Immunity

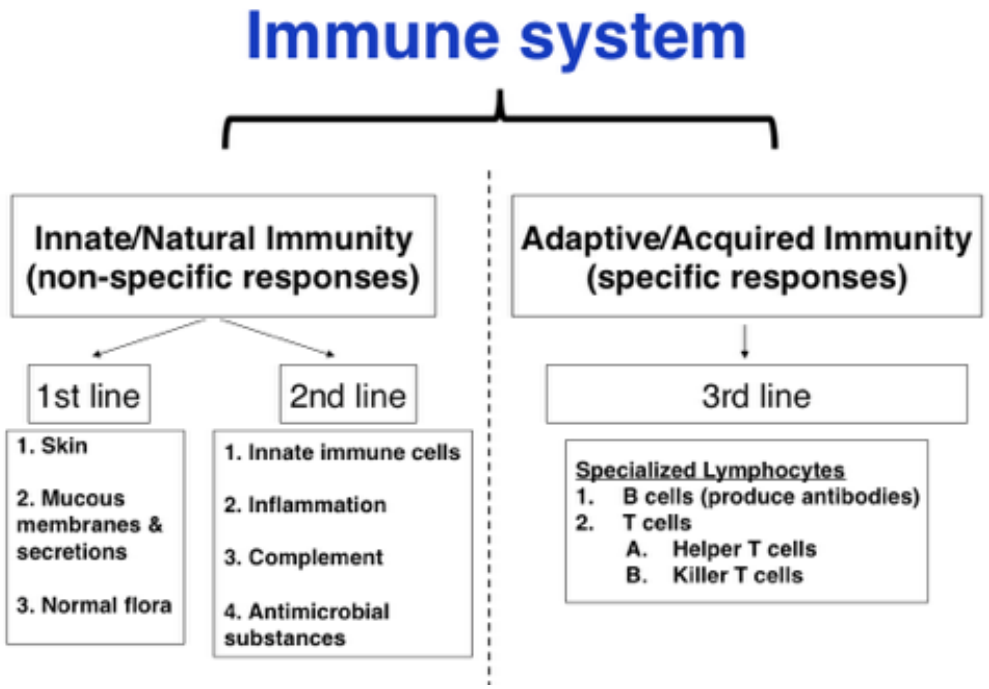
PHYSIOLOGY

DR HUNG DIEP

Definitions

- Antigen: a toxin or foreign body that induces an immune response
- Pathogen: a disease-causing antigen
- Antibody: a protein produced in response to a specific antigen
- Innate Immunity: system that does not require previous sensitisation to protect against foreign proteins
- Adaptive Immunity: an antigen-specific immune response

Immune Response



Innate Immunity

- System of immunity that does not require prior sensitisation
- Functions include:
  - Physical, chemical and biological barriers
    - Epithelial surfaces, peristalsis, mucus, gut flora, lacrimation
  - Recruiting immune cells
  - Activation of the complement cascade
  - Identification and removal of foreign substances
  - Activation of the adaptive immune system via antigen presentation

Innate Immunity

- Involve leucocytes, which are free roaming within the peripheral circulation
  - Produced by haematopoietic stem cells in the bone marrow
  - Interact with cellular debris, foreign bodies and microorganisms
- Cells include:
  - Natural Killer cells
  - Mast cells
  - Eosinophils
  - Basophils
  - Phagocytes
    - Macrophages, neutrophils, dendritic cells

Immune Cells

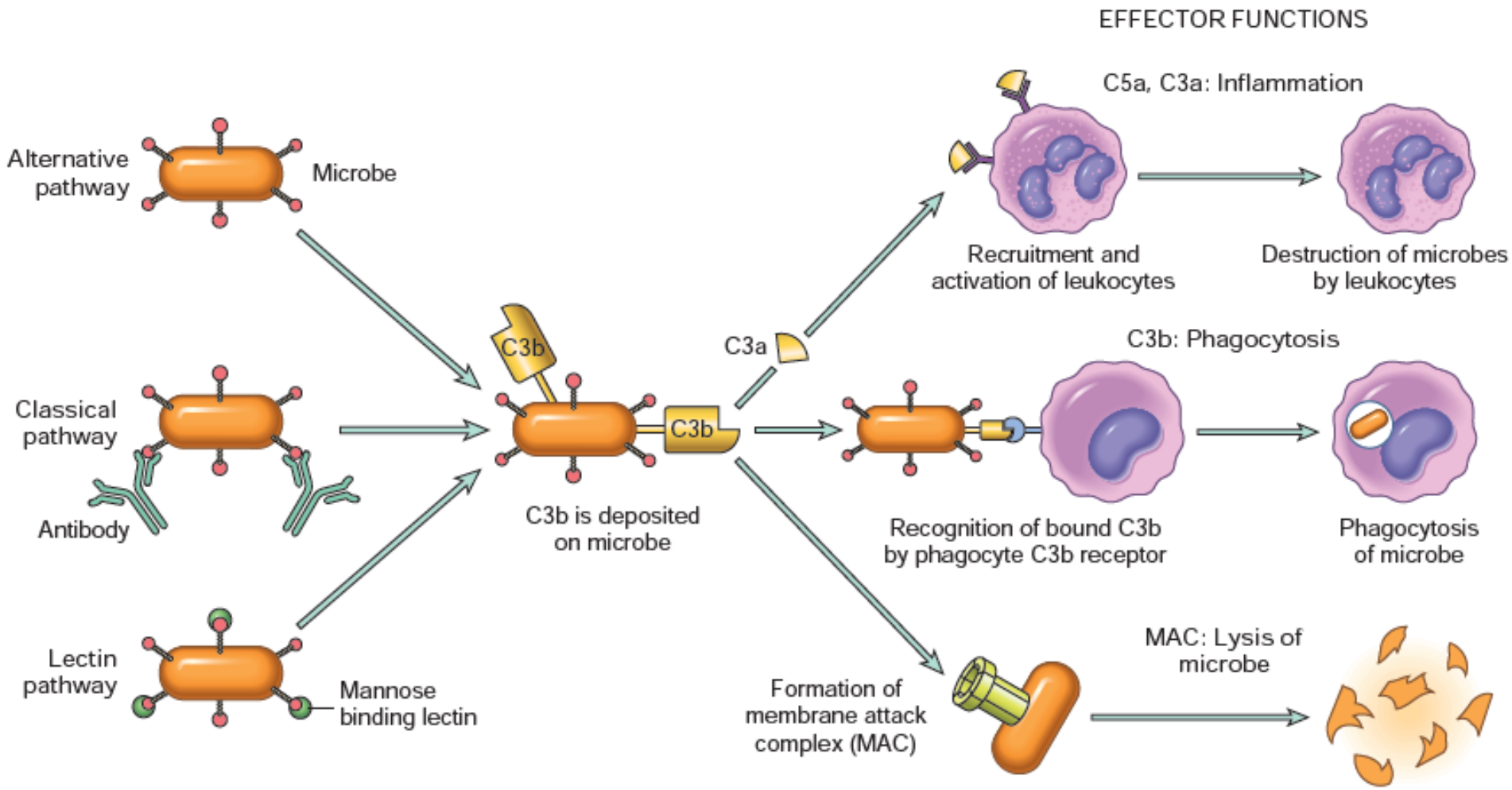
- Neutrophils – 70%
- Macrophages – 8-10%
- Eosinophils – 5%
- Basophils – 1%
- Lymphocytes – 15%

Immune Cells

Mast Cells	Reside in connective tissue and in mucus membranes When activated, release granules that include histamine, heparin, serotonin, ATP, hormonal mediators, cytokines, chemokines Histamine dilates blood vessels and causes recruitment of macrophages and neutrophils
Phagocytes	Facilitates endocytosis, with endosomes fusing with lysosomes Present in circulation, but can be activated by cytokines Include: - **Macrophages**: can move out of circulation (monocytes) into peripheral tissues (macrophages) - **Neutrophils**: most numerous phagocytes - **Dendritic cells**: phagocytic cells present in tissues in contact with the external environment
Basophils & Eosinophils	Play a role in allergic reactions and parasitic infections
Natural Killer Cells	Monitor compromised host cells, such as tumour cells or virus infected cells Cells with low MHC1 trigger the NK cells

Complement System

- System of proteins that functions in both innate and adaptive immunity
- Complement proteins circulate in inactive forms within the plasma
- When activated, leads to a cascade of reactions that ultimately result in proteolysis of C3
- Cleavage of C3 occurs via:
  - 1. **Classical pathway**: fixation of C1 to an antibody (IgM, IgG) that has combined with antigen
  - 2. **Alternative pathway**: microbial surface molecules, complex polysaccharides, other substances in the absence of an antibody
  - 3. **Lectin pathway**: plasma mannose-binding lectin binds to carbohydrates on microbes and directly activates C1


EFFECTOR FUNCTIONS
C5a, C3a: Inflammation
Alternative pathway
Microbe
Recruitment and activation of leukocytes
Destruction of microbes by leukocytes
C3b
C3a
C3b: Phagocytosis
Classical pathway
C3b
Antibody
C3b is deposited on microbe
Recognition of bound C3b by phagocyte C3b receptor
Phagocytosis of microbe
MAC: Lysis of microbe
Lectin pathway
Mannose binding lectin
Formation of membrane attack complex (MAC)

Inflammation

- Protective response to remove the initial cause of cell injury and the consequences of such injury
- Stimulated by chemical factors released by damaged cells
- **Acute inflammation**: rapid in onset and is of short duration, lasting for hours or a few days
  - Main characteristics are exudation of fluid and plasma proteins, and emigration of leucocytes, predominantly neutrophils
- **Chronic inflammation**: longer duration and is associated with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis and tissue destruction
  - May follow acute inflammation or be insidious in onset

Acute Inflammation

- Has 3 major components
  - 1. Alterations in vascular calibre that lead to increase in blood flow
  - 2. Structural changes in the microvasculature that permit plasma proteins and leucocytes to leave the circulation
  - 3. Emigration of the leucocytes from the microcirculation, their accumulation in the focus of injury, and their activation to eliminate the offending agent
    - **Margination**, **migration** across endothelium, **chemotaxis**
- Mediators include: histamine, bradykinin, serotonin, leukotrienes, prostaglandins

Acute Inflammation

- All acute inflammatory reactions may have one of 3 outcomes:
  - Complete resolution
  - Healing by connective tissue replacement (fibrosis)
  - Chronic inflammation

Chronic Inflammation

- Inflammation of prolonged duration (weeks or months), in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations
- Characterised by:
  - Infiltration with mononuclear cells, including **macrophages**, lymphocytes and plasma cells
  - Tissue destruction, induced by the offending agent or the inflammatory cells
  - Angiogenesis and fibrosis

Adaptive Immunity

- Highly specific to a single pathogen
- Triggered when a pathogen evades the innate immune system while also:
  - Generating a threshold level of antigen
  - Activating dendritic cells
- Major functions include:
  - Recognition of non-self antigens in the presence of self antigens
  - Generation of specific antigen responses
  - Development of immunological memory

Adaptive Immunity

- Two types:
  - 1. **Humoral immunity**: protects against extracellular microbes and their toxins
    - Mediated by B lymphocytes and their secreted products (immunoglobulins)
  - 2. **Cell-mediated immunity**: responsible for defence against intracellular microbes
    - Mediated by T lymphocytes

Lymphocytes

- Peripheral blood contains about 2% of lymphocytes
- B and T cells develop form the same precursors and are undifferentiable until after they are activated
- In adults, B and T cells undergo three stages of development:
  - 1. Undifferentiated and immature (present in marrow/thymus)
  - 2. Effector cells that have met their antigen and are actively involved in pathogen elimination
  - 3. Memory cells, which are survivors of past infections to provide long term immunity

B Lymphocytes

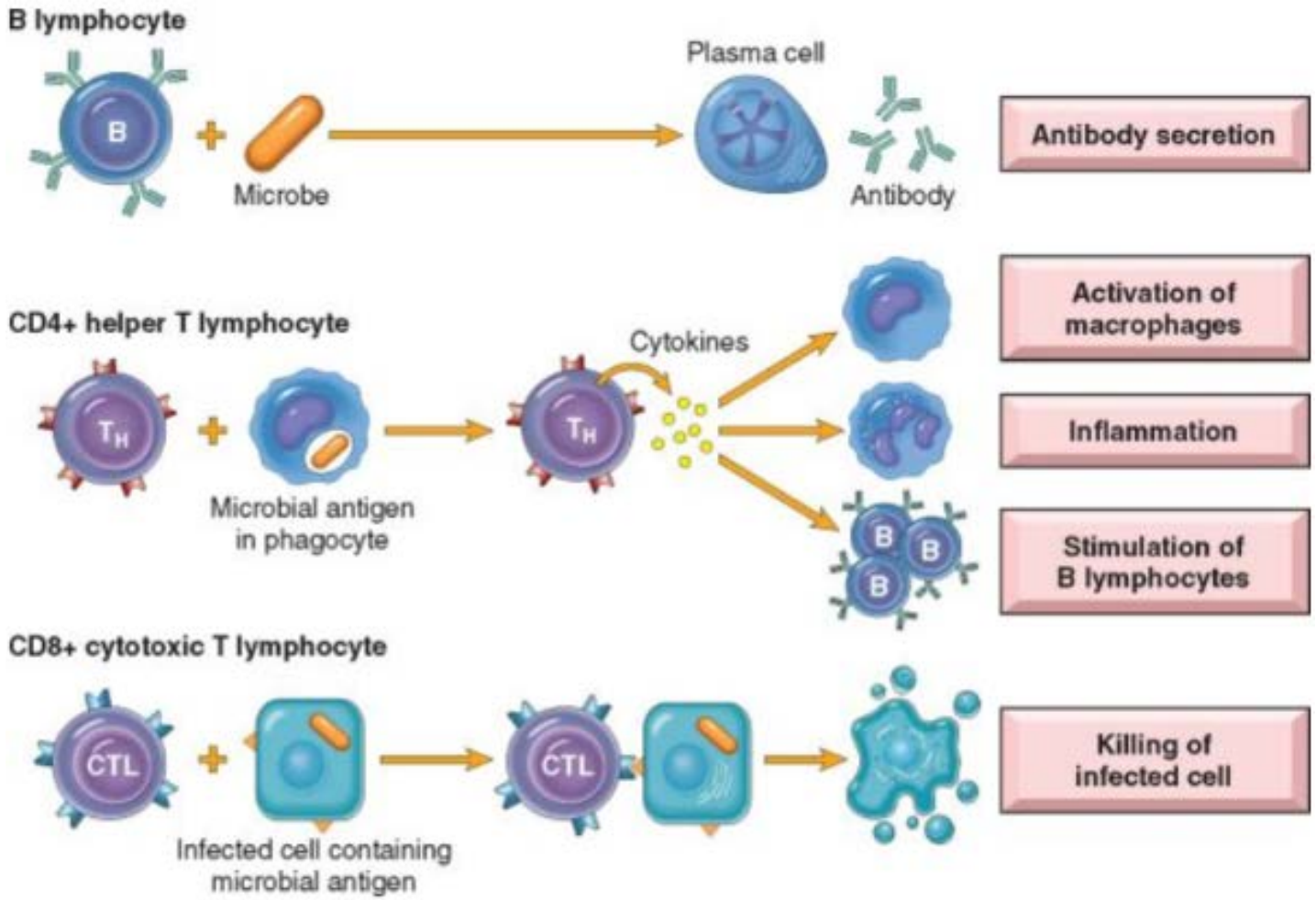
- Predominantly facilitate humoral immunity
- Produces antigen specific immunoglobulins
- Difference between B and T cells lies in their antigen presenting capacity
  - T cells require the antigen to be processed and displayed as part of MHC
  - B cells do not require antigens to be processed
- Once B cells encounter their specific antigen AND receive stimulation from a CD4 T helper cell (TH2 subtype), it develops into a plasma cell
- Plasma cells produce antibodies, and can survive for 2-4 days
  - Antibodies bind to antigens and make them easier targets for phagocytes and also trigger the complement cascade
- B cells undergo **somatic hypermutation** after activation to make more specific antibodies against the particular antigen

T Lymphocytes

- Predominantly facilitate humoral immunity, and also co-stimulates B cells
- T cell receptor diversity is facilitated by **somatic rearrangement** of genes during lymphocyte development
- CD4 T cells:
  - Helper cells that are immune response mediators
  - Have no cytotoxic or adaptive immune response
  - Activated by **MHC Class II**
  - Two types:
    - TH1: produces interferon-γ to activate macrophages and induce B cells to make opsonins and complement fixating antibodies to result in cellular immunity
    - TH2: characterised by the release of IL-5, which induces eosinophils in the clearance of parasites
    - Also produces IL-4, which assists in B cell isotype switching (IgM to IgG, IgA, IgE)

T Lymphocytes

- CD8 cells:
  - Cytotoxic T cells
  - Activated by **MHC Class I**
  - Once activated, undergoes clonal selection and massive replication
  - Travel the body looking for antigen-specific MHC Class I protein complexes
  - Lyse the pathogen infected cells and induce apoptosis in affected cells
  - Remain as memory cells to be activated with a later encounter


B lymphocyte
B
Microbe
Plasma cell
Antibody
Antibody secretion
CD4+ helper T lymphocyte
TH
Microbial antigen
in phagocyte
Cytokines
Activation of
macrophages
Inflammation
B
B
B
Stimulation of
B lymphocytes
CD8+ cytotoxic T lymphocyte
CTL
Infected cell containing
microbial antigen
CTL
Killing of
infected cell

Adaptive Immune Response

- Host cells express self antigens, while bacterial cells do not
  - Adaptive immunity relies on the immune system to be able to differentiate
- Antigen presentation can occur via the following:
  - Exogenous antigens: dendritic cells engulf exogenous pathogens and then migrate to the T cell enriched lymph nodes, and then present them as part of their MHC (class II)
    - Complex is recognised by CD4 T cells, which are then activated
  - Endogenous antigens: produced by viruses and intracellular bacteria replicating within a host cell
    - Host cell digests these and presents them on their MHC (class I) and this activates CD8 T cells

Questions