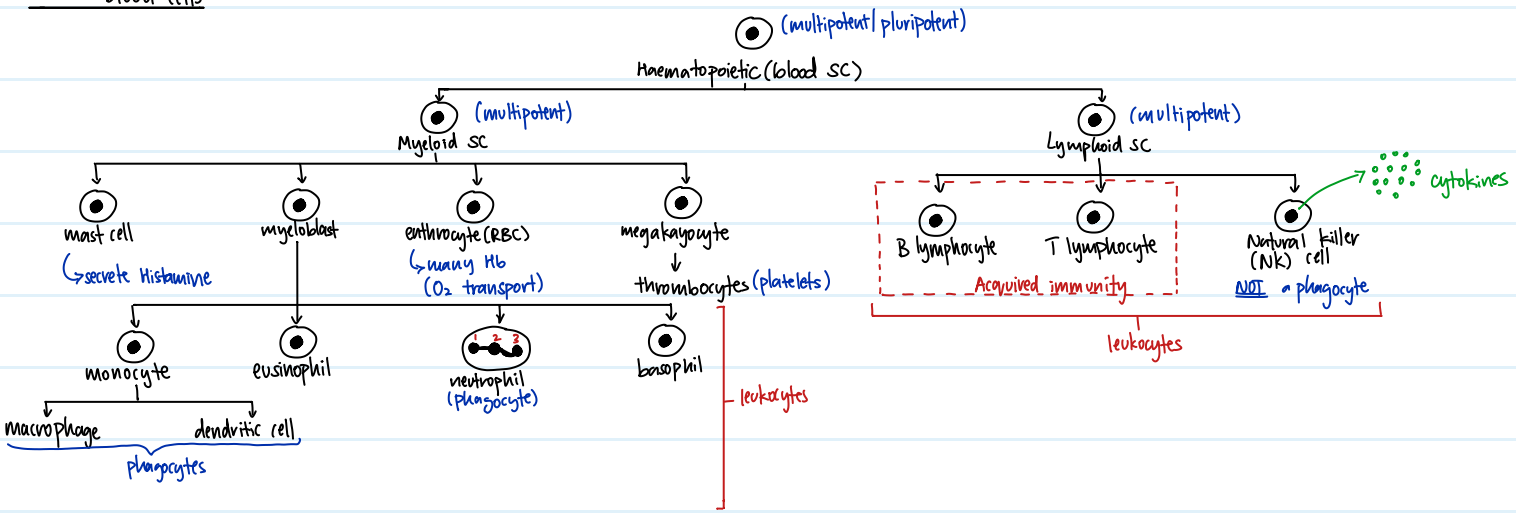
INFECTIOUS DISEASES

White blood cells



Antigen recognition

- Antigen receptors on white blood cells (WBCs) bind to antigens (found on cell wall/viral envelope as viral glycoproteins) on pathogens. } at epitopes (antigenic determinant) ↳specific
- B lymphocytes secrete antibodies that also bind to antigens.

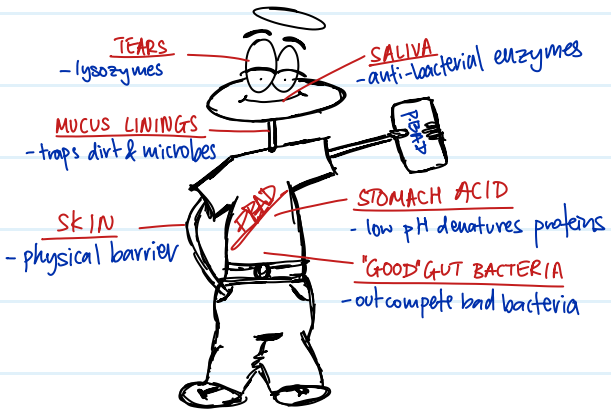
↳ Advantage: ① more than 1 type of antibody can recognise & bind to a specific pathogen ⇒ ↑ rate of pathogen removal

② Immunity against pathogen 1 may provide immunity against pathogen 2 with similar antigens

Innate immunity (non-specific) — 1st immediate response

- not specific & has no immunological memory

① Barrier defences — 1st line of defence:



② Internal defences — 2nd line of defence

- entry through wounds ⇒ LOCAL INFLAMMATORY RESPONSE → Phagocytes → Macrophages, Dendritic cells; → NK cells

- NK cells
  - detect viral or cancerous cells & release cytokines → trigger lysis / apoptosis of target cell
  - Perforin: forms pores in CSM
  - Grazymes: induces apoptosis

- Local inflammatory response (minor injury)
  i) mast cells secrete histamines → vasodilation (↑ blood flow to site) & ↑ capillary permeability to WBCs
  ii) macrophages secrete cytokines
  iii) histamine and cytokines recruit phagocytes that engulf & digest pathogen & cell debris via phagocytosis
  ⇒ swelling / tenderness / pus / pain

- Systemic inflammatory response (severe injury / infection)
  - Pyrogens released by pathogens & activated cytokines result in fever.

Antigen presentation (link betw. innate & adaptive)

- Antigen presentation activate adaptive immune system
- Antigen-presenting cells (APCs) like macrophages & dendritic cells activate T lymphocytes
- APCs take up pathogen by phagocytosis / receptor-mediated endocytosis
- Naive T cell bind to complementary antigen on APC ⟹ activated T cell
- B cell act as APC and only presents specific antigen to already activated Helper T cell.

Adaptive Immune System (Specific)

- 1° infection ⇒ slower & targets specific antigens
- 2° infection ⟹ faster, stronger, prolonged due to IMMUNOLOGICAL MEMORY

* B lymphocytes → mature in bone marrow
* T lymphocytes → mature in thymus gland

① Clonal selection

- 1° response ⇒ naive T/B cells activated when antigen complementary to receptors bind.

② Clonal expansion

- each cell undergoes multiple mitotic divisions to clone specific for a particular epitope.

i) Effector cells – short-lived & immediately act on pathogen

- Naive B cells → plasma cells that secrete antibodies (immunoglobin) (soluble) that target specific antigen on pathogen.
- Naive Helper T cells → effector Helper T cells ($CD4^+$ T cells due to presence of CD4 glycoproteins)
- Naive cytotoxic ("killer") T cells → effector cytotoxic T cells ($CD8^+$ T cells due to presence of CD8 glycoproteins)

ii) Memory cells – long-lived, generated after 1° response

- differentiate into effector cells during 2° response (memory T/B cells)

Cell-mediated Immunity (T cells)

i) Helper T lymphocytes ($CD4^+$)

① Antigens from APCs (macrophage, dendritic cell) bind to naive helper T cells at specific antigen receptors & CD4 coreceptors ⇒ ACTIVATED!! (produce cytokines)

② Cytokines activate naive Helper T cells & stimulate clonal expansion

③ Cytokines activate naive cytotoxic T cells; activate naive B cells based on antigen presented

④ differentiate into memory Helper T cells ⇒ IMMUNOLOGICAL MEMORY

ii) Cytotoxic "Killer" T cells ($CD8^+$)

① Foreign antigens bind to specific antigen receptors & CD8 coreceptor on naive cytotoxic T cells.

② cytokines stimulate clonal expansion ⇒ effector cytotoxic T cells (OR) memory cytotoxic T cells

③ Effector cells secrete perforin (form pores) & granzymes (induce apoptosis)

④ differentiate into memory cytotoxic T cells ⇒ IMMUNOLOGICAL MEMORY

Humoral Immunity (B cells)

secrete cytokines

① Take in antigen by receptor-mediated endocytosis & present only antigen its receptors specifically binds to ⇒ activate Helper T cells.

② Cytokines stimulate clonal expansion into plasma cells (OR) memory B cells.

③ Plasma cells secrete soluble antibodies with identical antigen binding sites.

↳ Neutralise → prevent entry into cell

↳ Opsonisation → cause pathogen to agglutinate / aggregate

↳ Activate complement system → form pores & trigger osmotic lysis

④ differentiate into memory B cells ⇒ IMMUNOLOGICAL MEMORY

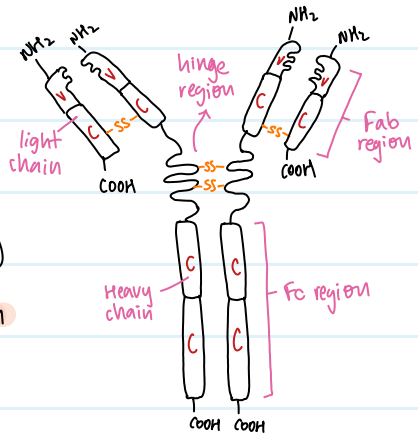
Antibodies / Immunoglobins (Ig)

① Ig D – cell surface (hydrophobic) receptor of B cells (important for activation)

② Ig A – Protect mucosal surface; prevent attachment of pathogens

③ Ig E – bind to mast cell & trigger histamine release

④ Ig G – similar to Ig M but more effective



Structure: – globular with quaternary structure

– 4 polypeptide chains (2 identical heavy chains, 2 identical light chains)

– Heavy chains—(disulfide bond) heavy chain; heavy chain—(disulfide bond) light chain] joined by hinge region

i) Fab (fragment antigen binding) region

ii) Fc (fragment crystallisable) region → mediates effector functions

* Variable (V) domains:

- extensive variation in a.a seq. in domains of diff. antibodies from diff. B cells.

- antigen binding site complementary to specific antigen

– 2 identical antigen binding site allows simultaneous binding ⇒ agglutination / aggregation

* Constant (C) domains:

- little / no variation in a.a seq. of same class type ⇒ activate complement system (→ cytotoxic reactions) & stimulate macrophages (→ phagocytosis)

- domain differ among diff. class types

* hinge region: flexible ⇒ facilitates agglutination / aggregation

Antibody Diversity

- Somatic recombination & Somatic hypermutation ⇒ diversity in V domains
- Class switching ⇒ same antigen specificity but different effector properties due to change in C domains.

① Somatic recombination: ⇒ V(D)J recombination

- light chain genes: V, J (joining), C segments
- heavy chain genes: V, D (diversity), J, C segments
- DNA rearrangement during development of B cells.
  - i) V(D)J recombinase (random) links 1 V segment and 1 J segment ⇒ single VJ exon.
  - ii) DNA rearrangement is permanent ⇒ passed on during clonal expansion

  (- light chain)
- VDJ recombination at heavy chain gene locus forms a single VDJ exon.
- Random pairing of light & heavy chains at Fab region ⇒ ↑ DIVERSITY

② Somatic hyper-mutation

- random point mutations only in activated B cells (after recombination!)
- Activation-induced cytidine deaminase (AID) catalyses deamination of cytosine to uracil in DNA
- base mismatch ⇒ DNA repair ⇒ ERROR-PRONE! ⇒ high rate of mutations
- affinity maturation ⇒ B cells with higher affinity survive & divide better.

③ Class-switching (isotope switching)

- stimulated by cytokines to secrete diff. class of antibodies (Fc affected)
- same antigen specificity but interact with diff. effector cells.
- genes for C segment removed irreversibly!
- IgG more effective in neutralisation & opsonisation; pass placenta ⇒ passive immunity.
- 2° response quantity: IgG > IgM

Viral infections

① Influenza virus:

- neuraminidase ⇒ penetrate mucus layer
- haemagglutinin ⇒ bind to specific sialic acid containing receptors on epithelial cells
  - ↳ local inflammation: histamine ⇒ runny nose, blocked nose, sore throat, coughing & cytokines
  - ↳ systemic inflammation: pyrogens ⇒ fever, body aches
  - * novel flu strains ⇒ "cytokine storm" ⇒ fluid accumulation in lungs ⇒ death
  - * susceptible to 2° bacterial infections ⇒ pneumonia

② HIV:

- infects macrophages & Helper T cells → fuse & form giant multinucleated cells/syncytium (pl: syncytia)
- syncytium may lyse or killed by cytotoxic T cells
- apoptosis of infected Helper T cells (↑ viral load) ⇒ depression of adaptive immunity ⇒ opportunistic infections

i) 1°(acute) infection: high viral load in blood

ii) Clinical latency: few/no symptoms, provirus integrated in DNA of host cells & remains dormant.

iii) Onset of Acquired Immunodeficiency Syndrome (AIDS):

- low $CD4^+$ T cells count (<200 cells/μL)
- virus mutates at extremely high rate ⇒ prevents recognition & elimination by antibodies

③ Mycobacterium tuberculosis

- obligate aerobe, intracellular parasite, layer of mycolic acids
- airborne droplets inhaled & engulfed by macrophages at alveoli ⇒ DORMANT
- 1° infection ⇒ asymptomatic / latent TB (mild flu) in granulomes/tubercles
- 2° infection ⇒ immunocompromised

i) Mycolic acids form lipid shell → virulence, protection from complement system

ii) inhibit fusion of phagosome + lysosome & acidification → protect from lysozymes & reactive oxygen radicals (persistance!)

iii) cytokines recruit more macrophages & NK cells & Helper T cells

iv) Granuloma/Tubercle ⇒ clusters of infected macrophage (→ die due to necrosis ⇒ caseous centre) & WBCs

v) extensive fibrous capsule (↓ O_2) → immunocompetent ⇒ arrested & be latent TB
→ immunocompromised → enlarge (liquefaction) → rupture to form a cavity

Prevention

① Vaccination

- induce immunological memory
- weakened | killed microbes ⇒ inactivated toxins | surface proteins
- imitate pathogen ⇒ 1° response } NO actual symptoms but produce memory cells & antibodies (few weeks) → prepared for 2° infection
- eg. Smallpox virus:
  - induce using cowpox ⇒ same family, similar disease } LESS VIRULENT!
  - vaccinia virus ⇒ same family, same antigens
    ↳ B & T memory cells with antigen receptors complementary to smallpox antigens. → eradicated

	Benefits	Risks
1)	Eradication|Reduction: ↓ morbidity (symptoms), ↓ mortality	Mutations: revert to virulent form
2)	Cost-effective	Serious infections: immunocompromised	immunodeficient
3)	Herd immunity: limits spread	Rare adverse reactions: allergy to egg protein

Immunity

	Active - induce immunity - memory cells	Passive - temporary immunity - no immunological memory
Naturally-acquired - not deliberate	direct infection by pathogen	maternal antibodies (fetus through placenta) (newborn through colostrum)
Artificially-acquired - tech (non natural)	Vaccination	antibody from animal via injection

Antibiotics : kill / inhibit bacterial growth

Target	Action
Cell wall	– beta-lactam antibiotics (penicillin) – interfere transpeptidation of bact. cell wall (→ peptidoglycan) synthesis – Penicillin-binding protein (PBP) - catalyse peptide cross-links (→ cell wall turgidity) betw. adj. peptides – Penicillin + PBP active site (covalent bond) ⇒ OSMOTIC LYSIS
CSM	– polymyxins → antibiotics } amphipathic → polar & non-polar functional groups – disrupt phospholipid bilayer – ↑ CSM permeability ⇒ leak of cell content ⇒ CELL DEATH
DNA replication	① inhibit nucleotide synthesis ↳ para-amino benzoic acid (PABA) synthesis folic acid (→ coenzyme for nucleotide synthesis) inhibited by sulphonamides & trimethoprim (antibiotics) ② inhibit enzymatic action in DNA replication ↳ Quinolones (antibiotic) inhibit bact. topoisomerase (DNA gyrase) – relaxation of supercoiled DNA
Protein synthesis	① rifampicin inhibit bact. RNA polymerase – phosphodiester bond NOT formed (transcription) ② tetracyclines & macrolides interfere with ribosome action (translation) – prevent binding of aminoacyl-tRNA to 'A' site (tetracycline) – inhibit peptide bond formation by peptidyltransferase – Block ribo. translocation (macrolide)