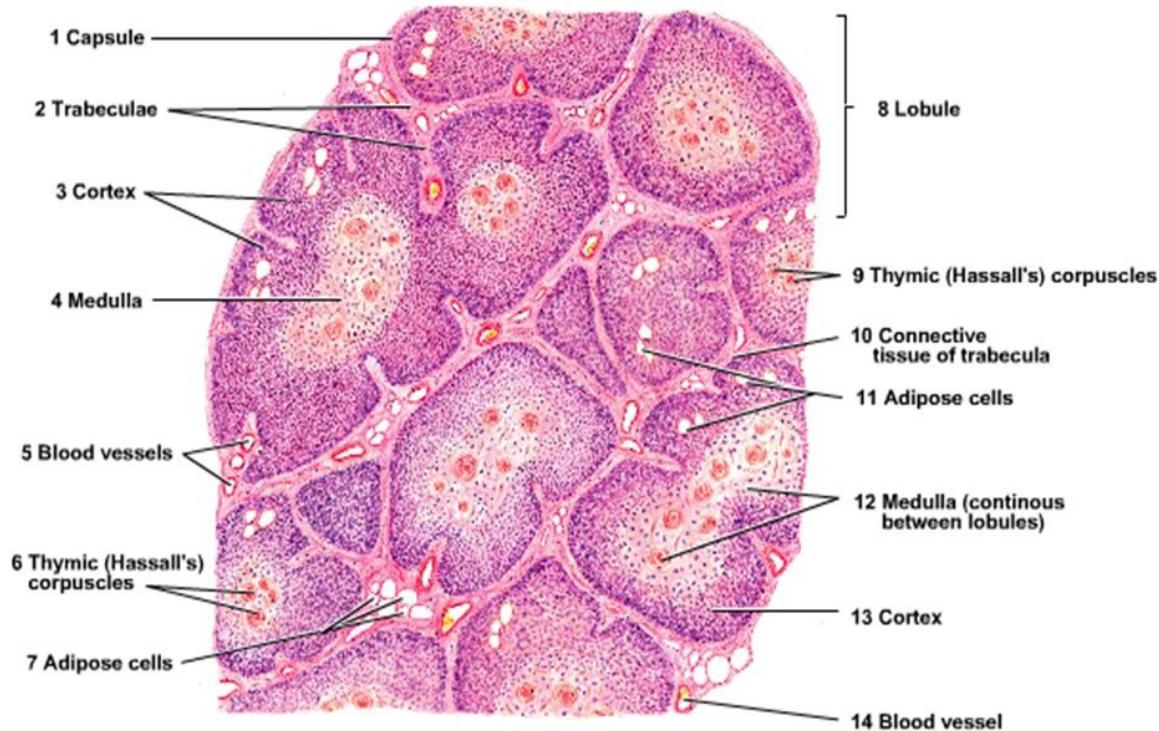
- behind sternum (breast bone)
- The thymus enlarges during childhood into adolescence and begins to **atrophy** at puberty due to hormonal changes
- It shrinks rapidly with age until its almost indistinguishable from the surrounding fatty tissue ie. **replaced by adipose tissue**



ORGANS OF THE IMMUNE SYSTEM



Thymus



ORGANS OF THE IMMUNE SYSTEM

Thymus

- Loss or lack of the thymus results in severe immunodeficiency and subsequent high susceptibility to infection
- The thymus contains mature lymphocytes, immature lymphocytes, and stroma
- Structured into an **inner medulla** and an **outer cortex**

ORGANS OF THE IMMUNE SYSTEM

Thymus - “T cell schooling”

- Immature T cells from the bone marrow *travel to the cortex tissues of the thymus through the bloodstream*
- They then undergo proliferative expansion during which antigen receptors are formed
- The growing T cells are sorted so that only those that express T-cell receptors (TcRs) and can bind to foreign MHC molecules will survive. So that surviving cells cannot mistake self-molecules for antigens (central tolerance)

ORGANS OF THE IMMUNE SYSTEM

Thymus - “T cell schooling”

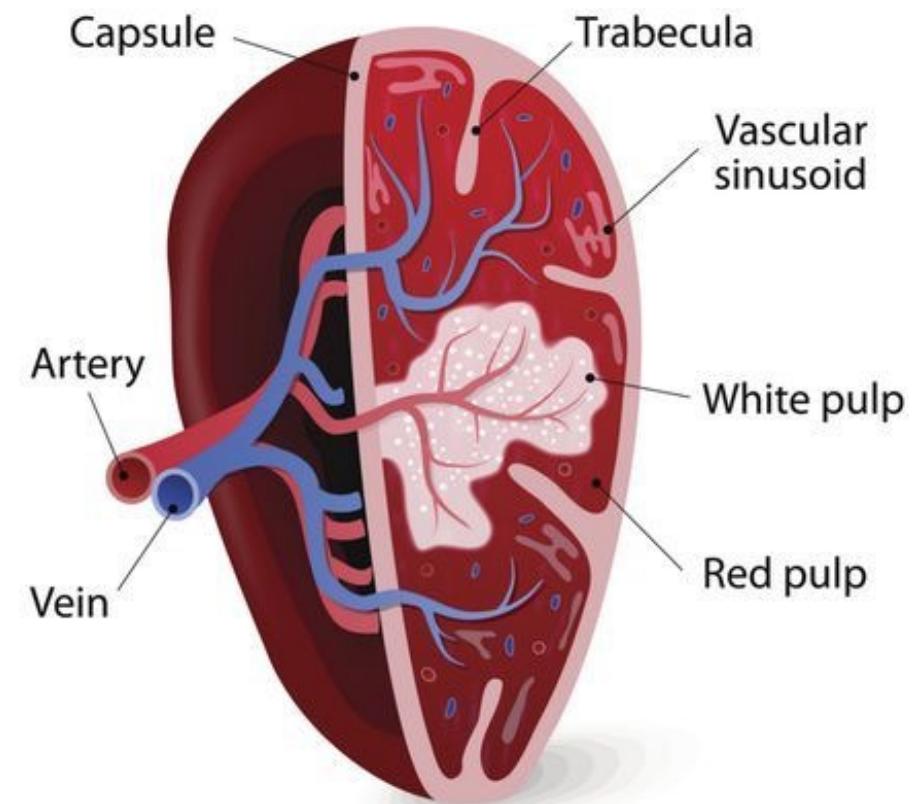
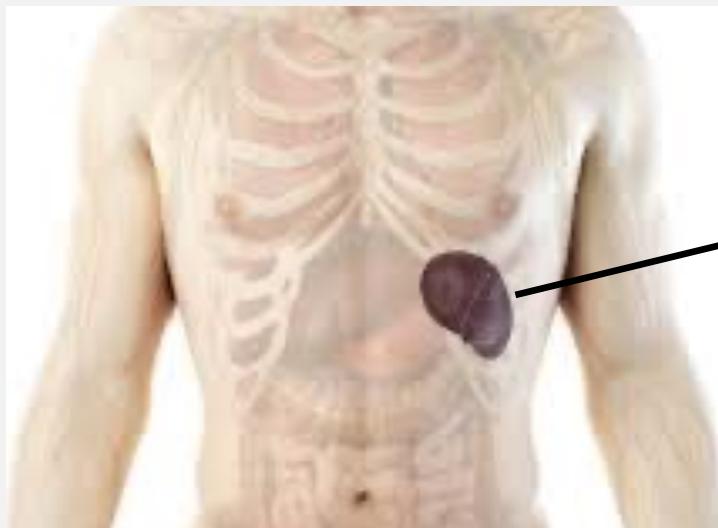
- Only 2-4% of T cells survive this sorting process.
- The thymus is most active early in life for building a large reservoir of T cells.
- ✓ Though removal of the thymus in childhood causes severe immunodeficiency, later in life this is not an issue because of the proliferation of thymus activity early in life

ORGANS OF THE IMMUNE SYSTEM

- **Thymus - “T cell schooling”**
- The thymus sorts T cells so that they will be inactive towards host molecules
- The thymus is mostly effective at preventing this occurrence;
 - ✓ But those with certain genetic characteristics (such as altered MHC complexes) may be more likely to develop autoimmune diseases with the few T-cells that aren't properly selected by the thymus.

ORGANS OF THE IMMUNE SYSTEM

Spleen



ORGANS OF THE IMMUNE SYSTEM

Spleen

- Similar in structure to a large lymph node and acts primarily as a **blood filter** and **storage for lymphocytes** of the immune system.
- Synthesizes antibodies in its **white pulp**.
- Removes antibody-coated bacteria along with antibody-coated blood cells through blood and lymph node circulation.

ORGANS OF THE IMMUNE SYSTEM

Spleen

Main functions of the spleen are:

- Produce immune cells to react with antigens
- Remove particulate matter and old blood cells by large phagocytic cells devouring old red blood cells, bacteria, cell particles, toxins
- Also produce blood cells during foetal stage
- Red pulp is made of connective tissue which contains macrophages

ORGANS OF THE IMMUNE SYSTEM

Spleen

- It is the site of **blood filtration** in the spleen.
- White pulp contain large amounts of lymphocytes including antigen -presenting cells.
- The spleen is a centre of activity of the mononuclear phagocyte system.
- Its absence causes a predisposition to infections such as pneumonia (gram-ve), and protozoa and diminished responsiveness to some vaccines.

ORGANS OF THE IMMUNE SYSTEM

Tonsils :

Are lympho-epithelial tissues located near the oropharynx and nasopharynx or behind the tongue.

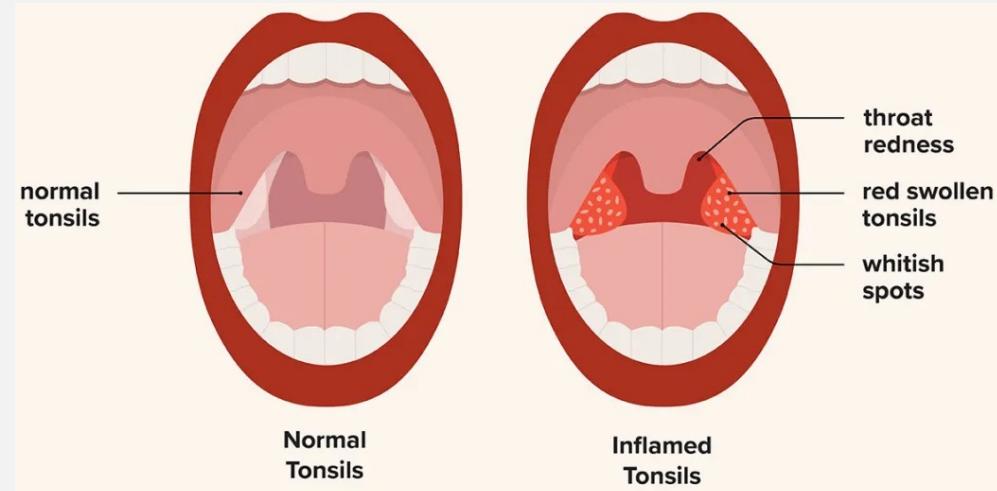
- One of the immune system's first lines of defence against ingested or inhaled foreign pathogens
- Contain very deep and narrow folds in their tissues called **crypts**



ORGANS OF THE IMMUNE SYSTEM

Tonsils :

- Contain specialized macrophage cells that collect antigens produced by respiratory tract pathogens
- Captured antigens are presented to B and T cells within the tonsil, then the B cells **migrate to germlinal centres within the tonsil** as an adaptive immune response is initiated



ORGANS OF THE IMMUNE SYSTEM

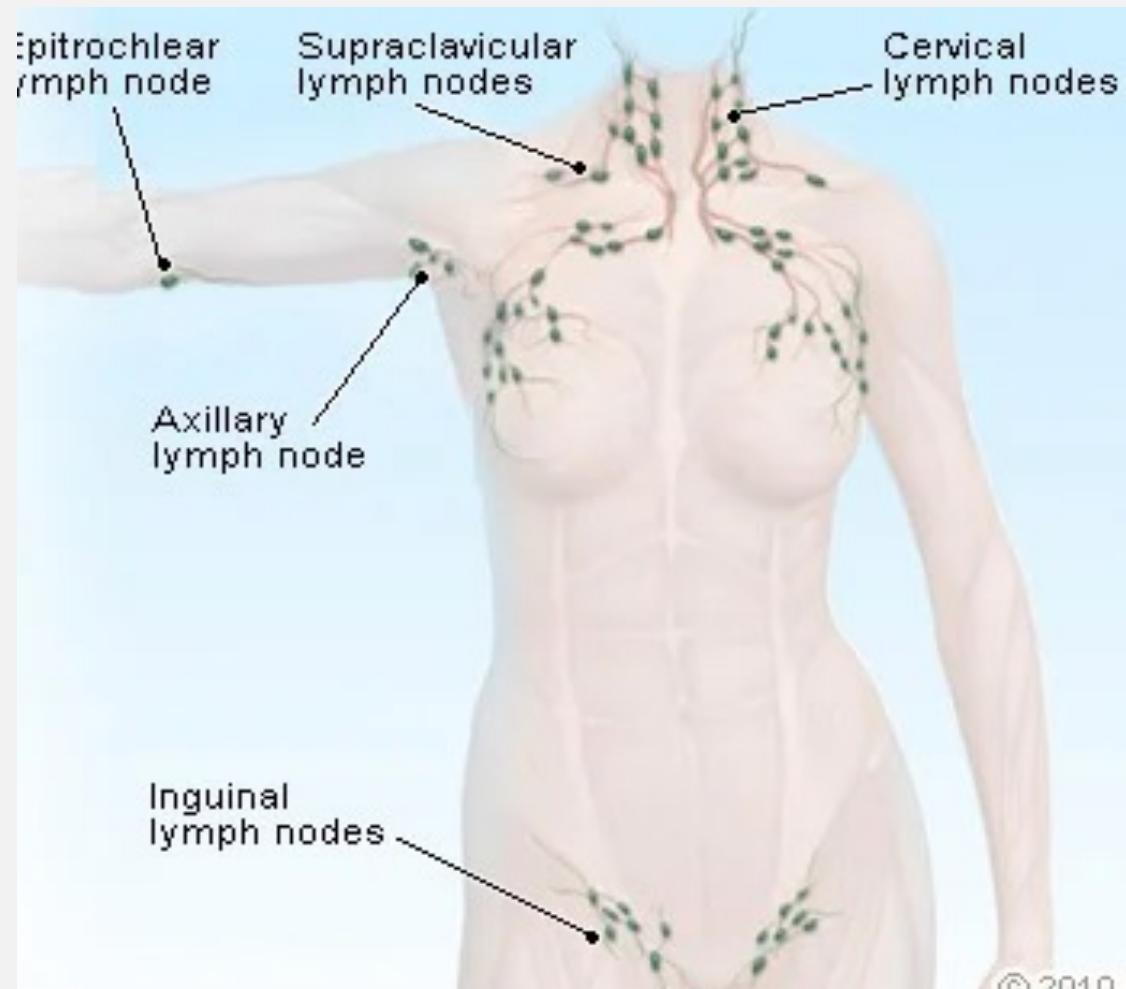
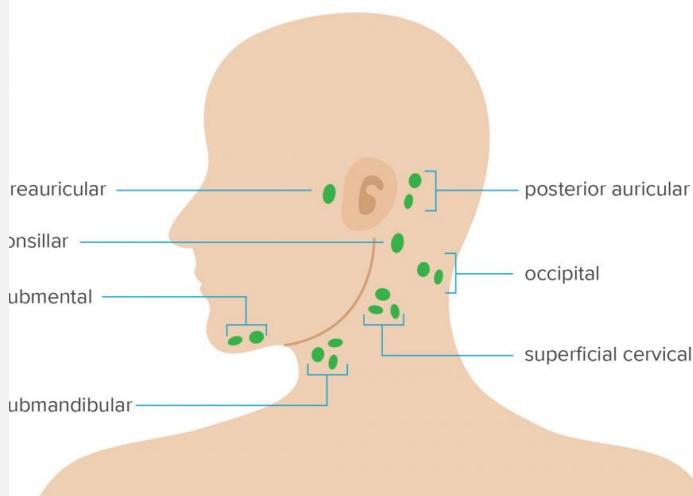
Lymph nodes:

- Distributed widely throughout areas of the body and are commonly found in clusters at the underarm and abdominal areas along the lymphatic system and linked by lymphatic vessels

ORGANS OF THE IMMUNE SYSTEM

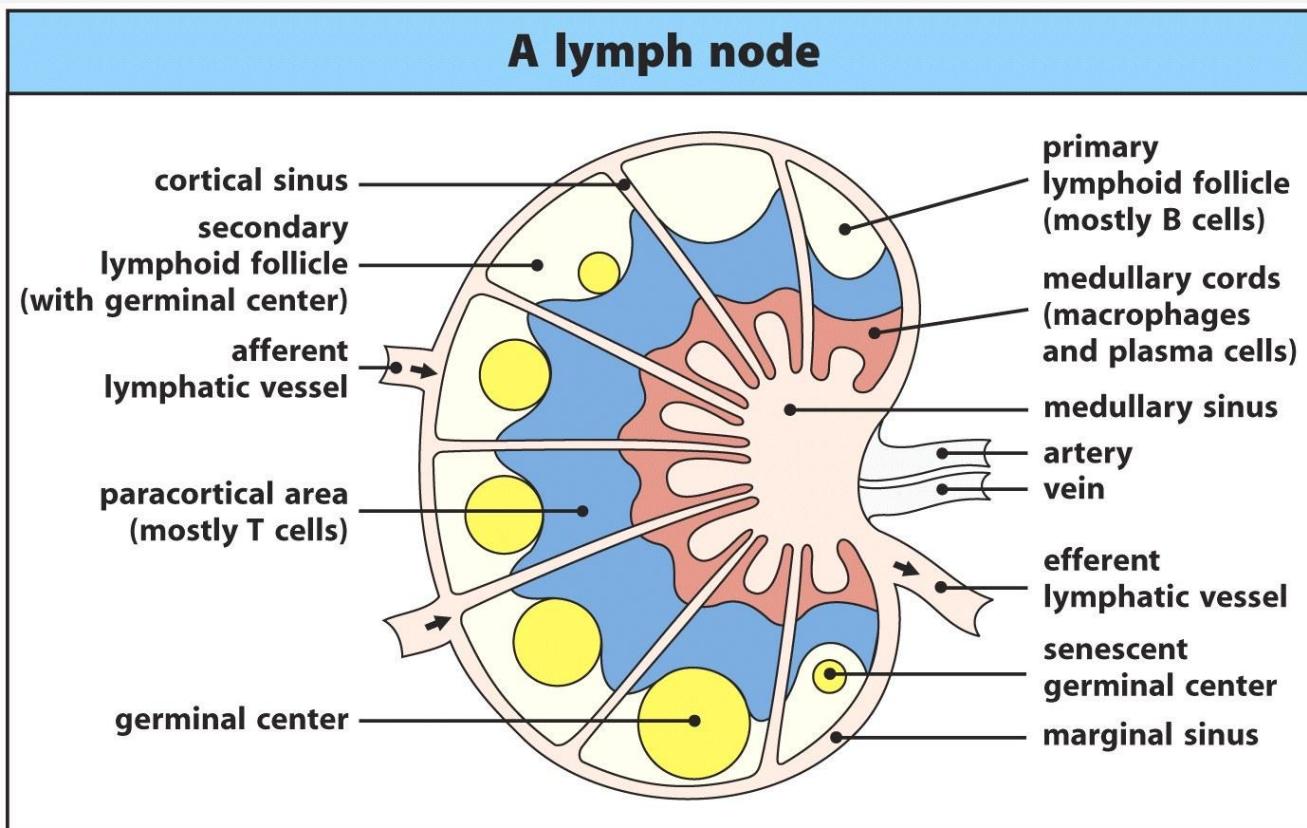
Lymph nodes:

Facial Lymph Nodes



ORGANS OF THE IMMUNE SYSTEM

- **Lymph node** consists of lymphoid follicles with an inner portion called the **medulla** and outer portion called the **cortex**



ORGANS OF THE IMMUNE SYSTEM

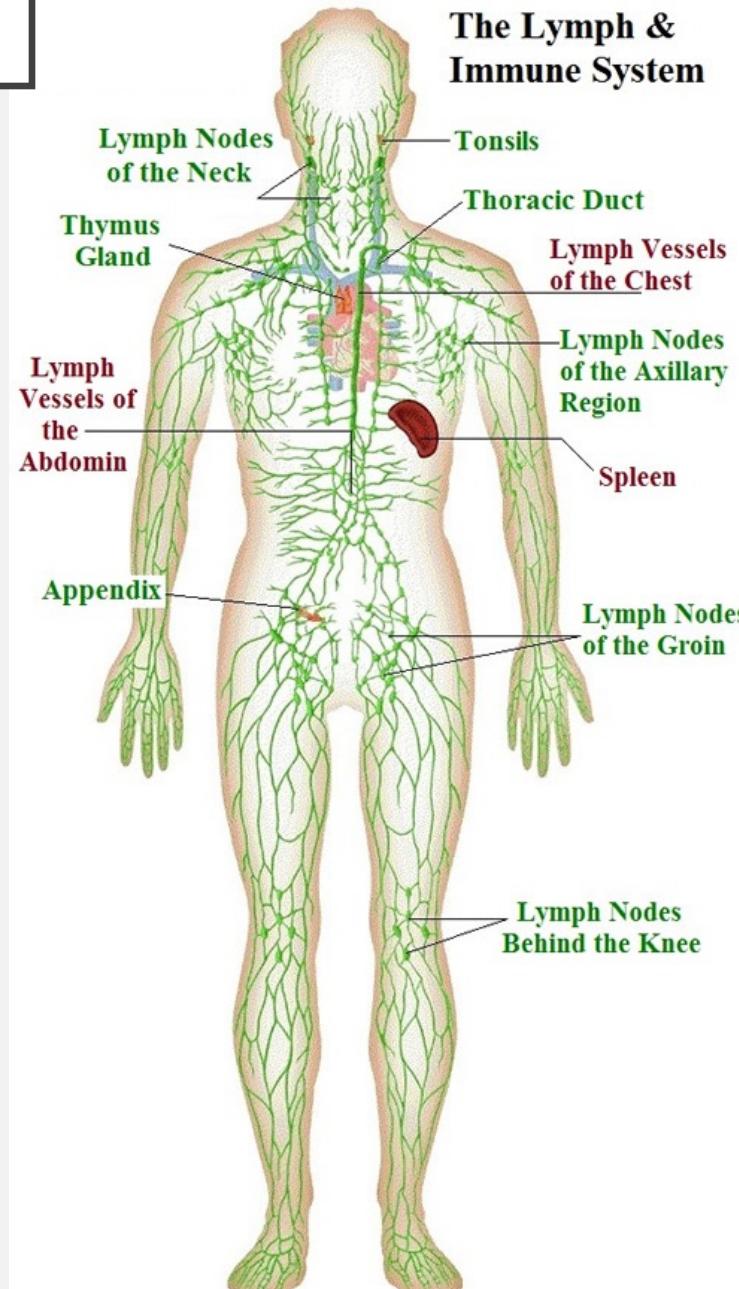
- **The selection of B cells, or *B lymphocytes*, occurs in the germinal centre of the lymph nodes**
- The Lymph nodes act as filters or traps for foreign particles and are important in the proper functioning of the immune system
- They are packed tightly with lymphocytes and macrophages



ORGANS OF THE IMMUNE SYSTEM

Lymphatic circulatory system

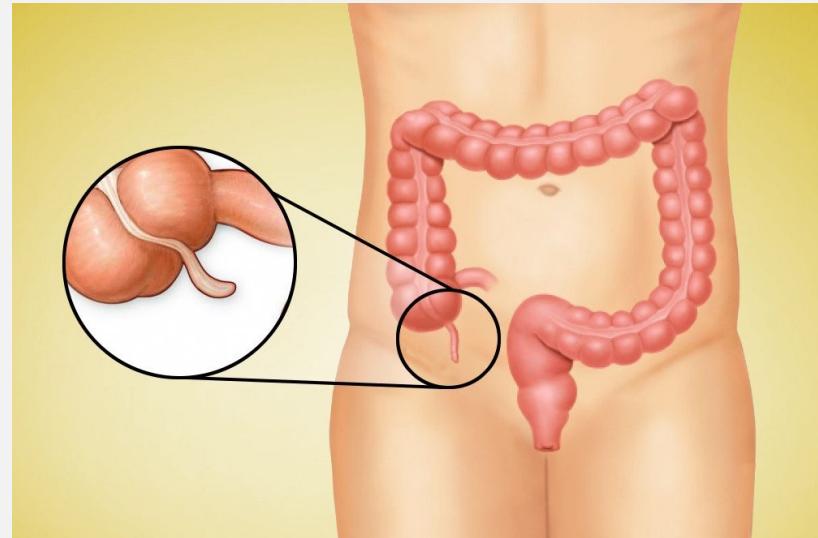
- Part of the circulatory system, comprising a network of lymphatic vessels that carry a clear fluid (lymph), unidirectionally towards the heart.
- Transports white blood cells to and from the lymph nodes into the bones
- Transport antigen-presenting cells (eg. Phagocytic cells and dendritic cells) to the lymph nodes where an immune response is stimulated



ORGANS OF THE IMMUNE SYSTEM

Appendix

- Contains aggregated lymphoid tissues and white blood cells.
- Activates B and T cells in the presence on invading pathogens

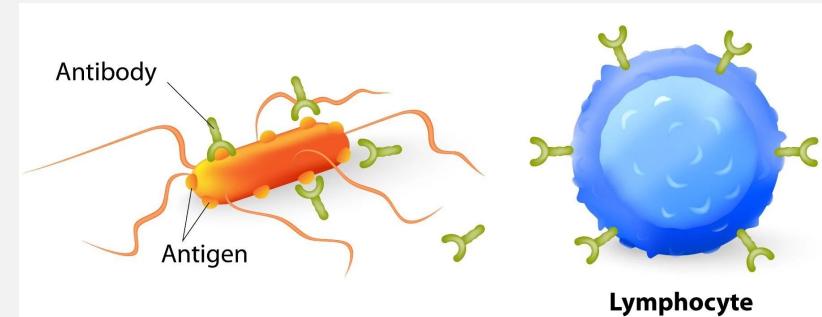


IMMUNE RESPONSE

HUMORAL IMMUNE RESPONSE

HUMORAL IMMUNITY

- Humoral immunity is named so because it involves substances found in the body fluids (humors)
- Also referred to as **antibody-mediated immunity**.
- It involves:
 - ✓ Germinal centre formation and isotype switching
 - ✓ Affinity maturation
 - ✓ Antibody production and memory
- cell generation.



HUMORAL IMMUNITY

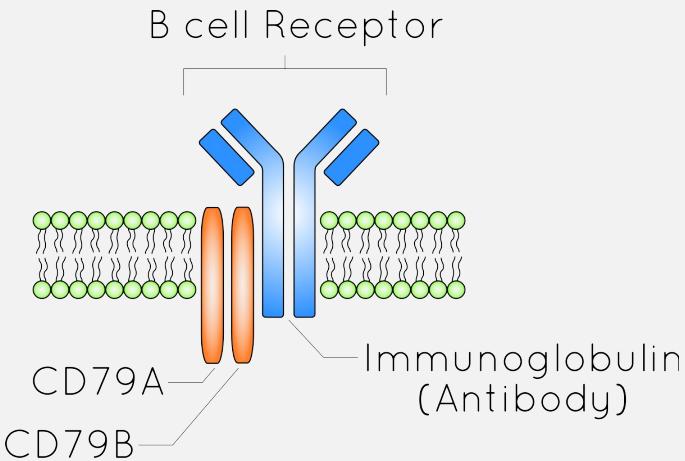
- It also refers to the effector functions of antibody:
 - ✓ T cell activation (Th2) >>> cytokine production,
 - ✓ Pathogen and toxin neutralization,
 - ✓ Complement activation
 - ✓ Promotion of opsonisation for phagocytosis and pathogen elimination.

HUMORAL IMMUNITY

Antibody Production

B cells are activated by:

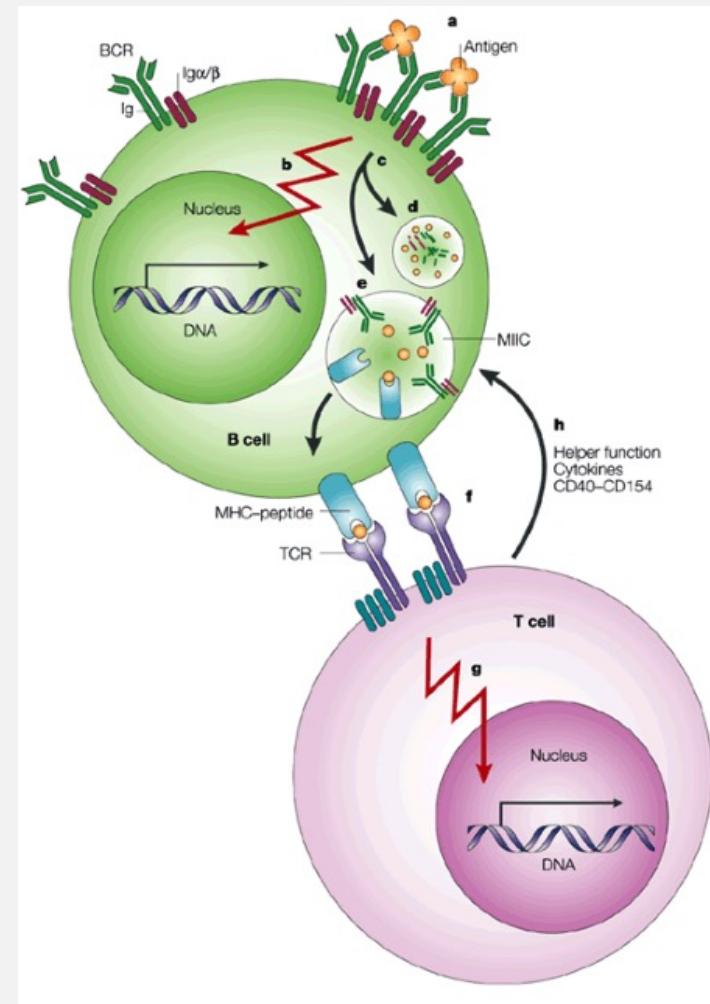
- Antigens cross linking B cell receptors(BCR)
- Activated T cell in the presences of T dependent antigens (MHC Class II)
 - Isotype switching to IgG, IgA, and IgE



>>> trigger B cell proliferation and differentiation into plasma cells.

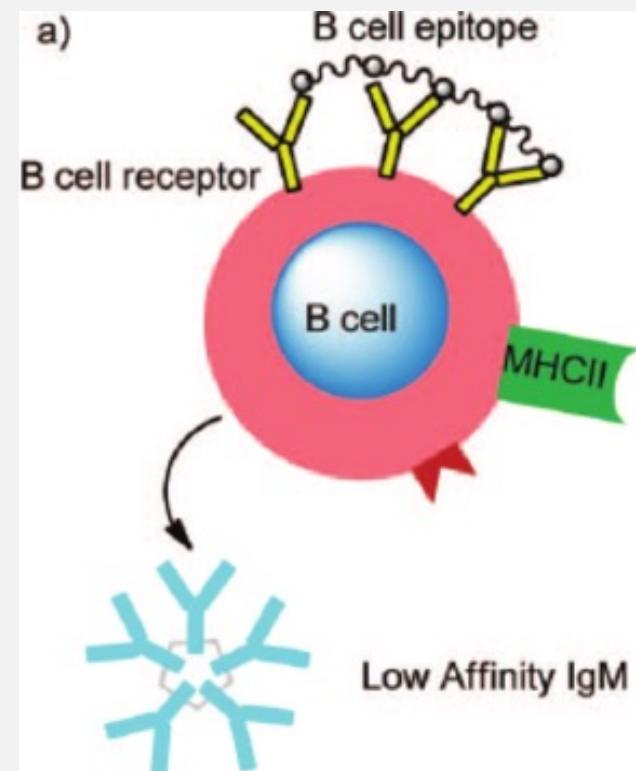
HUMORAL IMMUNITY

- Antigens bounded to BCR are internalized with its BCR; antigen are degraded (processed), combined with Class II MHC molecule, and presented to effector Th2 cells
- Effector Th2 cells bind B cells via cell adhesion molecules(CAM), and TCR



HUMORAL IMMUNITY

- T cell CD40 ligand (CD40L) binds B cell CD40 to send co-stimulatory signal (cytokines IL-4, IL-5, and IL-6) for B cell activation
- B cell divide and differentiate into antibody-secreting plasma cells
- IgM is secreted before isotype switching

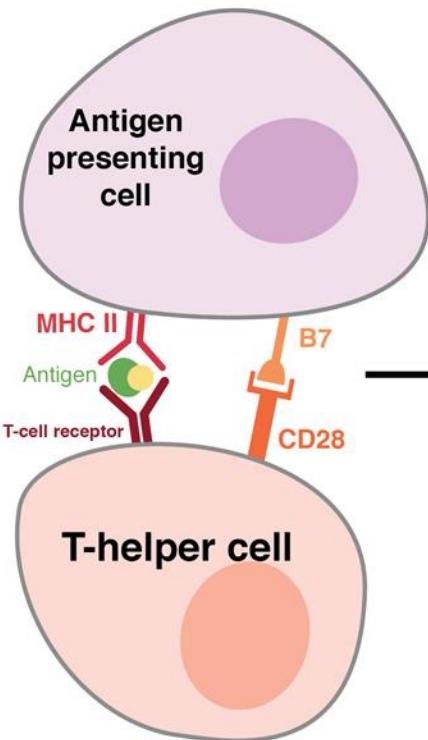


HUMORAL IMMUNITY

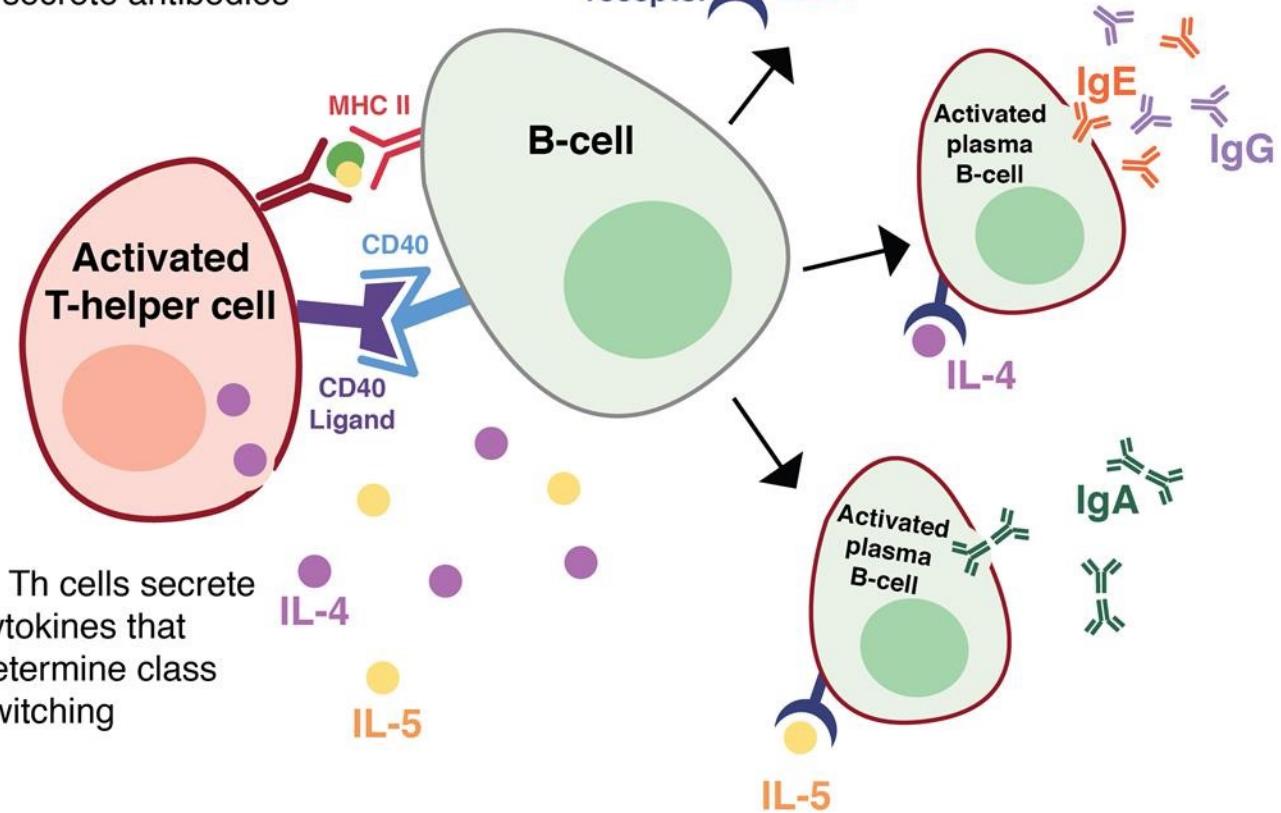
- Isotype switching (IgG, IgE, IgA, IgD) increases the functional diversity of Ig molecules
- It requires DNA recombination (rearrangement and splicing)
- Cytokines secreted favours switching to a specific class of immunoglobulins.
- B cells differentiate into few plasma cells that are short-lived, they migrate to the medullary cords and begin secreting IgM.

Activation and Class-switching of B-cells

1. APC presents antigen to T-helper cells



3. Activated Th cells interact with B-cells via CD40 ligand, activating B-cells to proliferate, differentiate, and secrete antibodies

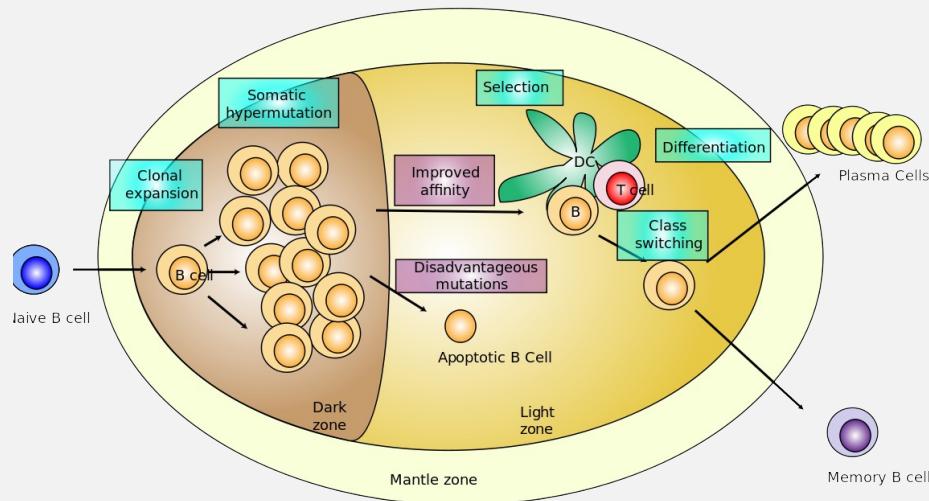
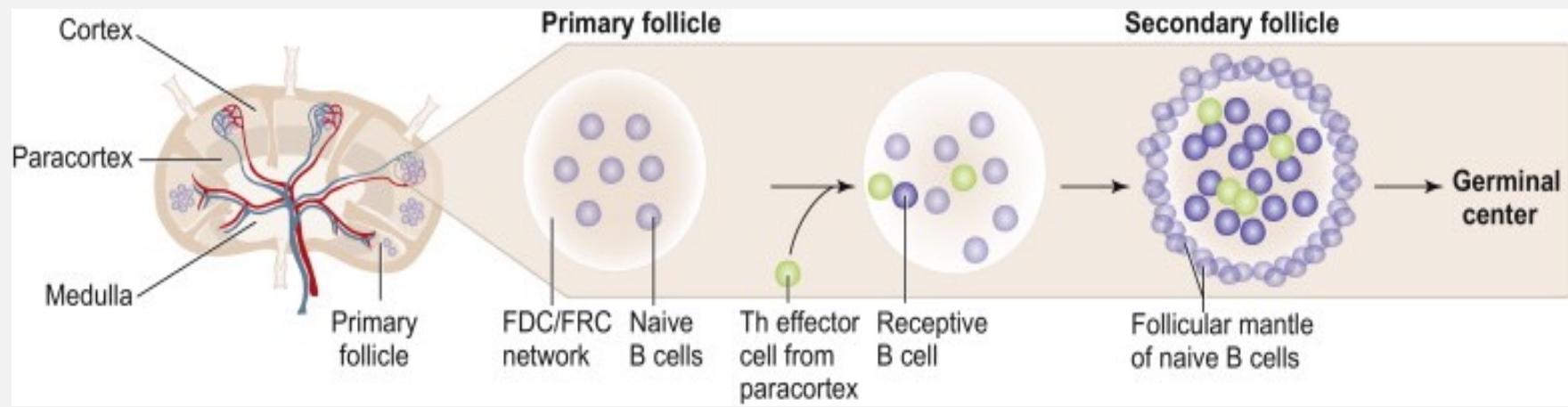


2. B7 is expressed and interacts with CD28, activating T-helper cells

HUMORAL IMMUNITY

- They migrate to the **primary follicles of the lymph node**, which are present in unstimulated peripheral lymphoid tissues, in the foetus, and in germ free animals.
 - They contain mainly **follicular dendritic cells (FDC)** and IgM⁺ IgD⁺ B cells (naïve resting B cells).
 - B cell **blasts** (dividing cells) form secondary follicles (**germinal centres**), surrounded by the Th2 cells that activated the B cells

HUMORAL IMMUNITY



HUMORAL IMMUNITY

- Antigen-binding specificity is achieved by **somatic hypermutation** in rapidly dividing B cells in the germinal centres.
- Mutation occurs in the hypervariable (antigen-binding) regions of H and L chains
- B cells which remain specific for the stimulating antigen are selected by binding antigen held on FcR and complement receptors on **follicular dendritic cells (FDC)**
 - Do not express MHC Class II molecules or
 - Act as APC for T cells.

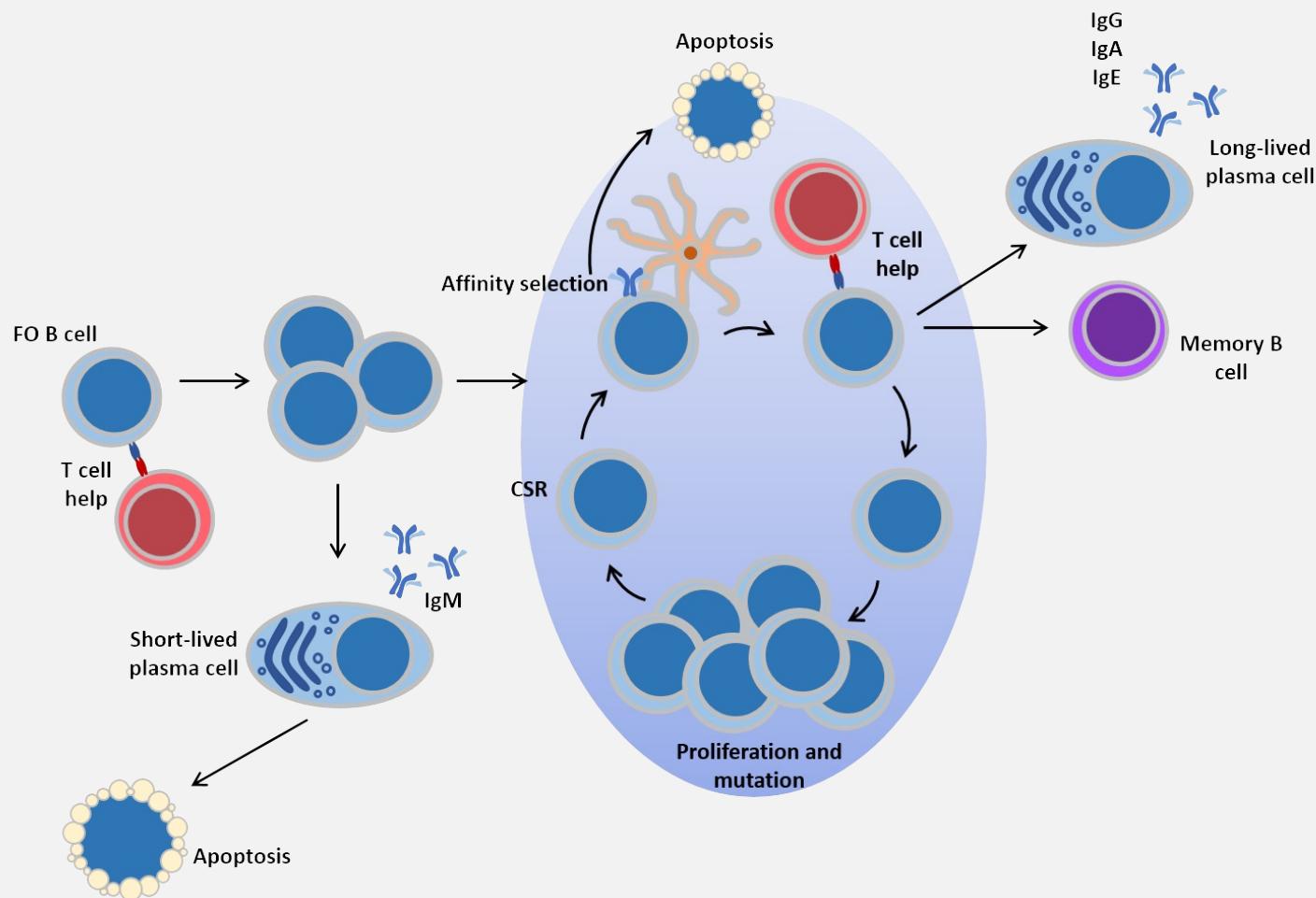
HUMORAL IMMUNITY

- Only B cells which bind antigen with high enough affinity continue to secrete antibody and differentiate into plasma cells; B cells with low affinity to antigen binding undergo **apoptosis**
- When antigen levels drop due to antigen clearance, further Th2 cell interaction with B cells signals them to become plasma cells or **memory cells**

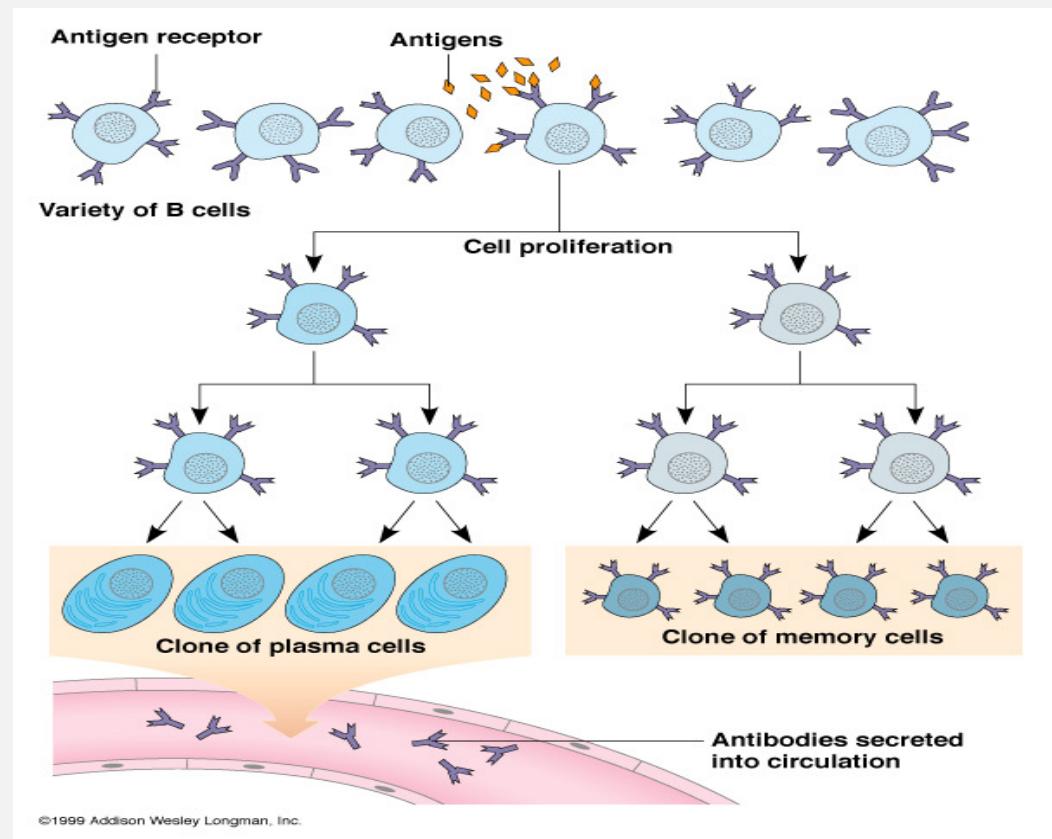
HUMORAL IMMUNITY

- **Plasma cells** no longer divide or respond to antigen but produce / secrete **only antibodies**
- Other B cells become memory cells, which can be rapidly re-stimulated by antigen
- They often have membrane IgG, IgA, or IgE and higher levels of ICAM-1 and CR
- Polyclonal activation happens when some antigens (**polyclonal B cell activators eg. LPS or carbohydrates**) bind B cell membrane receptors and provide co-stimulatory signals.
 - B cells divide and secrete antibody, specific IgM

HUMORAL IMMUNITY



CLONAL SELECTION OF B CELLS IS CAUSED BY ANTIGENIC STIMULATION



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Dorcas Owusu

HUMORAL IMMUNITY

Antibodies or immunoglobulins (secreted by B cells)

- Targeting an infective organism
 - Recruitment of immune cells
 - Neutralisation of toxins
 - Removal of foreign antigens from circulation
 - Complement activation
 - Stimulation of cells that can ‘eat’ foreign substances
 - Activation of mast cells

CELL MEDIATED IMMUNE RESPONSE & DEVELOPMENT

CELL-MEDIATED IMMUNITY

- Cell-mediated immunity (CMI) involves (1) activation of T cells, (2) Production of antigen-specific cytotoxic T-lymphocytes and (3) Release of cytokines in response to an antigen.

Their functions include:

- Activating antigen-specific cytotoxic T-lymphocytes (CTLs) to destroy:
 - virus-infected cells
 - cells with intracellular bacteria
 - cancer cells displaying tumour antigens

CELL-MEDIATED IMMUNITY

- **Activating macrophages and Natural killer(NK) cells to destroy intracellular pathogens**
- Stimulating cells to **secrete a variety of cytokines** that influence the function of other cells in the adaptive or innate immune responses.
- Pathogens that are protected from antibody and the compliment system due to their intracellular locations are targeted by the cellular immunity.

CELL-MEDIATED IMMUNITY

- The progenitors of these cells migrate to and colonise the thymus. T cell development occurs in the thymus (**thymic education**)
- Developing progenitors within the thymus, also known as **thymocytes**,
 - undergo a series of maturation steps that can be identified based on the expression of different **cell surface markers**

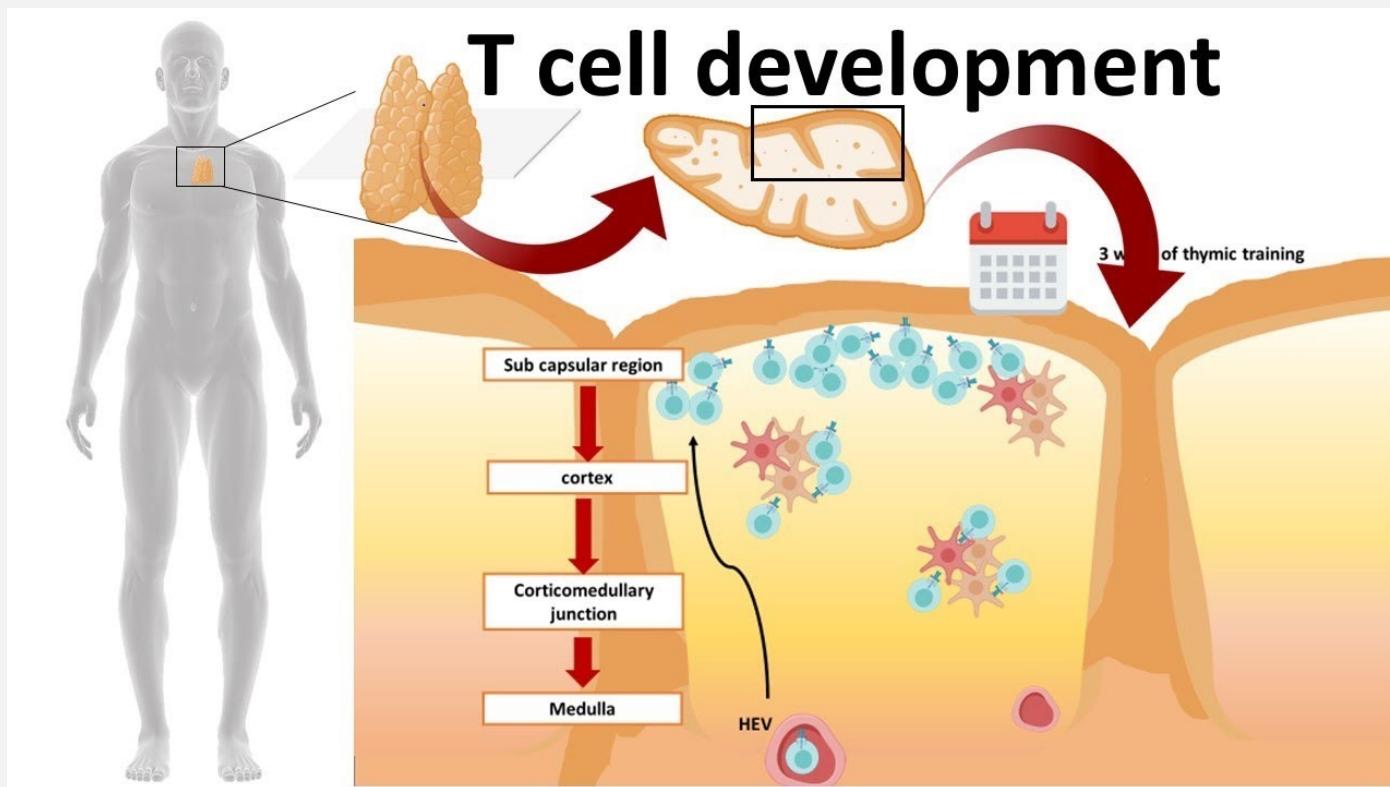
CELL-MEDIATED IMMUNITY

- Developing thymocytes interact with the ***thymus stromal*** in the ***outer cortex*** and an ***inner medulla*** region of the thymus
 - Differentiate
 - Undergo positive and negative selection.
- In the thymus, T cells develop their specific T cell markers, including:
 - TCR, CD3, CD4 or CD8, CD2

CELL-MEDIATED IMMUNITY

- The **thymus** is a multi-lobed organ composed of **cortical** and **medullary** areas surrounded by a capsule.
- T cell *precursors enter the subcapsular cortical areas, where they proliferate.*
- As they differentiate, they move from the cortex towards the *medulla of the thymus; where they undergo cell development.*
- Most cells that enter the thymus die by apoptosis without successfully completing the steps required for becoming a mature naive T cell.

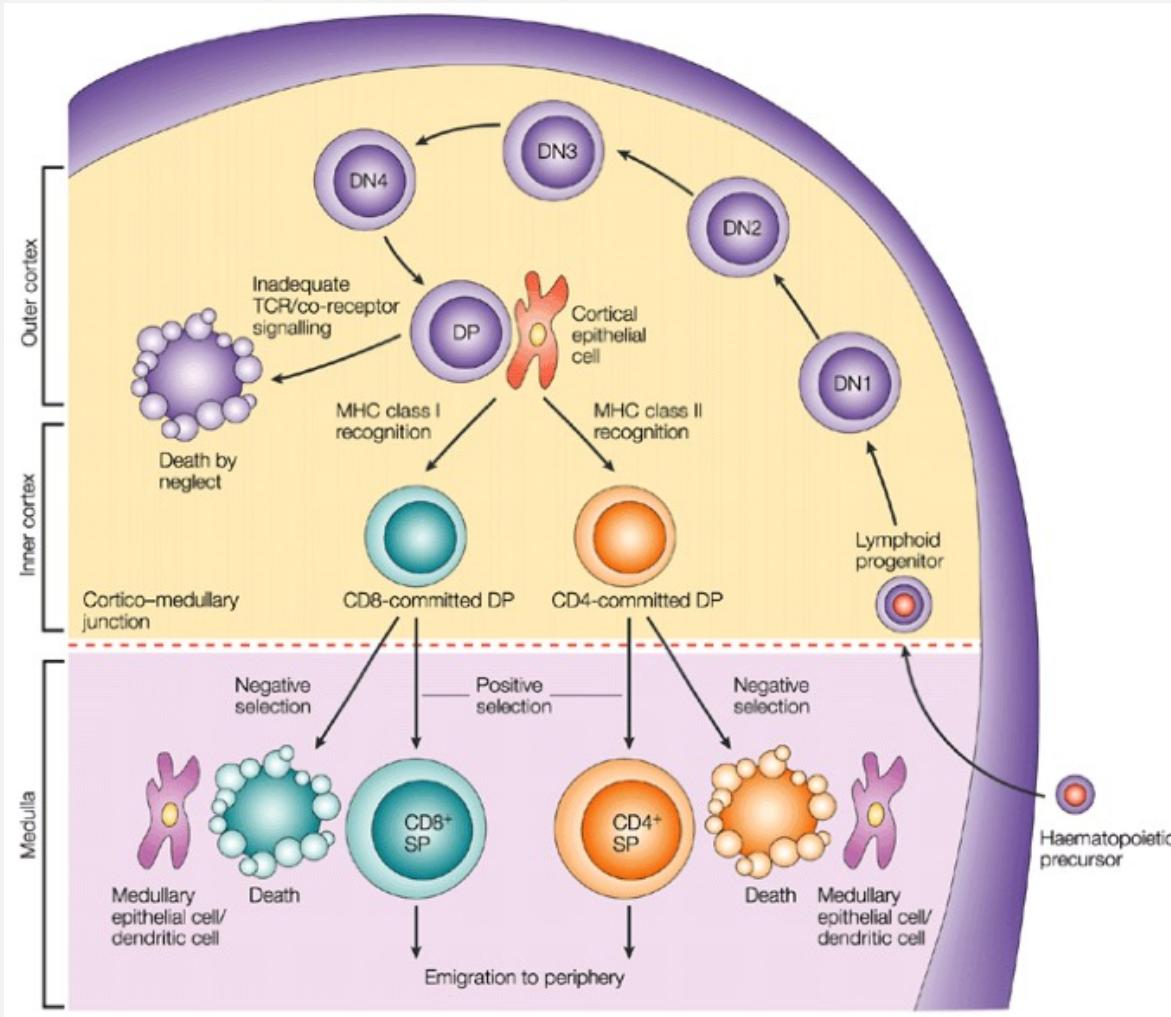
CELL-MEDIATED IMMUNITY



CELL-MEDIATED IMMUNITY

- Progenitor cells begin to express CD2 but are **double negative(DN)** for CD4 and CD8 (CD4⁻ CD8⁻)
- Productive rearrangement of TCR **beta chain** followed by its expression on the T cell membrane with CD3 and surrogate **alpha chain** leads to the expression of both CD4 and CD8(**double positive, DP**)
- Double positive T cells move into the **cortico-medullary junction**, where they undergo **positive and negative selection** and mature into Th and Tc cells

CELL-MEDIATED IMMUNITY



CELL-MEDIATED IMMUNITY

- **Positive selection** occurs when DP - T cells bind cortical epithelial cells expressing Class I or Class II MHC
 - Enough affinity to get the *survival signal*
 - Positive selection on Class I MHC will produce a CD8+ Tc cell
 - Positive selection on Class II MHC will yield a CD4+ Th cell.

CELL-MEDIATED IMMUNITY

- **Negative selection** occurs when double positive T cells bind to bone-marrow derived APC (macrophages and dendritic cells) expressing Class I (self-antigens) or Class II MHC
- MHC presents self peptides in the absence of pathogen
- Enough affinity to receive an ***apoptosis signal.***
- remove thymocytes that may cause autoimmunity, allow for tolerance of self by the immune system

CELL-MEDIATED IMMUNITY

- The remaining cells exit the thymus as mature naive T cells (2-4% survive)
- Typical T cells that leave the thymus (via the corticomedullary junction) are **(1)self-restricted, (2)self-tolerant, and (3)single positive.**
- T cell development is greatest during foetal development and before puberty. After puberty the thymus shrinks and T cell production declines
- Gamma delta T cells are still being investigated, Some are not MHC restricted and have limited diversity in their TCR

CELL-MEDIATED IMMUNITY

- **Naïve resting T cell** are stimulated by antigen peptide complexes presented with:
 - MHC Class I to cytotoxic CD8⁺ T cells
 - MHC Class II to helper CD4⁺ T cells

--- along with co-stimulation signals from the APC (dendritic cells, macrophages and B cells)

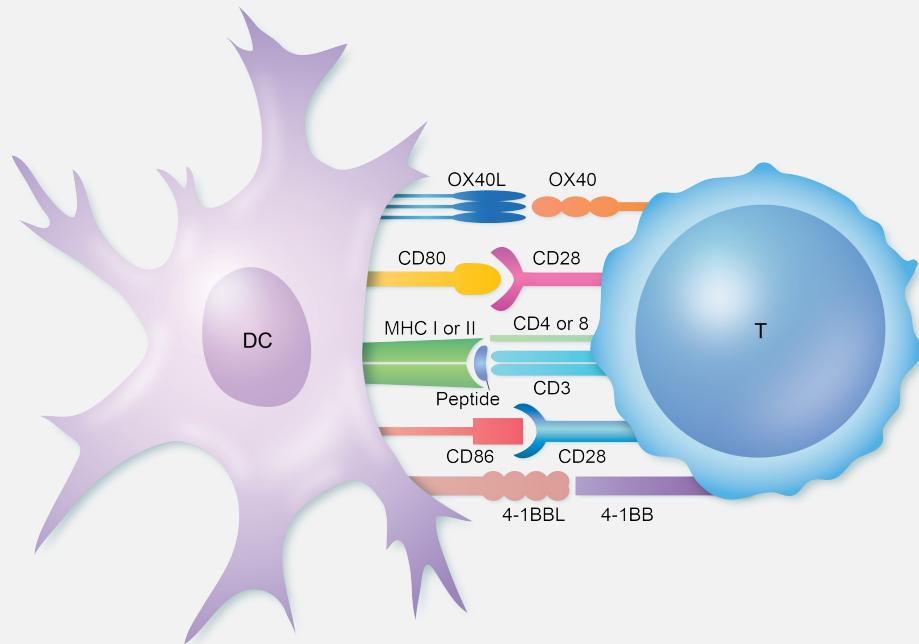
>>> T cells proliferate and differentiate into clones of **effector T cells**

CELL-MEDIATED IMMUNITY

- Naïve mature T cells recirculate the body through the secondary lymphoid organs, lymphatic circulatory system and the blood
- T cells in circulation encounter antigen on the surface of **antigen presenting cells (APCs)**, in circulation or in the secondary lymphoid organs).
- **T cell receptor (TCR)** binds to the antigen as it is held with MHC complex of APC.

CELL-MEDIATED IMMUNITY

- CD4 and CD8 molecules then bind to the MHC molecule to establish a complex
- T cells need secondary signals from other **co-stimulatory molecules** to produce many millions of T cells (clonal expansion) that recognise the specific antigen or regulate proliferation
- Given survival signals by several molecules to mount an effective immune response



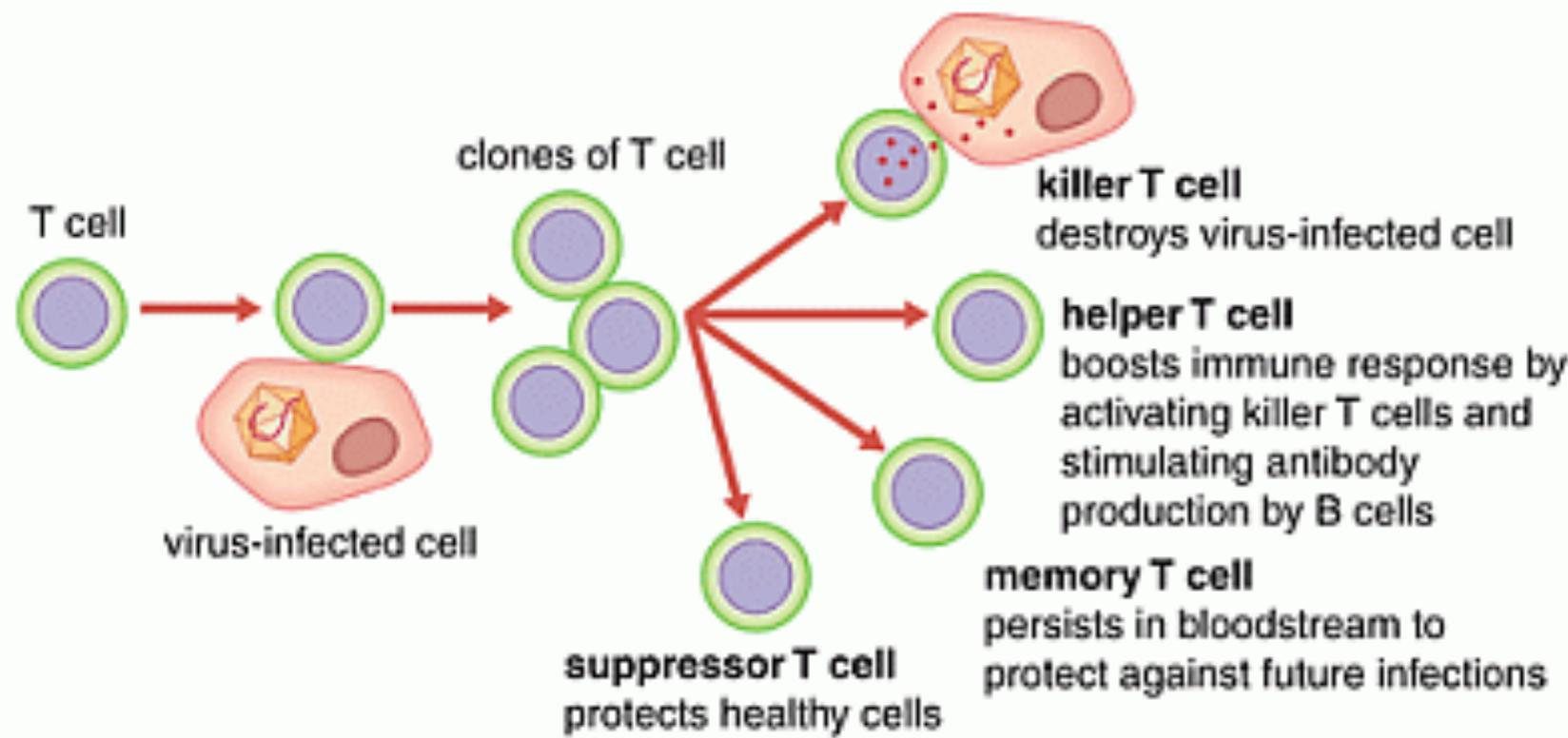
CELL-MEDIATED IMMUNITY

- Cytokines secreted further determines which subtype of T cell
 - **Th1** - effectors against intracellular bacteria and protozoa (IFN- γ and IL-2)
 - **Th2** - effectors against extracellular parasites including helminths (IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25)
 - **Th3** - involved in mucosal immunity (TGF- β and IL-10)

CELL-MEDIATED IMMUNITY

- The resulting **effector T cell** population moves out to the site of the infection or inflammation to clear or assist clearance of pathogen.
- Immune cells at the site of the infection or inflammation (neutrophils, mast cells, and epithelial cells) also release cytokines, chemokines, short peptides which induce further activation and proliferation of the effector T cells.

T CELL ACTIVATION AND PROLIFERATION



CELL-MEDIATED IMMUNITY

T cell exhaustion (progressive loss of function)

- (1) Persistent antigen exposure and (2) lack of CD4 T cell help
- Longer exposure time and higher antigen load increases the severity of T cell exhaustion
 - Eg. during chronic infections, sepsis and cancer

CELL-MEDIATED IMMUNITY

Memory T cells

- After clonal expansion and elimination of foreign agent, some T cells(either CD4⁺ or CD8⁺) become memory T cells which are quickly converted into large numbers of effector T cells upon re-exposure to the specific invading antigen

CELL-MEDIATED IMMUNITY

SUMMARY

- T cells also function through the release of lymphokines (cytokines... etc.) into the blood which:
 - Signals B cells through contact for growth and activation
 - Activates phagocytic cells for phagocytosis
 - Stimulate of cytotoxic T cells during infection
 - Signal growth in cells, including other T cells, macrophages and eosinophils

- **T cell development**



ANTIBODIES

ANTIBODIES

Basic Structure

- Made up of : A flexible **Y-shaped molecule** with four protein chains:
 - 2 identical light chains
 - 2 identical heavy chains

ANTIBODIES

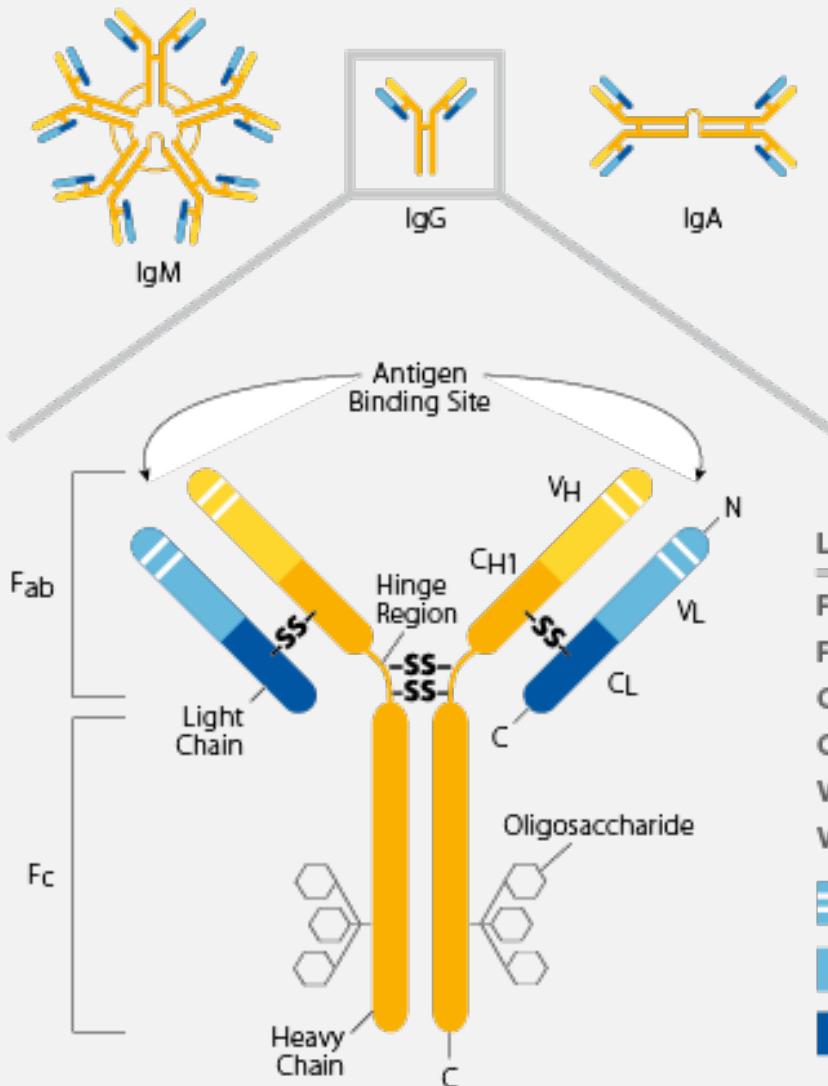
Basic Structure

- **Variable Regions:** Two sections at the end of Y's arms.
Contain the antigen binding sites (Fab).
- **Constant Regions:** Stem of monomer and lower parts of Y arms.
- **Fc region:** Stem of monomer only. Important because they can bind to complement or cells.

ANTIBODIES

- Heavy chains and light chains are ***held together by disulphide bonds***, forming a bilaterally symmetric structure
- The variable regions of the H and L chains form the ***antigen-binding sites*** of the immunoglobulin
- The hinge region is where the H chains comes into contact with the C region domains.
 - It is flexible therefore allowing the distance between the antigen binding sites to vary

ANTIBODY STRUCTURE



ANTIBODIES

- Microbes enter the body through the epithelial cells of the mucosal membranes of the respiratory, digestive, genital tracts or through skin broken by a scrape, cut, insect bite or hypodermic needle.
- Once inside, the microbe may begin replicating locally or get into the circulation and move throughout the body.

ANTIBODIES

- The Fc regions of the immunoglobulins allow them to bind Fc receptors and cross tissue barriers to reach pathogens
- There are five immunoglobulin classes (isotypes) of antibody molecules found in serum: IgG, IgM, IgA, IgE and IgD

ANTIBODIES

- They are distinguished by the type of heavy chain they contain or their valency (the number of arms available to bind antigen)
- The variation in heavy chain polypeptides allows each immunoglobulin class to function in a different type of immune response or during a different stage of the body's defence.
- The amino acid sequences that confer these functional differences are located mainly within the Fc domain

ANTIBODIES

- Difference in their valency arises from the ability of certain immunoglobulins to form multimers through linkage of their Fc domains via a J chain
 - Eg. IgM is a pentamer of five identical “Y” shaped monomers.
 - The complete IgM protein contains 10 heavy chains, 10 light chains and 10 antigen binding arms (giving IgM a valency of 10)

ANTIBODIES



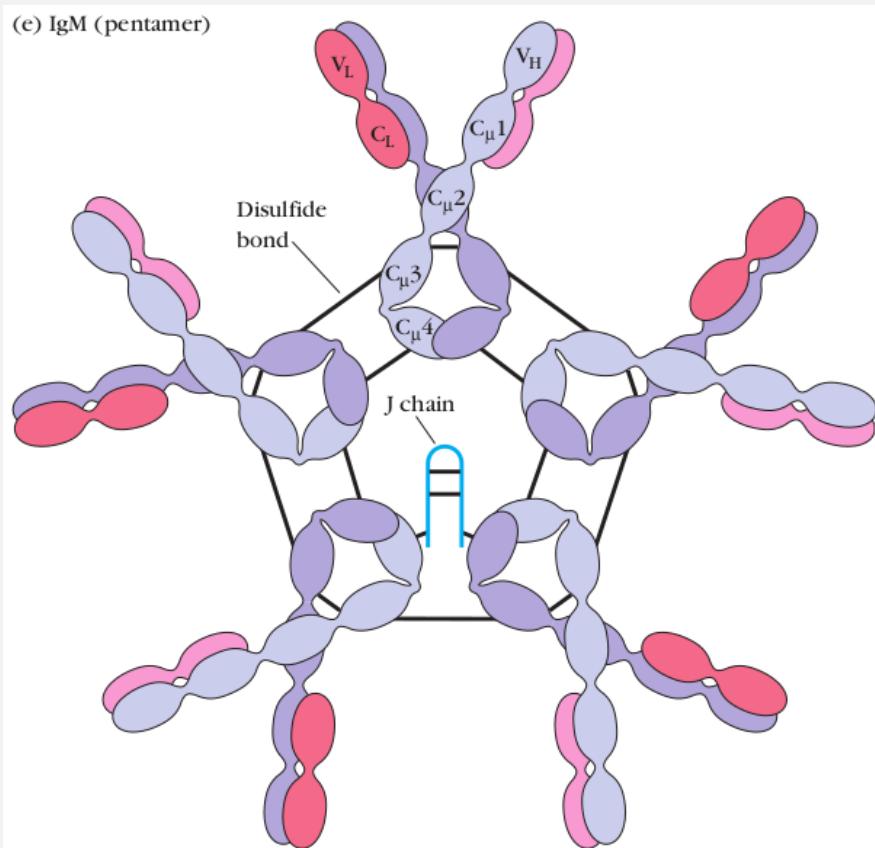
IgM

- Secreted first in a primary response, it is low affinity antibody
- Because it is a pentamer, it fixes complement very efficiently to promote inflammation and pathogen lysis.
- Large and cannot enter the tissues very efficiently
- IgM: is the first immunoglobulin to be synthesized by infants and the first to appear in the blood stream during the course of an infection
 - Most efficient in agglutination and complement fixation; important against bacteria and viruses

ANTIBODIES

IgM

- Molecular weight is about 90,000Da
- Serum conc: 0.5-2mg/L
- H chain: mu (65,000)
- Total percentage : 10%
- Biological half-life: 5-10days
- Distribution: mostly intravascular
- Functions in primary response
- Classical complement activation



ANTIBODIES



IgG

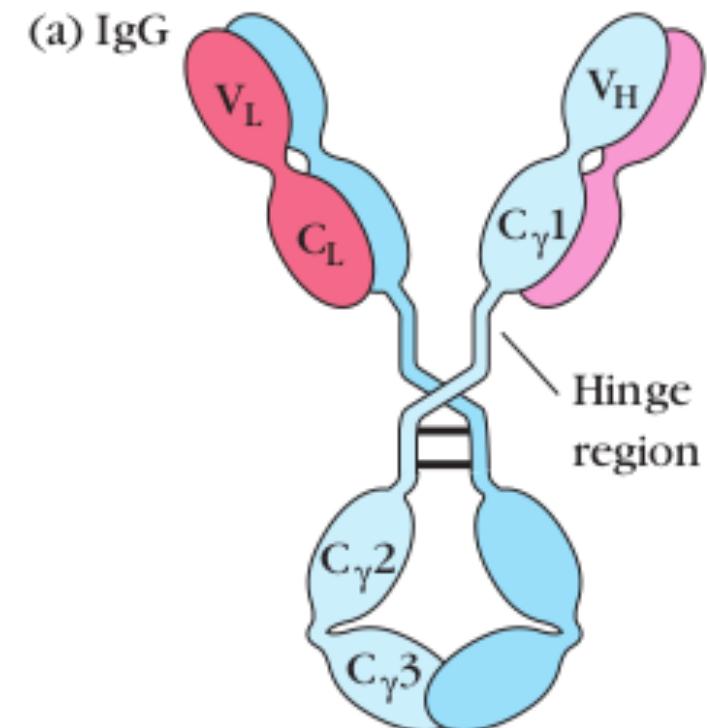
IgG

- Once isotype switching occurs, IgG predominates in serum and in tissues.
- Neutralizes pathogens, bacteria exotoxins, toxins and opsonizes them for phagocytosis
 - Neutralisation in tissues
- Activate complement on the pathogen surface
- Can cross the placental barrier
 - IgG in fetal circulation offers additional protection during the first few months of life

ANTIBODIES

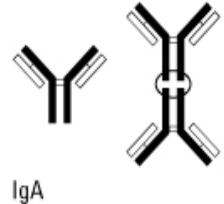
IgG

- Molecular weight is about 150,000
- H chain: gamma (53,000)
- Serum conc: 10-16mg/L
- Total percentage : 75%
- Biological half-life: 21-24days
- Distribution: intra and extravascular
- Functions in secondary response



ANTIBODIES

IgA



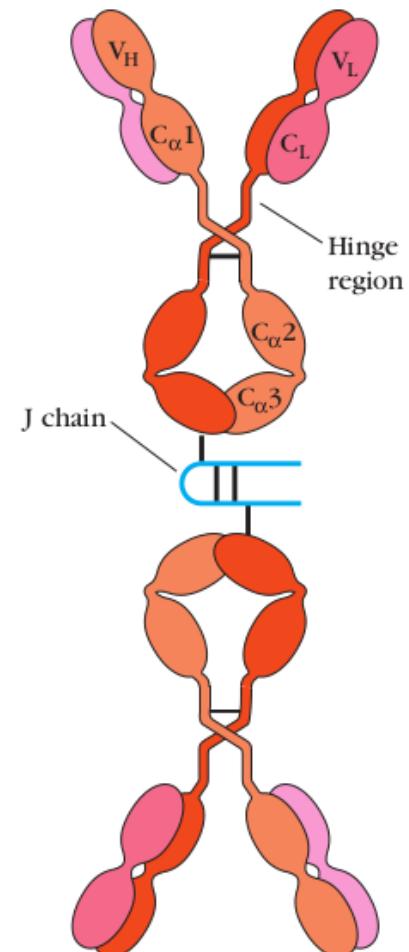
- IgA is the predominant antibody that is secreted across epithelial cells of the respiratory, digestive and genital tracts to block pathogen entry into the body.
- Found in secretions such as colostrum, saliva, tears,
 - Prevent attachment of pathogens to the mucous membranes
- Does not fix complement
- During first few weeks of birth, baby gets majority of antibodies through mother's milk(colostrum) rich in IgA.
 - Maternal IgA in milk can neutralize pathogen in the infant's digestive tract until the infant's immune system is mature enough to take over that task.

ANTIBODIES

- **IgA**

- Molecular weight is about 320,000
- H chain: alpha (55,000)
- Serum conc: 1-4mg/L
- Total percentage : 15%
- Biological half-life: 11-14days
- Distribution: intratravascular and secretions
- Functions in protecting mucus membranes

(d) IgA (dimer)



ANTIBODIES

IgE

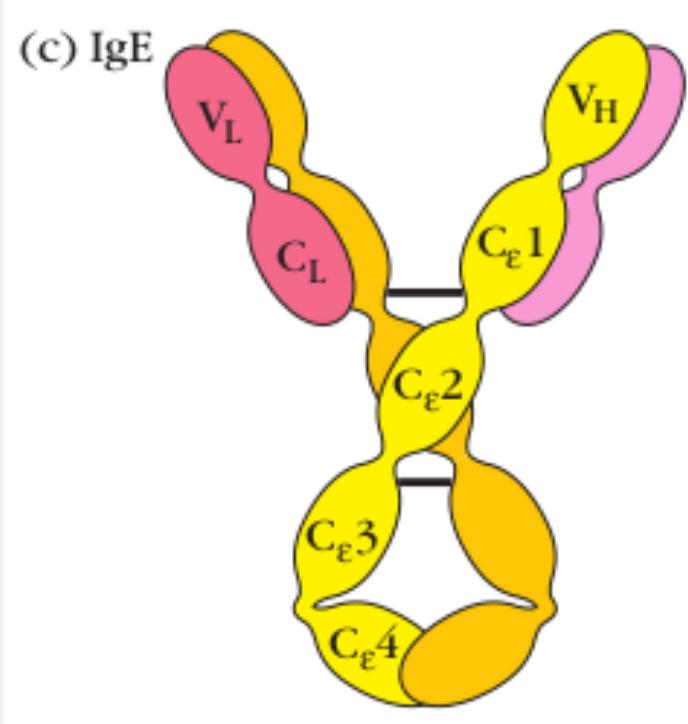
- Least abundant, and mediates allergic or hypersensitivity reactions.
- IgE binds FcR on mast cells lining the blood vessels throughout the body.
- When pathogen binds to the IgE on mast cell, the mast cells immediately release inflammatory mediators that trigger coughing, sneezing or vomiting to expel pathogens from the body.
- Major defense against parasitic infection especially helminthes(worms)
- Mostly present in mucous membrane, skin and lungs
- Does not fix complement



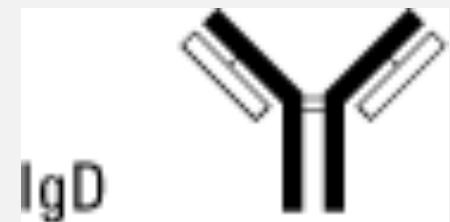
ANTIBODIES

IgE

- Molecular weight is about 200,000
- H chain (MW) : epsilon (73,000)
- Serum conc: 10-400ng/L
- Total percentage : 0.004%
- Biological half-life: 1-5days
- Distribution: basophils and mast cells in saliva and nasal secretions
- Functions in secondary response



ANTIBODIES



IgD

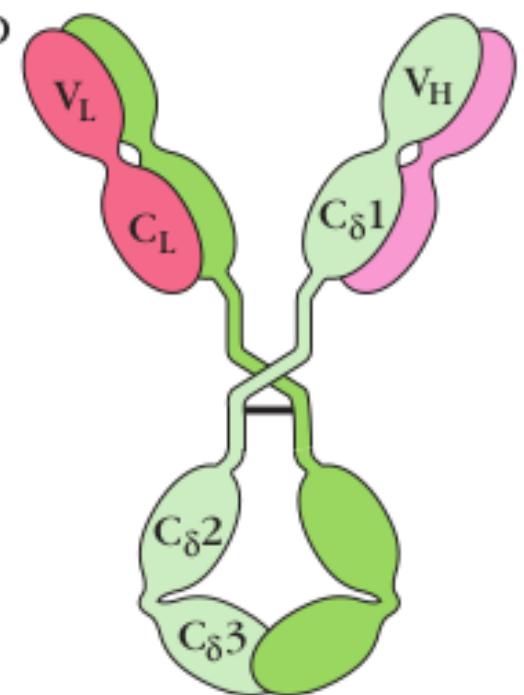
- Expressed in the plasma membranes of immature B lymphocytes
- Co-expressed with another cell surface antibody, IgM
- Present in small amounts in blood
- Function is still incompletely understood

ANTIBODIES

IgD

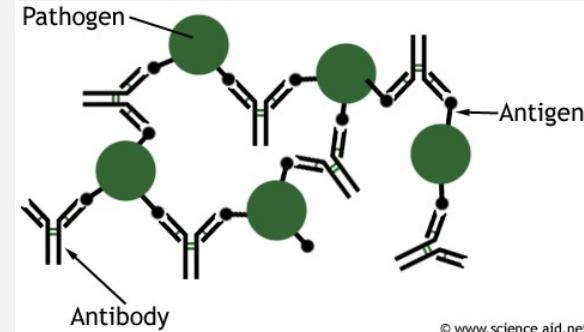
- Molecular weight is about 180,000
- H chain (MW) : delta (70,000)
- Serum conc: 0-0.4mg/L
- Total percentage : 0.2%
- Biological half-life: 2-8days
- Distribution: lymphocyte surfaces
- Functions – unknown yet

(b) IgD



ANTIGEN AND ANTIBODY INTERACTIONS

ANTIGEN-ANTIBODY INTERACTION

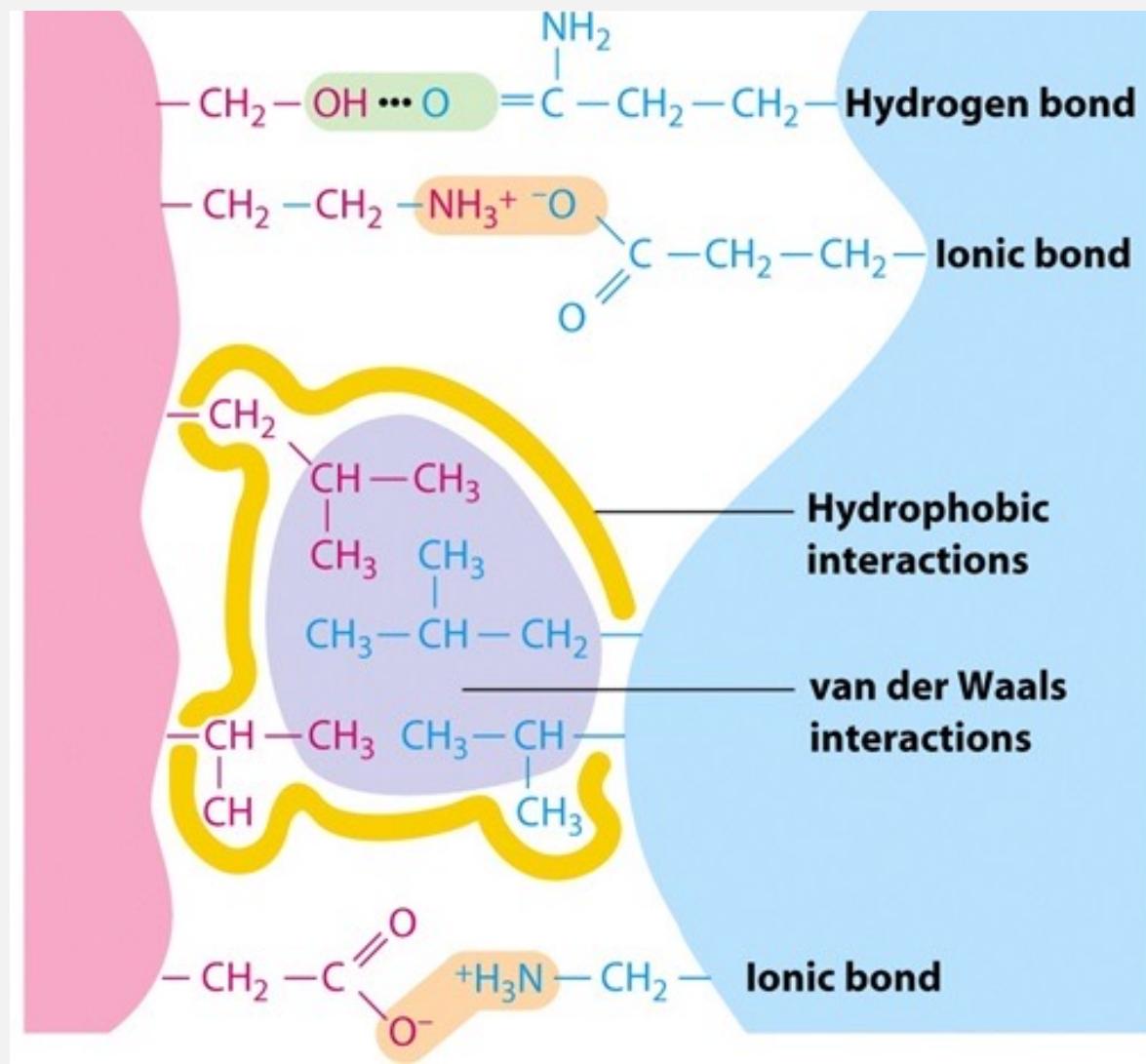


Binding of antigen to antibody

Involves:

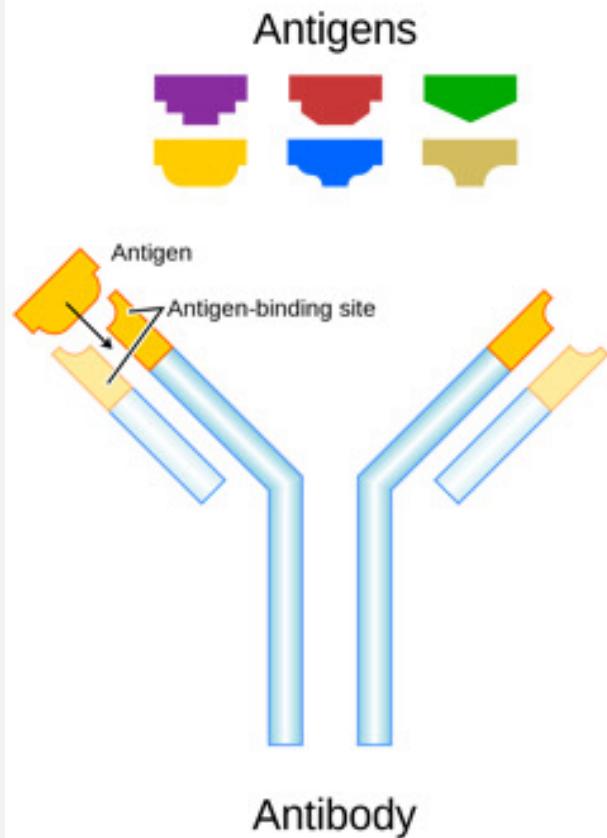
- Electrostatic Interactions-Attraction of positive charge to a negative charge (Glu to Lys).
- Hydrogen Bonds-Bridging of a COO- to the H of an OH group.
- Hydrophobic Bonds-Interaction of hydrophobic –R groups of Ag and Ab.

ANTIGEN- ANTIBODY INTERACTION



ANTIGEN AND ANTIBODY BINDING

- Occurs in variable region of antibody molecule
- Instantaneous
- Exothermic
- May form complexes
- Cytotoxicity mediated by complement (lysis)

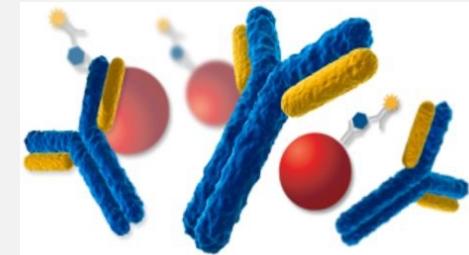


ANTIGEN-ANTIBODY

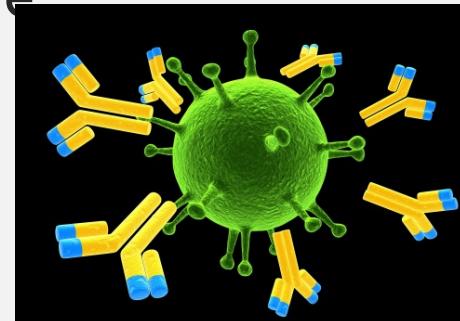
Antigen – Antibody reaction

- **In-Vivo:**
 - Basis of Ab mediated immunity in infections
 - Tissue injury- hypersensitivity / autoimmune diseases
- **In-Vitro:**
 - Diagnosis of infections
 - Epidemiological surveys
- Ag-Ab reactions in vitro – Serological reactions or immune assays

ANTIGEN-ANTIBODY



- **Immunoassays** rely on the ability of an antibody to recognize and bind a specific macromolecule in what might be a complex mixture of macromolecules.
- Macromolecule bound by an antibody is referred to as **an antigen** and the area on an antigen to which the antibody binds is called **an epitope**.



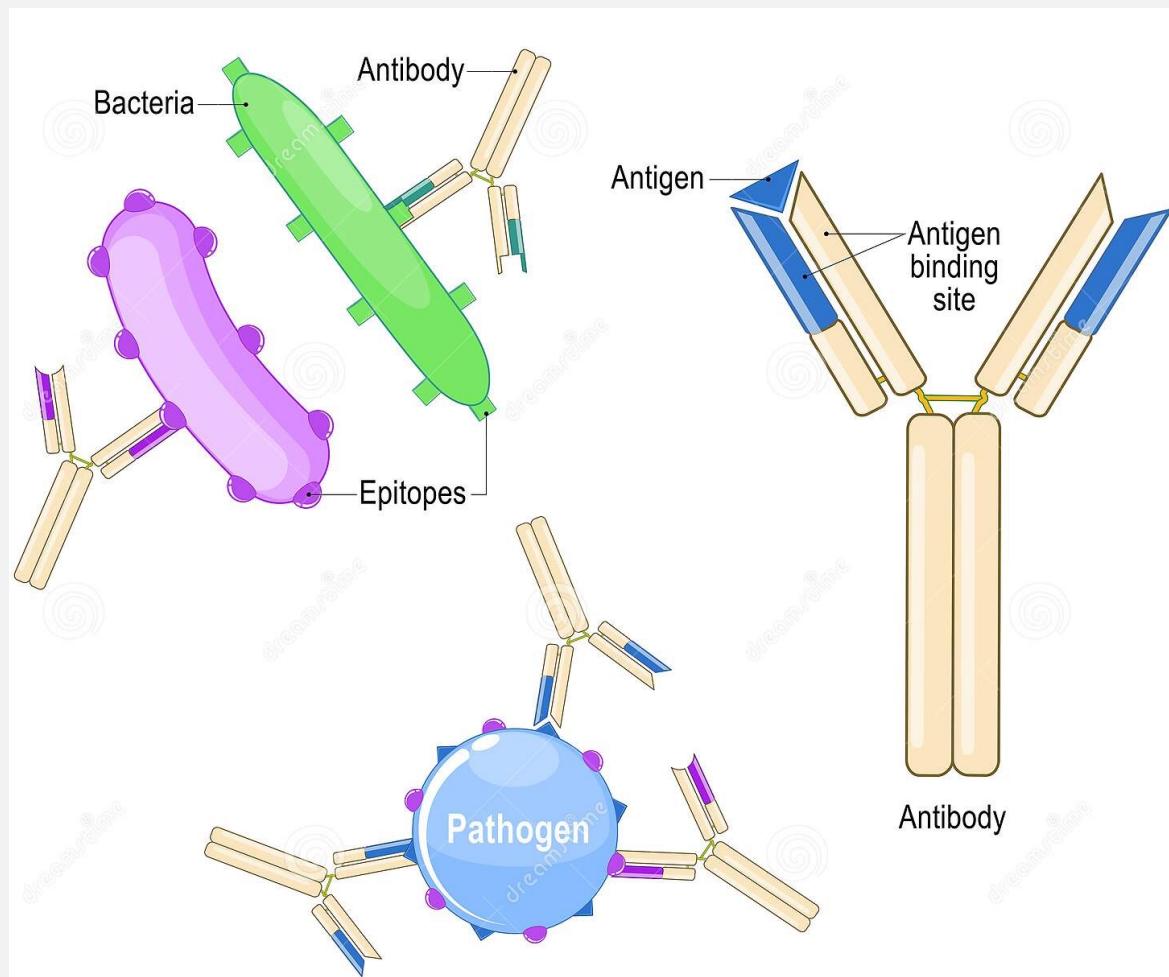
ANTIGEN-ANTIBODY

Characteristics of Ag-Ab Reactions

- I. **Specificity:** Specific antibody can distinguish even minute differences in structure, charge, etc. of an antigens epitope and binds only with its specific Ag
- *Eg. Antibodies produced against blood group B antigens, bind with B antigens only. They never bind with A or D blood group antigens*

ANTIGEN-ANTIBODY

Characteristics of Ag-Ab Reactions



ANTIGEN-ANTIBODY

2. **Antibody Affinity:** strength of the reaction between a single antigenic determinant and a single binding site of antibody

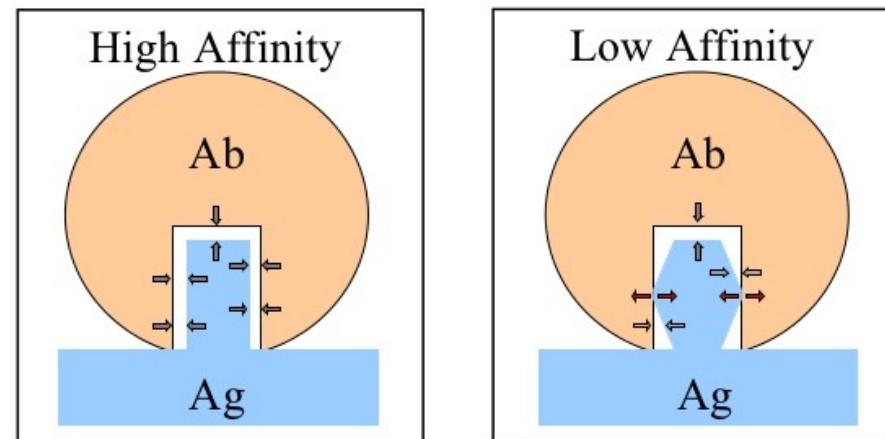
- The binding strength depends on ***distance and compatibility*** of two substances.
- The distance between the two objects and the sum of the ***attractive and repulsive forces***, such as electrostatic forces, hydrogen bonding, hydrophobic bonding, Van der Waals force etc. operating between the epitope and paratope also influence the affinity

ANTIGEN-ANTIBODY

- Affinity is the equilibrium constant that describes the strength of antigen-antibody reaction.

Affinity

- Strength of the reaction between a single antigenic determinant and a single Ab combining site



Affinity = Attractive and repulsive forces

ANTIGEN-ANTIBODY

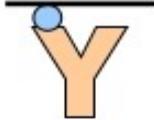
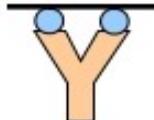
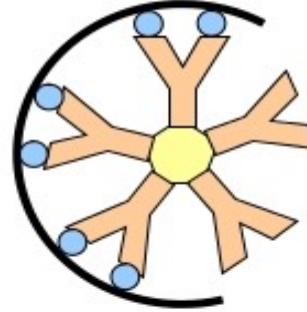
3. Antibody Avidity:

- Antibody molecules and antigens are multivalent.
- This ***multi-valency*** of Abs and Ags tend to increase chances of interaction and also strength of bonding.
- The overall strength of an antibody binding to multivalent antigen is known as "**avidity**".
- ***Antibody binding to an antigen at more than one site increases strength of the bond or avidity proportionately.***
- Avidity is influenced by valency of both antibody and antigen.
 - High avidity of antigen and antibody could compensate low affinity.

ANTIGEN-ANTIBODY

Avidity

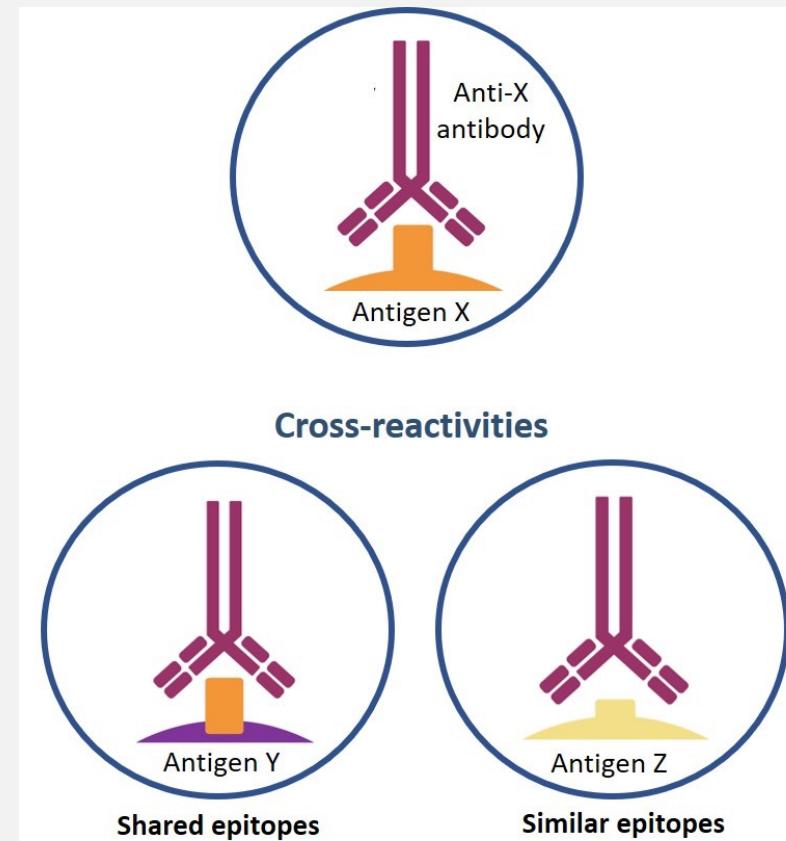
- The overall strength of binding between an Ag with many determinants and multivalent Abs

		
$K_{eq} = 10^4$ Affinity	10^6 Avidity	10^{10} Avidity

ANTIGEN-ANTIBODY

4. Cross Reactivity:

- There is a possibility of presence of **similar epitopes on different antigens.**
- Hence antibodies produced for a specific antigen can cross react with antigens having similar epitopes
 - often observed among polysaccharide antigens that contain similar oligosaccharide residues



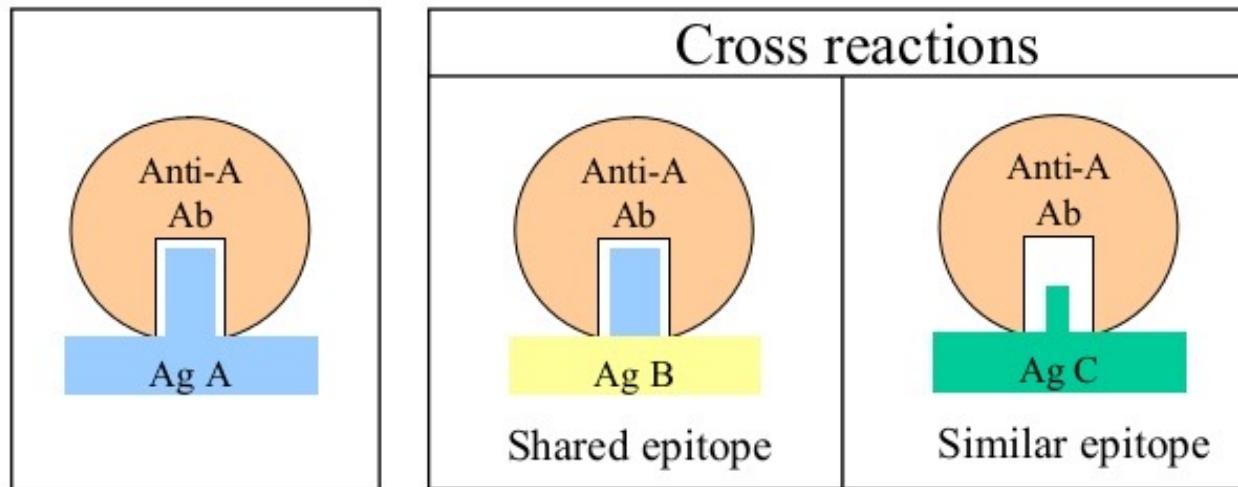
ANTIGEN-ANTIBODY

- Cross reactivity character of Abs has been used differently in various diagnostic tests.
 - Eg. *Treponema pallidum* (*syphilis*) infection induces production of antibodies that cross-react with cardiolipin - a substance found in cardiac muscle.
 - Since it is much easier to obtain pure cardiolipin than pure *Treponema* antigens, cardiolipin is used in diagnostic test for syphilis ([Wassermann test](#)).
 - Eg. antibodies produced against Rickettsia cross-react with antigens from Proteus.
 - Since the latter are much easier to obtain, they can be used to test for the former.

ANTIGEN-ANTIBODY

Cross Reactivity

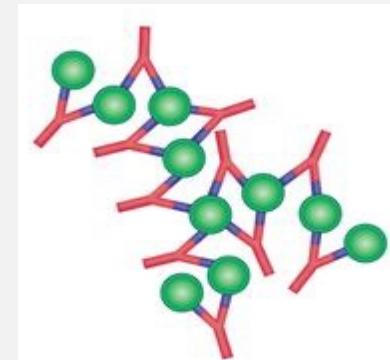
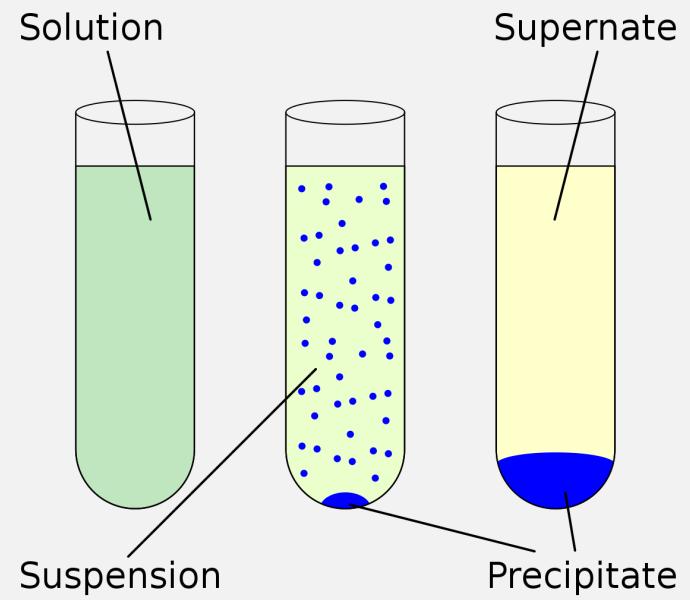
- The ability of an individual Ab combining site to react with more than one antigenic determinant.
- The ability of a population of Ab molecules to react with more than one Ag



ANTIGEN-ANTIBODY

5. Antigen Precipitation:

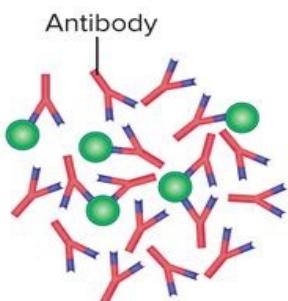
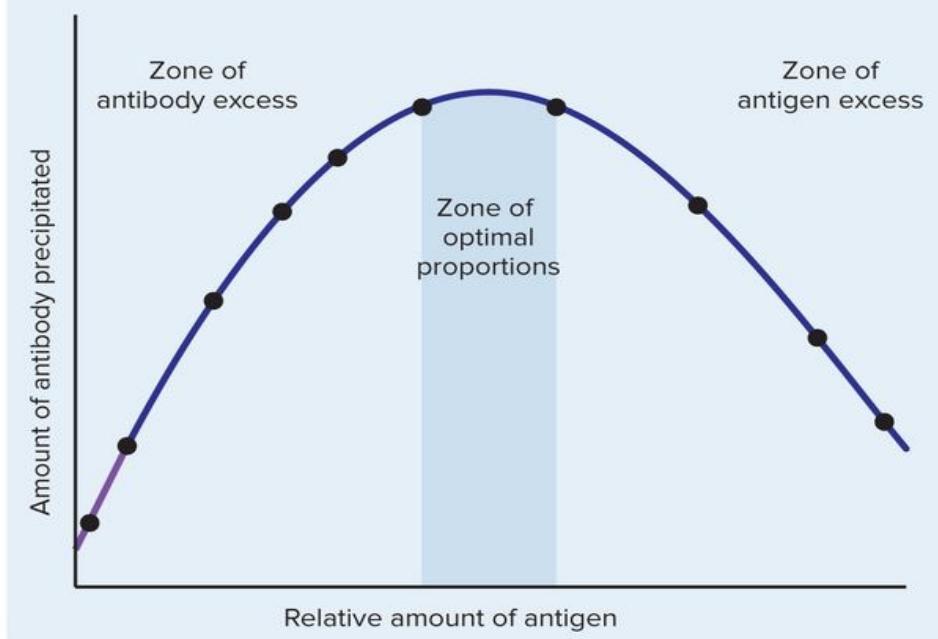
- Soluble antigen molecules can be precipitated by antibodies.
- Antigen interaction enables antibodies to neutralize, opsonize and inactivate toxic substances and pathogens.
- The soluble antigens that can precipitate Abs are known as "**precipitins**"



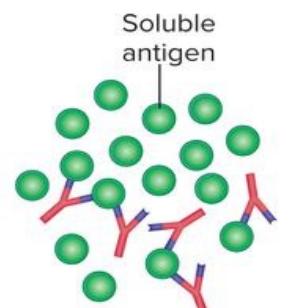
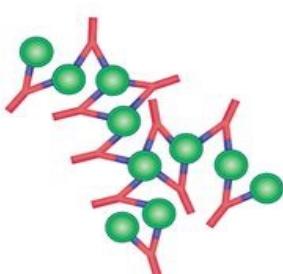
ANTIGEN-ANTIBODY

- The precipitin reaction is influenced by the **number of paratopes of antibody for the given antigen and by the number of epitopes** found on antigen molecule
 - ie. *the concentration of Ags and Abs*

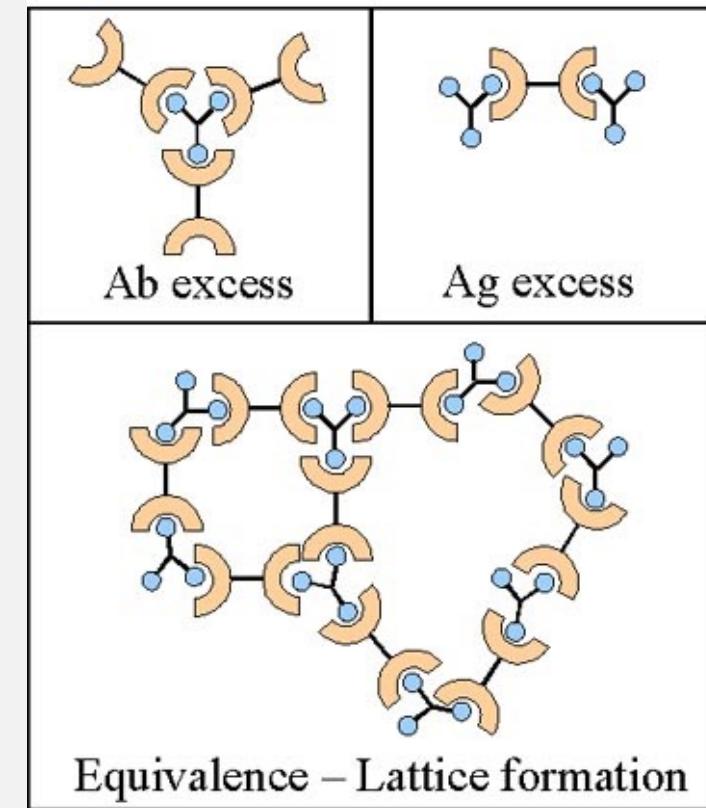
ANTIGEN-ANTIBODY



In the zone of antibody excess, little or no cross-linking occurs; no visible precipitate forms.



In the zone of antigen excess, little or no cross-linking occurs; no visible precipitate forms.



ANTIGEN-ANTIBODY

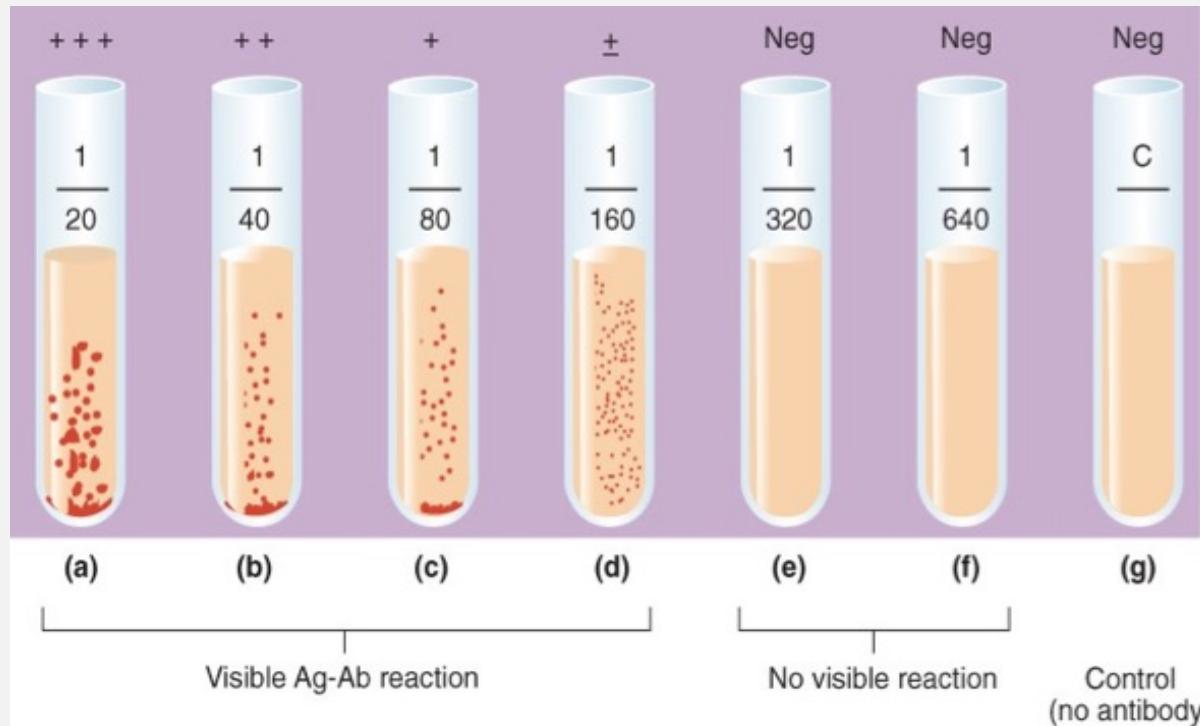
Antigen and Antibody Bonus effect

- The antigen with multivalency or multiple binding sites can react with different antibodies simultaneously.
- An antigen that is bridged by two or more antibodies at a time have its binding strength of Ag-Ab complex increases proportionately.
- This added strength of Ag- Ab complex is referred as “bonus effect”
- The presence of antibodies with different paratopes to match with all the epitopes of the antigen enhances the bonding strength of Ag - Ab complex

ANTIGEN-ANTIBODY

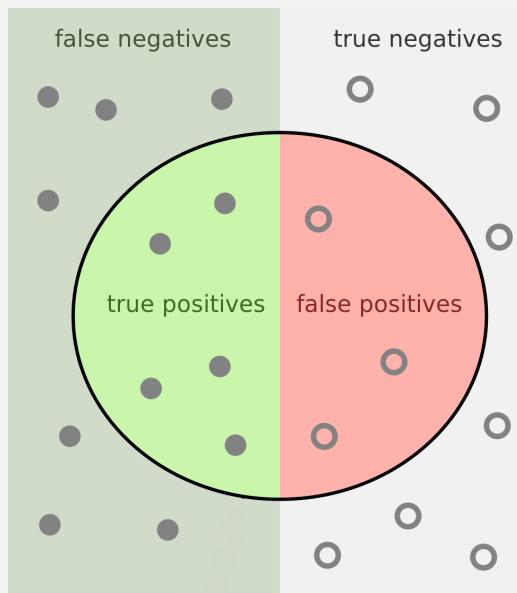
Measurements

- **Antibody Titre:** highest dilution of serum which gives observable reaction with the antigen



ANTIGEN-ANTIBODY

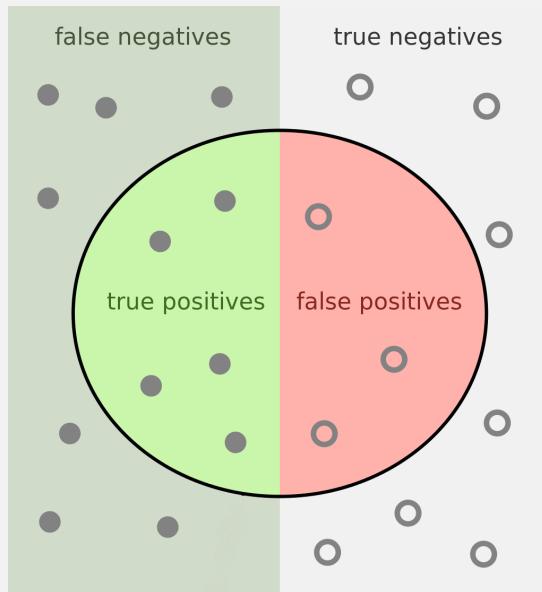
- **Sensitivity:** ability of the test to detect even minute quantities of antigen or antibody
 - Highly sensitive: No/Low false negative results



$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

ANTIGEN-ANTIBODY

- **Specificity:** ability of the test to detect only the specific antigen or antibody
 - Highly specific: No/Low false positive results



$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

IMMUNE DEFICIENCIES

IMMUNE DISORDERS

- Immune deficiency
- Hypersensitivity
- Autoimmunity

IMMUNE DEFICIENCY

Disease Outcome:

- infections that develop and re-occur more frequently are more severe, and last longer than usual

IMMUNE DEFICIENCY

- Some immunodeficiency disorders: ***shorten life span.***
- Others ***persist throughout life*** but do not affect life span, and a few ***resolve with or without treatment***

Result from defects that occur in immune mechanisms due to:

Primary - Hereditary and congenital deficiencies

- These disorders are usually present at birth and are usually hereditary
 - evident during infancy or childhood
 - Few are not recognized until adulthood.

IMMUNE DEFICIENCY

Caused by mutations in a specific gene

- Mutation gene on the X (sex) chromosome results in X-linked disorder.
- Primary immunodeficiency disorders are classified by which part of the immune system is affected:
 - *Humoral immunity*, which involves B cells
 - *Cellular immunity*, which involves T cells

IMMUNE DEFICIENCY

Both humoral and cellular immunity

- Phagocytes
- Complement proteins (proteins with various immune functions, such as killing bacteria and other foreign cells and making foreign cells easier for other immune cells to identify and ingest)
 - The affected component of the immune system may be **missing**, **reduced in number**, **abnormal** or **malfunctioning**.
 - Problems with B cells are the most common primary immunodeficiency disorders, accounting for more than half.

IMMUNE DEFICIENCY

Cellular immunity: T cells (lymphocytes)

- Eg. T-cell deficiency disease called **DiGeorge syndrome** arises from a developmental defect occurring in the foetus that results in the **defective development of the thymus**
- Consequently the infant has either no mature T cells or very few.
- Severe cases - no thymus has developed
 - ✓ -transplantation of a foetal thymus into the infant

IMMUNE DEFICIENCY

Chronic mucocutaneous candidiasis

- persistent or recurring infection with Candida (a fungus) due to ***malfunction of T cells (lymphocytes)***. Causes frequent or chronic fungal infections of the mouth, scalp, skin, and nails
 - Treated with antifungal drugs and sometimes with immune globulin

X-linked lymphoproliferative syndrome (Duncan's syndrome)

- Results from a T-cell and natural killer cell defect and is characterized by an ***abnormal response to Epstein-Barr virus infection***, leading to liver failure, immunodeficiency, lymphoma

IMMUNE DEFICIENCY

- **Humoral immunity:** B cells (lymphocytes) and their production of antibodies
- I. Eg. **X-linked infantile gammaglobulinemia**, which affects only males, B lymphocytes are **unable to secrete all classes of immunoglobulins.**
 - ✓ periodic injections of large amounts of immunoglobulin G (IgG).

IMMUNE DEFICIENCY

Deficiency of a specific antibody

- ***undetectable level of immunoglobulin A (IgA)*** in the blood and secretions
 - ✓ Management include preventive measures to reduce the risk of infection, and prompt and effective treatment of infections.

IMMUNE DEFICIENCY

Transient hypogammaglobulinemia of infancy

- Significantly decreased serum IgG with or without decreased IgA and IgM levels in infants over 6 months of age
 - They have recurrent infections

Causes include:

1. Suppressive maternal antibodies (IgG) which cross the placenta and suppress foetal immunoglobulin production;
2. Genetic variation in certain families with risk to immunodeficiency;
3. Abnormal T-lymphocytes that fail to stimulate antibody production by B-cells
4. Unbalanced cytokine production
5. Abnormal or immature B-cells

IMMUNE DEFICIENCY

Both Humoral and Cell mediated

- The group of disorders called **severe combined immunodeficiency** diseases(SCID) result from a **failure of precursor cells to differentiate into T or B cells**.
 - Eg. Ataxia-telangiectasia
- ✓ Bone marrow transplantation

IMMUNE DEFICIENCY

Hyper-immunoglobulinemia E syndrome

- Levels of immunoglobulin E (IgE) are very low and characterized by recurring boils, sinus and lung infections, and a severe rash that appear during infancy

IMMUNE DEFICIENCY

Phagocytes: movement or killing activity of these cells

- Eg. The immune disorder called **chronic granulomatous disease** results from an inherited defect that prevents phagocytic cells from producing enzymes needed to break down ingested pathogens.
 - ✓ Treatments include administration of a wide spectrum of antibiotics.

Chédiak-Higashi syndrome (rare)

- Autosomal recessive primary immunodeficiency disorder that involves phagocytic cell defects
- Abnormal lysosomes cannot fuse with phagosomes, so ingested bacteria cannot be lysed normally

IMMUNE DEFICIENCY

Cyclic neutropenia

- Recurrent episodes of **abnormally low levels of neutrophils**
 - May cause fever, a general feeling of ill health (malaise), and/or sores (ulcers) of the mucous membranes of the mouth and abnormal susceptibility to recurrent infections
- ✓ treatment of the infections / synthetic drug to stimulate the bone marrow's production of neutrophils

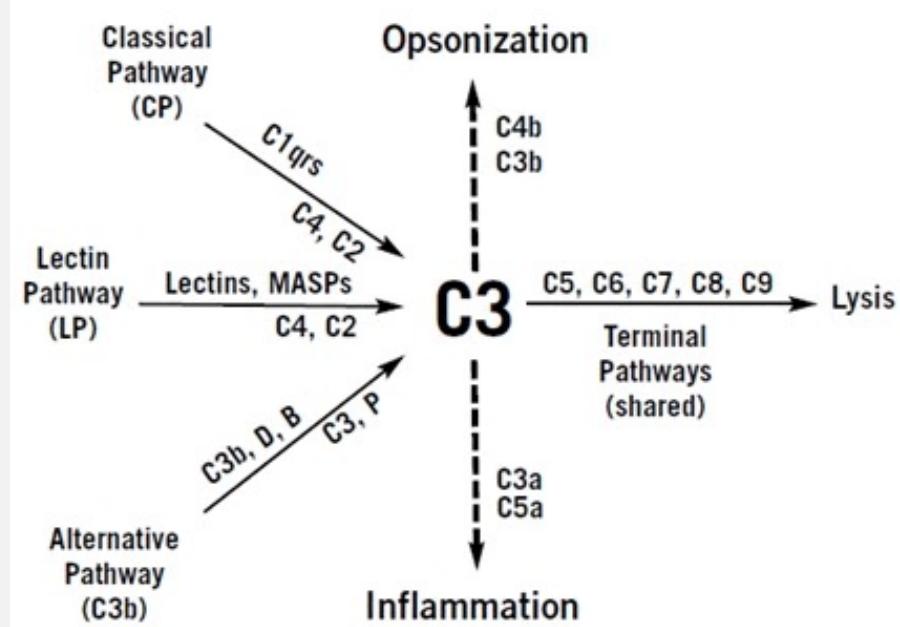
IMMUNE DEFICIENCY

Leukocyte adhesion defects

- LAD syndromes are characterized by defects **affecting how white blood cells (leukocytes) respond and travel to the site of a wound or infection**
- Increased susceptibility to developing recurrent bacterial and fungal infections.
- Treatment : bone marrow transplant

IMMUNE DEFICIENCY

- Complement proteins: *Deficiency of complement proteins*
- Complement component I (C1) inhibitor deficiency C3 deficiency
- C4 deficiency
- C5, C6, C7, C8, and/or C9 deficiency



IMMUNE DEFICIENCY

- Recurrent mild or serious bacterial infections, autoimmune disease, or episodes of painless or painful swelling under the skin / intestines
- Accompanied by upper respiratory infections, otitis media, along with lupus-like symptoms.
- Angioedema in the brain can be fatal.

IMMUNE DEFICIENCY

Secondary immunodeficiency disorder:

- These disorders generally develop later in life and often result from prolonged (chronic) and/or serious disorders / disease such as diabetes or cancer
 - Drugs
 - Radiation therapy
 - They are more common than primary immunodeficiency disorders.

IMMUNE DEFICIENCY

- Diabetes - white blood cells do not function well
(when the blood sugar level is high ??????)
- *Human immunodeficiency virus (HIV) infection* results in acquired immunodeficiency syndrome (AIDS), the most common severe acquired immunodeficiency disorder
- *Cancers that affects the bone marrow* (such as leukemia and lymphoma) can prevent the bone marrow from producing normal white blood cells (B cells and T cells).

IMMUNE DEFICIENCY

- *Undernutrition*, all nutrients or only one can impair the immune system.
- Undernutrition which causes body weight to decrease to less than 70% of recommended weight, the immune system becomes severely impaired
- *Older people* and people who are *hospitalized* may develop immune system impairment

IMMUNE DEFICIENCY

Deficiencies caused by infection:

Damage to lymphocytes that is inflicted by viruses is common but usually transient

Eg: During infectious mononucleosis, EBV infects B cells, causing them to express viral antigens.

T cells that react against these antigens then attack the B cells and a temporary deficiency in the production of new antibodies lasts until the overt viral infection has been overcome

IMMUNE DEFICIENCY

Eg. HIV selectively infects helper T cells and prevents them from producing cytokines and from functioning in cell-mediated immunity.

Persons with AIDS may be unable to overcome infections by a variety of microbes that are easily disposed of by persons uninfected with HIV

Eg. Severe infections by certain parasites, such as trypanosomes

Eg. Chickenpox (varicella), Cytomegalovirus infections, Measles, some bacterial infections

IMMUNE DEFICIENCY

Deficiencies caused by drug therapy

Eg. Immune deficiency also results from the use of some strong drugs to treat cancers. The drugs work by **inhibiting the multiplication of rapidly dividing cells.**

Although the drugs act selectively on cancer cells, they also can interfere with the generation and multiplication of cells involved in immune responses.

Prolonged or intensive treatment with such **drugs impairs immune responses.** Although the **immune impairment is reversible**

IMMUNE DEFICIENCY

- ***Medically induced suppression of the immune system*** also interfere with the development of T and B cells, are used to prevent the rejection of organ or bone marrow transplants or to reduce serious autoimmune responses
- Corticosteroids (***immunosuppressant***) are used to suppress inflammation due to various disorders, such as rheumatoid arthritis
- ***Chemotherapy and radiation therapy can also suppress*** the immune system, sometimes leading to immunodeficiency disorders.

IMMUNE DEFICIENCY

Eg. of medications:

- Anticonvulsants (used to treat seizures)
- Immunosuppressants (drugs that suppress the immune system)
- Corticosteroids
- Chemotherapy drugs
- Other drugs such as antibodies that target and suppress specific parts of the immune system

IMMUNE DEFICIENCY

Other Secondary Immune deficiency disorders

- **Blood:** Aplastic anaemia
 - Leukemia
 - Multiple myeloma (a cancer)
 - Sickle cell disease
- **Hormonal:** Diabetes mellitus(??)
- **Kidney:** Build up of toxic substances in the blood (uraemia)
 - Chronic kidney disease
 - Nephrotic syndrome

IMMUNE DEFICIENCY

- **Liver:** hepatitis
 - Liver failure
- **Spleen:** removal of spleen
- **Others:**
 - Burns
 - Alcoholism
 - Smoking

IMMUNE DEFICIENCY

Aging and Immunodeficiency

- The immune system becomes less effective in several ways as people age.
- Thymopoiesis is reduced in aging leading to reduced frequency and number of naive T cells, leading to increasing number of memory cells
- Changes in the B cell repertoire. Fewer naive B with more cell pool of antigen-experienced memory cells, some of which are 'exhausted' B cells
- Accumulation virus-specific CD8+ T cells compromises immune function and restricts the overall immune repertoire.

IMMUNE DEFICIENCY

Aging and Immunodeficiency

- Vaccine efficacy is reduced because the changes in the overall, CD8⁺, CD4⁺ and putative antigen presenting cell underlie an altered interaction between these cells.
- Undernutrition with deficiency of one or more essential nutrients which is common among older people, impairs the immune system
- Two nutrients that are particularly important to immunity (calcium and zinc) may be deficient in some older people. Due to the intestine becoming less able to absorb them or having less in their diet

IMMUNE DEFICIENCY

- Certain disorders (such as diabetes and chronic kidney disease), which are more common among older people, and certain therapies (such as immunosuppressants), which older people are more likely to use also impair the immune system.
- Find out more



TUMOUR IMMUNOLOGY

TUMOUR IMMUNOLOGY

- *Tumour is an uncontrolled growth of cells, with a progression that leads to damage of critical tissues often leading to death*
- Carcinogens are **molecule** (natural or synthetic) or **physical agents** (radiation) that promote cancer formation by transforming cell's DNA

TUMOUR IMMUNOLOGY

- From **oncogene theory**, genes susceptible to transformation by retroviruses are common to all vertebrate cells.
- These *genes are highly conserved* because they *control key functions; regulating cell growth*.
- **Proto-oncogenes** encode **growth factors receptors**, and **signal transducers**.
 - Mutation (chromosomal translocation, point mutation and gene amplification)
 - Activated genes >>> **oncogenes**

TUMOUR IMMUNOLOGY

- **Proto-oncogenes are mutated they become overexpressed or express in the wrong tissues, showing abnormal growth mechanism of somatic cells**
- Such aberrant proliferation is seen:
 - *carcinoma* in epithelial cells
 - *sarcoma* in muscles and connective tissues, like fat and bones
 - *leukemia* in blood forming cells, like WBC
 - *lymphomas* in lymphatic system

TUMOUR IMMUNOLOGY

- Tumour antigens appear in the body as a result of a mutation, a gene activation or a clonal amplification of a mutated gene product
- Cancer immuno-surveillance allows continuous recognition of tumour antigens and elimination of nascent transformed cells

TUMOUR IMMUNOLOGY

- **Tumour antigens:**
 - Activated by carcinogens and
 - Activated by non-carcinogens: overexpression and out of place expression of normal cellular gene production of foetal and germ origin due to somatic mutations(viruses)

TUMOUR IMMUNOLOGY

Tumour antigens:

- In order for the immune system to react against a tumour cells, they must *have antigens that are recognized as foreign*
- A *variety of antigens* that may be recognized by T and B lymphocytes have been identified in human and animal cancers.

TUMOUR IMMUNOLOGY

- **Tumorigenesis** may lead to expression of *new antigens* (neoantigens) or *alteration in existing antigens* that are found on normal cells
- These antigens may include:
 - *membrane receptors,*
 - *regulators of cell cycle and apoptosis*
 - *molecules involved in signal transduction pathways*
- *Identified tumour antigens may be used as components of tumour vaccines or antibodies and effector T cells generated against these antigens may be used for immunotherapy.*

TUMOUR IMMUNOLOGY

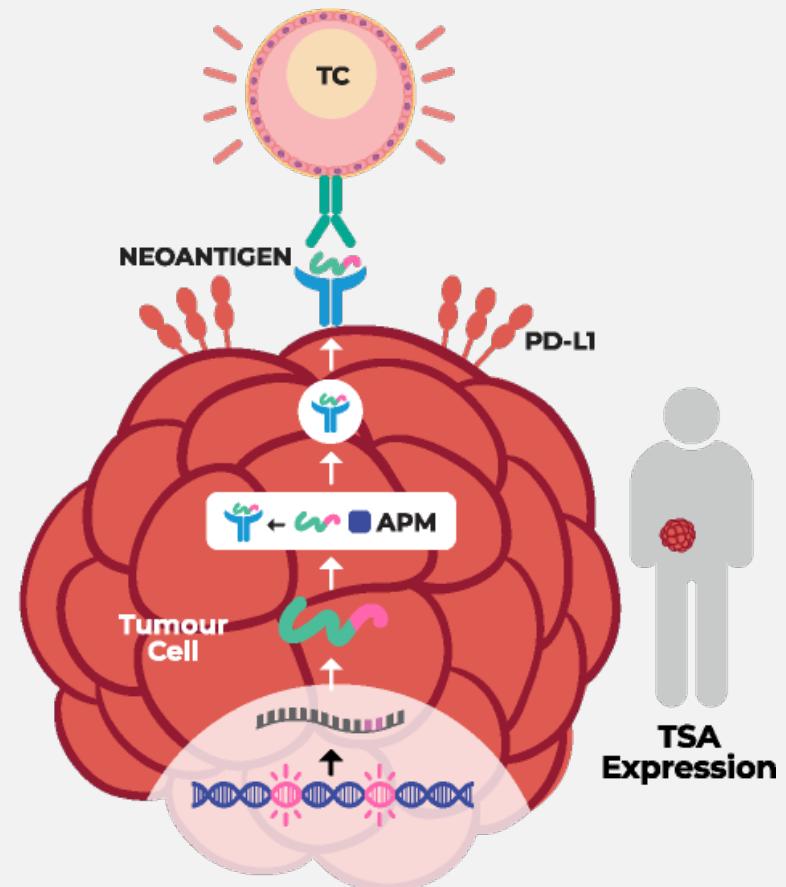
Tumour antigens may be classified is based on their patterns of expression.

- There are 2 main types of tumour antigens.
 - I. *Tumour specific antigens (TSAs) or Tumour-specific transplantation antigens (TSTA):*
- Antigens that are expressed on tumour cells but not on normal cells.
 - Some of these are unique to individual tumours.

TUMOUR IMMUNOLOGY

I. *Tumour specific antigens (TSAs)*

- **Eg.** products of oncoviruses; HPV (E6, E7 proteins occurring in cervical carcinoma)
- **Eg.** EBNA-1 protein of EBV, in Burkitt's lymphoma cells
- **Eg.** Ras protein of mutated oncogenes
- **Eg.** p53 of anti-oncogenes



TUMOUR IMMUNOLOGY

- Virus-induced tumours express cell surface antigens (distinct from antigens of the virion itself) which are *shared by all tumours induced by the same virus.*
- These antigens are characteristic of the tumour-inducing virus, *regardless of tissue origin* of the tumour or animal species in which the tumour exist.

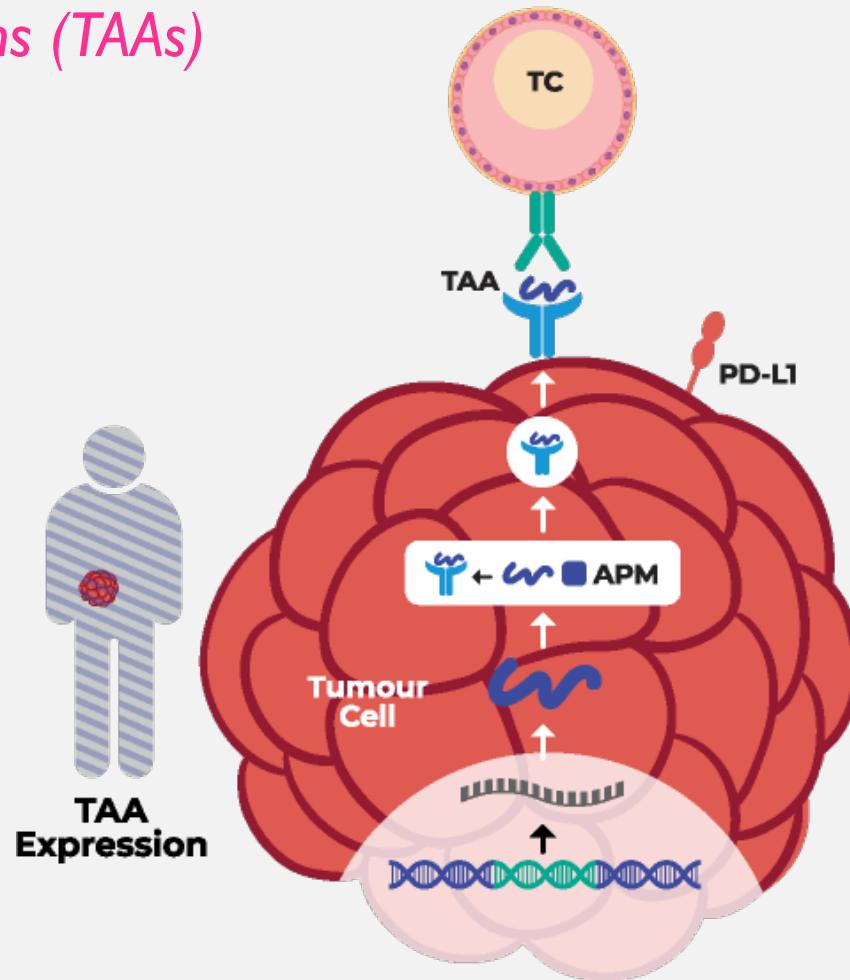
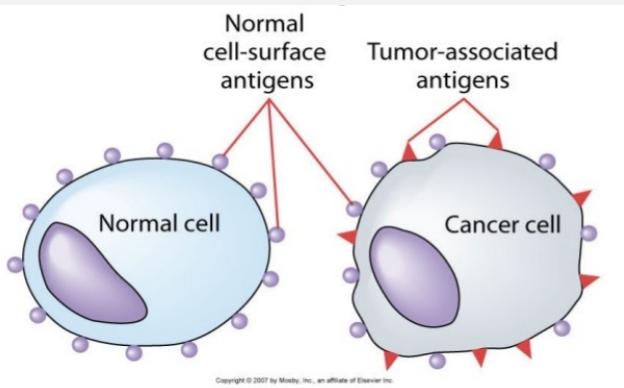
TUMOUR IMMUNOLOGY

2. *Tumour associated antigens (TAAs) or Tumour associated transplantation antigens (TATA):*

- Antigens that are expressed by tumour cells and normal cells; in most cases, normal cellular constituents expression is aberrant or dysregulated in tumour
- Eg. AFP (α -fetoprotein) produced by hepatocellular carcinoma
- Eg. CEA (carcinoembryonic antigen), occurring in ovarian and colon cancer

TUMOUR IMMUNOLOGY

2. Tumour associated antigens (TAAs)



TUMOUR IMMUNOLOGY

Onco-foetal Antigens

- **Proteins that are expressed at high levels on cancer cells and in normal developing (foetal) but not adult tissues.**
- The genes encoding these proteins are *silenced during development* and are **de-repressed** *during malignant transformation.*
- Eg. *carcinoembryonic antigen (CEA, CD66) and alpha-fetoprotein (AFP) made by liver and germ cell tumours.*

TUMOUR IMMUNOLOGY

- Chemicals or UV express *neo-antigens*, the majority of these tumours are often *weakly immunogenic* or non-immunogenic.
- Some of these antigens may be *secreted* while others may be *membrane-associated molecules*.

TUMOUR IMMUNOLOGY

Chemically-induced tumours

- They are different from virally-induced tumours in that they are extremely heterogeneous in their antigenic characteristics.
- ***Thus, any two tumours induced by the same chemical, even in the same animal, rarely share common tumour specific antigens.***
- These unique antigens on chemically-induced tumours are referred to as tumour specific transplantation antigens (TSTA).

IMMUNE SYSTEM INTERACTS WITH TUMOUR CELLS

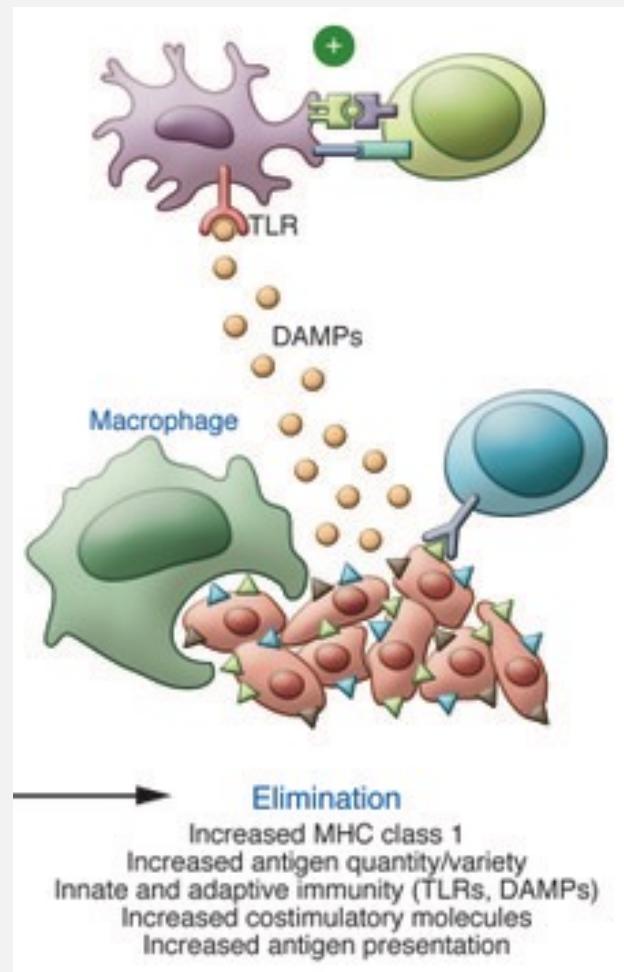
Immunoediting:

three phases: *elimination*, *equilibrium* and *escape*

- ***Elimination phase*** uses the classical concept of immunosurveillance.
- Innate and adaptive immune system work in conjunction to potentially eradicate the developing tumour.
- These cells and molecules include macrophages, NK cells, CD4+ T cells, CD8+ T cells and $\gamma\delta$ cells.

IMMUNE SYSTEM INTERACTS WITH TUMOUR CELLS

- *Elimination phase*

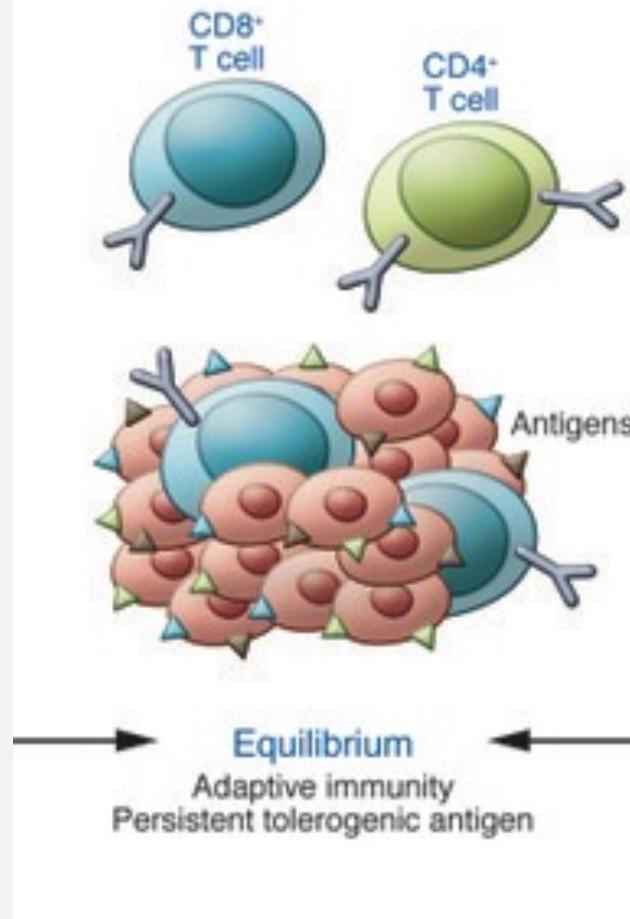


IMMUNE SYSTEM INTERACTS WITH TUMOUR CELLS

- ***Equilibrium phase*** tumour cells are chronically maintained over a long period of time.
- ***Allows for new populations*** of tumour-cell variants to escape the control of the immune system and subsequently become clinically detectable in the third phase

IMMUNE SYSTEM INTERACTS WITH TUMOUR CELLS

- *Equilibrium phase*



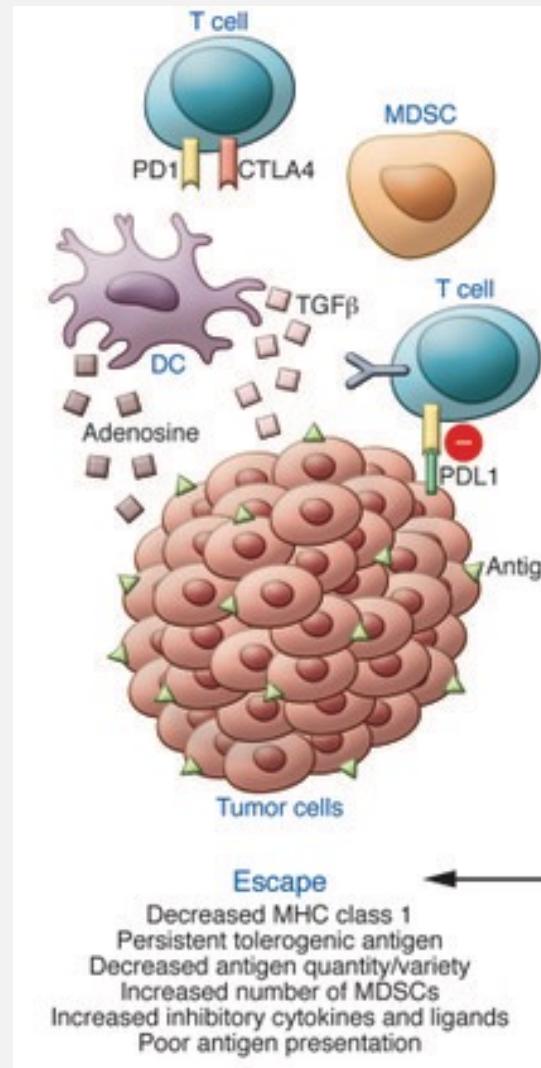
IMMUNE SYSTEM INTERACTS WITH TUMOUR CELLS

- ***Escape phase:*** tumour cells outweigh the balance of the immunological restraints of the equilibrium phase.
- Pro-oncogenic or immunosuppressive mutations survive to pass on their mutations to daughter cells, which may undergo further successive mutation and selective pressure.

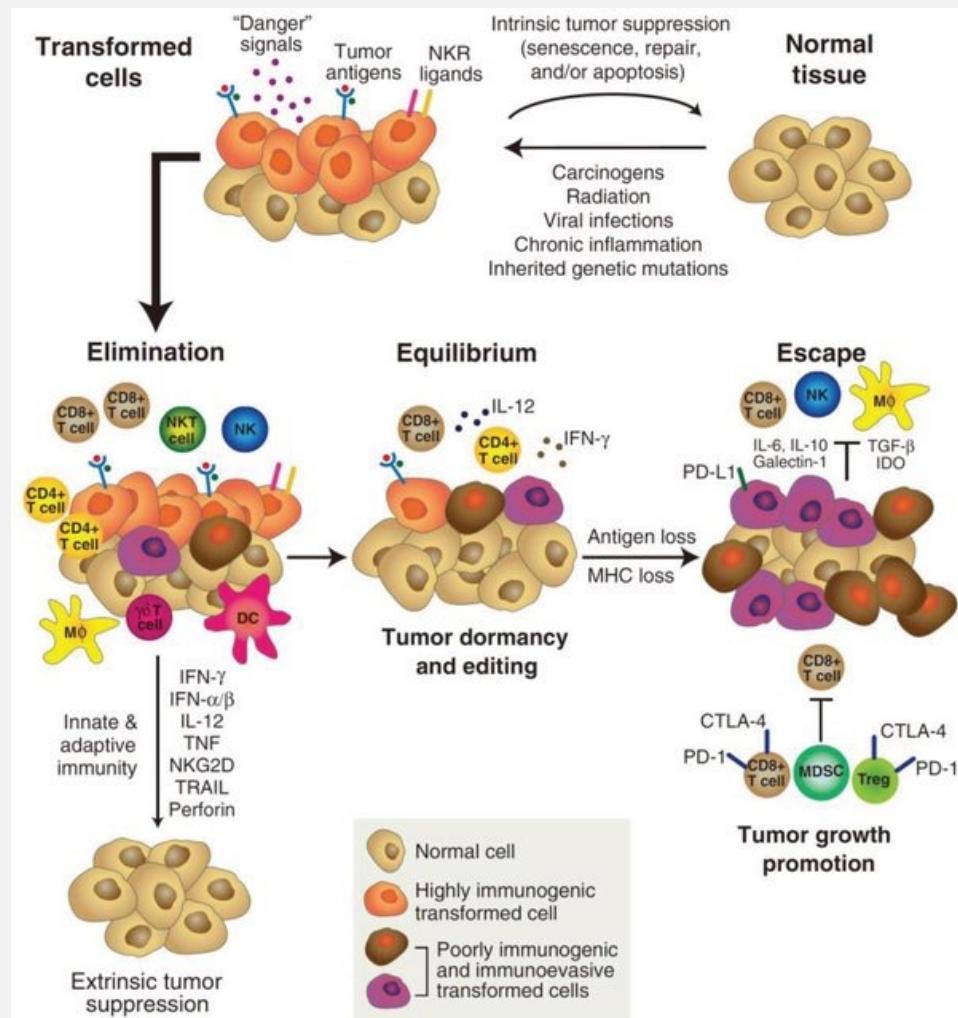
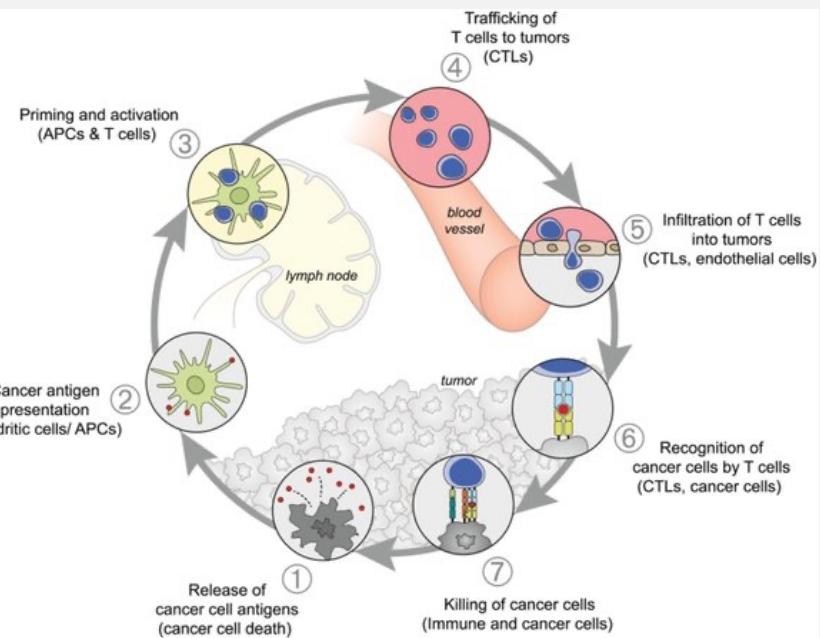
>>> cells with decreased immunogenicity and can hardly be eliminated.

IMMUNE SYSTEM INTERACTS WITH TUMOUR CELLS

- *Escape phase:*



SUMMARY



ADAPTIVE RESPONSE TO TUMOUR CELLS

- Tumours can be destroyed by T lymphocytes, antibody-dependent cell-mediated cytotoxicity (ADCC), natural killer [NK] cells, NK/T cells, ***activated macrophages*** and ***neutrophils***.
- Cytokines plays an important role in aiding the immune effector mechanisms in cancer immunity.

ADAPTIVE RESPONSE TO TUMOUR CELLS

- Tumours are destroyed by tumour-specific cytotoxic T cells, with the aid of cytokines mediated by cytotoxic T lymphocytes (CTLs) such as IFN- γ and TNF- α .
- CD4+ Th cells is involved in induction, regulation, and maintenance of CTLs.

ADAPTIVE RESPONSE TO TUMOUR CELLS

- ***Antibody-dependent cell-mediated cytotoxicity (ADCC):***
- Binding of tumour specific antibodies to the surface of the tumour cells, the interaction of granulocytes and macrophages, which possess surface receptors for the Fc portion of the antibody attached to the tumour cell
- Destruction of the tumour cells by substances that are released from these cells
- NK cells

IMMUNE EVASION BY TUMOUR CELLS

Due to impaired immune reactivity, cancer cells may escape destruction. Tumours evade immune recognition by several mechanisms

- ❖ Tumours may *not express neo-antigens* that are immunogenic or they may fail to express co-stimulatory molecules required for the activation of T cells.
 - Lower their MHC I expression and avoid being detected by the cytotoxic T cells

IMMUNE EVASION BY TUMOUR CELLS

- ❖ Some tumours *lack or are poor expressers of MHC* antigen.
 - Defects in antigen presentation pathway, leads to down-regulation of tumour antigen presentations.
 - Defects in Transporter associated with antigen processing (TAP) or Tapasin

IMMUNE EVASION BY TUMOUR CELLS

- ❖ Escape cytotoxic T cells by stopping expression of molecules essential for co-stimulation of cytotoxic T cells, such as CD80 or CD86
- ❖ Some tumours may evade the immune system by *secreting immunosuppressive molecules* such as:
 - induce regulatory cells particularly the CD4+CD25+ FoxP3+ T regulatory cells.
 - immunosuppressive tumour products; e.g. transforming growth factor- β

IMMUNE EVASION TUMOUR CELLS

- ❖ Some tumour cells express molecules to *induce apoptosis or to inhibit T lymphocytes*(negative regulators):
 - **FasL** on its surface, tumour cells may induce apoptosis of T lymphocytes by FasL-Fas interaction
 - **PD-L1** on the surface of tumour cells leads to suppression of T lymphocytes by PDI-PD-LI interaction
- ❖ Some tumours may *shed their antigens* which in turn may interact and block antibodies and T cells from reacting with the tumour cells.

IMMUNO-DIAGNOSIS OF TUMOURS

- Monoclonal antibodies *labelled with radioisotope* have been used for *in vivo* detection of relatively small tumour foci.
- Antibodies have also been used *in vitro* to *identify the cell origin of undifferentiated tumours*, particularly of lymphocytic origin.
- Immuno-*histological staining* is used to confirm suspected metastatic foci, especially in bone marrow.

IMMUNO-THERAPIES OF TUMOURS

- **Augmenting the weak host immune response to the tumours or at administering tumour-specific antibodies or T cells, a form of passive immunity**
- *Monoclonal antibodies:* Fc receptor bearing cells such as NK cells, macrophages and granulocytes may bind to the antigen-antibody complexes on the tumour cell surface and mediate tumour cell killing through antibody-dependent cell-mediated cytotoxicity.

IMMUNO-THERAPIES OF TUMOURS

- *Tumour specific antibodies*: recombinant fusion proteins that include anti-tumour antibodies and cytokines. These help by concentrating cytokine mediated immune effector responses at the tumour site
 - increase the response of tumour-specific CTLs
- Augmentation of Host Immunity to Tumours With Cytokines and Co-stimulators
 - Eg. HPV antigen vaccines may reduce incidence of cervical carcinoma.

IMMUNO-THERAPIES OF TUMOURS

- *Antibody- drug conjugates* are molecules joined to a chemotherapy drug, radioactive particles, or toxins
 - antibodies acts on homing devices that take the molecules directly to the tumour
- *Immunostimulatory monoclonal antibodies.* Specifically, targeted is anti-CTLA-4 that has been used with tumour vaccines to stimulate tumour response.
 - Monoclonal anti-CTLA-4 is an antibody that restricts CTLA-4 -mediated T cell suppression