Cells of the Immune System

Lymphoid organs
(responsible for development & immune response & organisation of cells)

① **Primary Lymphoid Organs** - bone marrow & thymus

regulate development of immune cells from immature precursors.

② **Secondary Lymphoid Organs** - spleen, lymph nodes, specialised gut & mucosal tissues.

coordinate interaction b/w antigenic & antigen-binding cells & development into effector or memory cells.

① Hematopoietic Stem Cells (HSCs)

- give rise to all mature and functioning blood cells.
- adult stem cell that divides into daughter & progenitor cells
  - Common Myeloid-Erythroid Progenitor Cells (CMPs)
  - Common Lymphoid Progenitor Cells (CLPs)
- isolated as $Lin^{\ominus}$ & then purified as cells that express CD34.

HSCs give rise to different cell types. How to

differentiate?

1. appearance under microscope
2. staining with dye
3. Fluorescent microscopy

Cells of Myeloid Lineage

- First responders to infection

- Erythrocytes
- Granulocytes
  - Neutrophil
  - Basophil
  - Mast cell
  - Eosinophil
- Monocytes
- Macrophages
- Dendritic cells

Granulocytes → multilobed nuclei
→ granules responsive to pathogens

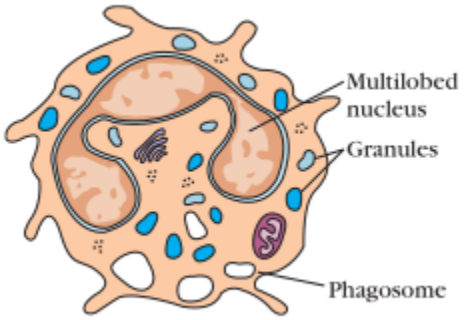
2. Neutrophils

- most abundant WBCs (50-70%)
- differentiates in bone marrow
- circulate for 7-10 hours before entering tissue
- lifespan of few days
- Leukocytosis - ↑ in no. of circulating neutrophils in response to infection

- Innate cells release chemokines → attract neutrophils

  ↓ Phagocytosis

  ↓ NETosis



③ Basophils

- non-phagocytic granulocytes
- granules filled with basophilic proteins
- important in response to parasites like helminths & allergy

Mode of action

Circulating antibodies bind

↓

Degranulation

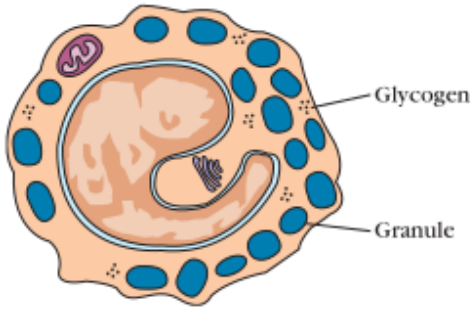
↓

Release of histamine

↓

↑vessel permeability & smooth muscle activity

- may modulate adaptive immune response.



(4) Mast Cells

- released from bone marrow into blood as undifferentiated cells
- mature only after they leave blood into tissues
  - ↓
  - skin, connective, mucosal
- histamine
- development of allergies.

(5) Eosinophils

- motile phagocytic cells
- migrate into tissue spaces from blood
- cluster around invading worms → degranulate proteins that destroy membrane of worms
- release cytokines to regulate B and T lymphocytes
- contribute to allergy and asthma symptoms

Myeloid Antigen-Presenting Cells

- Monocytes
- Macrophages
- Dendritic cell

- cellular bridges b/w innate and adaptive immune responses

(6) Monocytes

- ~5-10% of WBCs
- In bone marrow, granulocyte-monocyte progenitor cells → pro-monocytes
  - enter blood
  - Mature monocytes
    - Inflammatory
      - enter tissues quickly in response to infection
    - Patrolling
      - smaller group of cells crawling slowly along blood vessels

(7) Macrophages

- derived from monocytes that migrated into tissues
  - long term resident in tissues - regulate repair & regenerati
  - inflammatory macrophages - APC + phagocyte

- e.g., osteoclasts in bone
  microglial cells in brain
  alveolar macrophages in lung

- Activated, inflammatory macrophages are more effective than resting ones —
  - greater phagocytic activity
  - increased ability to kill ingested microbes
  - increased secretion of inflammatory & cytotoxic mediators
  - ability to activate T cells
  - more effective as Antigen Presenting Cell for T_H cells.

- Macrophages express a receptor for a certain class of antibody.

if an antigen is coated with appropriate antibody (opsonisation), phagocytosis is enhanced.
because antigen-antibody complex binds to membrane receptors more readily than antigen alone.

Most of the antigen presented is eliminated — some found on macrophage membrane; hence **APC**

⑧ Dendritic Cell

- covered with long membranous extensions that extend & retract dynamically – increasing surface area for browsing lymphocytes.
- **antigen capture** in one place & **antigen presentation** in another
- arise from both myeloid and lymphoid lineage

Outside lymph nodes

immature forms of cells monitor signs of invasion → capture of intruding or foreign antigens → migrate to lymph nodes

↓

antigen presentation to naive T cells → Adaptive immune response

- Immature dendritic cells take on antigens by
  - phagocytosis
  - receptor-mediated endocytosis
  - pinocytosis
- During maturation, shift from antigen-capturing phenotype to antigen-presenting phenotype.
  - ↳ loss of phagocytosis & pinocytosis capability & gain of antigen presenting capability and expression of costimulatory molecules.

- arise from bone marrow

Note

cytokines induce differentiation of B cells → memory cells, plasma cells

(9) Erythrocytes

- arise from myeloid-erythroid precursor
- high conc. of hemoglobin
- circulate, delivering oxygen to surrounding tissue
- damaged RBCs release free radicals that induce innate immune activity
- enucleate in mammals only

(10) Megakaryocytes

- large myeloid cells that reside in bone marrow
- give rise to platelets
  - ↳ responsible for blood clotting
  - ↳ no nuclei of own

Cells of Lymphoid Lineage

Lymphocytes → B cells
→ T cells
→ NK cells

Cluster of Differentiation (CD) molecules

- specific surface proteins found on cells of many type
- indicative of functional capacity of cell
- over 350 CD molecules discovered.

Some points:

(1) All receptors on an individual cell's surface have identical specificity
(2) All daughter cells or clones of a lymphocyte have same specificity

(11) B-Lymphocytes

- B - Bursa of Fabricius in birds
- displays B-cell receptor (BCR) - immunoglobulin that binds to antigen
- each B-cell expresses specific antibody on surface
- improved ability to bind antigen through a process known as somatic hypermutation and can generate antibodies of different classes through a process known as class switching.

- activated B cells → plasma cells (effector cells)
  - ↳ secrete antibody
  - ↓ do not divide

(12) T-lymphocytes

- T = site of maturation is thymus
- expresses T cell receptor (TCR) complex
  - ↳ unlike BCR (recognising soluble antigen) recognises only processed pieces of antigen, bound to MHC molecules
- all T cells express CD3 (expressed in immature thymocytes)

$CD3^+$ T cells → T_H ($CD4^+$)
$CD3^+$ T cells → T_C ($CD8^+$)

- MHC molecules
  - Class I: expressed by all nucleated cells in vertebrates
  - Class II: professional antigen presenting cells & some others during inflammation
- T cells → T_H, T_C on the basis of CD4 or CD8

- Naive $CD8^+$ T cells → browse all antigen presenting cell surfaces with TCR
  ↓
  antigen bound to MHC-I ← activation & proliferation into T_C.
  ↓
  eliminates all cells that have MHC-antigen complex

  (need help from mature $CD4^+$ T cells)

- Naive $CD4^+$ T cells → browse all antigen presenting cell surfaces with TCR.
  ↓
  recognition of antigen-MHC complex → activate, proliferate & differentiate

  → T helper type (1/2)

  Type 1
  - regulates immune response to intracellular pathogens

  Type 2
  - regulates immune response to extracellular pathogens

Also, T_H17 (secreting IL-17) & T-follicular helper cells (T_{FH}) regulating humoral immunity & B cell development in germinal centers

- regulatory T cells (T_{REG}) → inhibit immune response
  - ↳ arise naturally from autoreactive T cells in thymus or can be induced at site of immune response.
  - → $CD4^+$ & $CD25^+$ & FoxP3 expressing
  - → help us quell autoreactive reactions not avoided already, but may also limit our normal T-cell response to a pathogen.

(13) Natural Killer Cells

- lymphoid cells closely related to B and T cells
- part of innate immunity system
- distinguished by expression of NK1.1 and cytotoxic granules ↗ background killing mechanism.
- efficient cell killers of tumor and virus infected cells
- recognise abnormal cells by absence of MHC class I
  - ↳ have receptors for self-MHC I molecules → binding inhibits killing → non-binding means no Self MHC-I molecules ⇒ apoptosis induced
- express receptors for immunoglobulin, and bind antibodies that bind pathogen → make connections with variety of target cells → cytotoxic granule induces killing

(14) NKT cells

- share features with both NK cells and T cells

have antibody receptors, cytotoxic granules released when activated

express TCR and CD4 however, not very diverse, can only recognise certain lipids and glycolipids presented by CD1

- also releases cytokines that can enhance or suppress an immune response

Primary Lymphoid organs

Stem cell niches – specialised anatomic microenvironments that regulate the ability of stem cells to self-renew and differentiate.

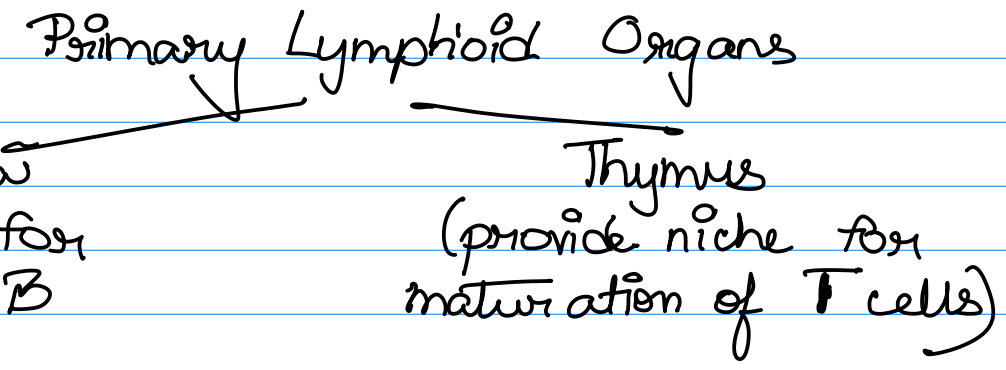
↳ Typically populated by a supportive network of stromal cells.

↳ express soluble and membrane-bound proteins that regulate cell survival, proliferation, differentiation and trafficking.

HSC development

↳ by mid to late gestation, take up residence in bone marrow

but, also found in blood, naturally recirculating b/w bone marrow and other tissues



Bone Marrow

- most active site of self-renewal and hematopoiesis of HSCs (adult stem cell niche)
- contains
  - osteoblasts
  - endothelial cells
  - reticular cells
  - sympathetic neurons

  } regulates HSC differentiation and hematopoiesis.

- different microniches in the bone marrow
  1. endosteal niche - area surrounding bone & in contact with osteoblasts
     [occupied by quiscent HSCs in close contact with osteoblasts that regulate stem cell proliferation]
  2. vascular niche - area surrounding blood vessels and in contact with endothelial cells
     [helps HSCs who have been mobilised to leave the endosteal niche either to differentiate or circulate]

- more differentiated a cell is, closer it is to the center of the bone.

- mature, functional cells (like antibody secreting B cells) can also take up residence in the bone marrow

Thymus

- T cells undergo selection in thymus

T cell precursors travel via blood from bone marrow to thymus → thymocytes generate unique antigen receptor (TCR) → selected on the basis of reactivity to self-MHC peptide complexes expressed on thymic stromal cell surface

- those with too-high affinity for self-MHC undergo apoptosis (negative selection)
- those that bind self-MHC with intermediate affinity (positive selection)

Majority of cells do not survive because they have too low affinity for self-antigen-MHC combinations and fail to undergo positive selection.

T cells enter thymus in blood vessels at corticomedullary junction ($CD4^+$, $CD8^-$) → Subcapsular cortex they proliferate and generate TCR and both CD4 & CD8 (double positive)

↓

Selection by cortical thymic epithelial cells (cTEC)

undergo negative selection by medullary thymic epithelial cells (mTEC) who express proteins from different organs to test for autoreactivity

↓

mature thymocytes are single positive ($CD4^+$ or $CD8^+$) leave the thymus via same junction

→ encounter antigens presented in 2° lymphoid tissue.

Secondary Lymphoid Tissue

antigens encountered and immune responses initiated here.

Secondary Lymphoid Organs → Spleen
→ Lymph nodes
→ MALT

- maintain anatomically distinct T & B cell activity regions
- develop lymphoid follicles for development and selection of antibody-producing B cells.

Connected to each other through blood and lymphatics

- Lymphocytes enter via blood vessels and leave via lymphatic system
- Lymphatic system – network of thin-walled vessels that help in immune cell trafficking
- Lymph vessels – filled with protein rich **lymph**, which seeps through the thin walls of vessels into surrounding tissue → **interstitial fluid**

Edema is prevented by draining fluid from tissues → remainder of lymphatic fluid pass the walls primary Lymph vessels.

↓

Lymphatic vessels → Thoracic duct

↓

enters blood through left subclavian vein

(except for right arm and right side of the head → right subclavian vein)

- Activity enhances lymph circulation.

Heart does not pump lymph → low pressure. flow of lymph achieved through surrounding smooth muscles.

Lymph Node

- most specialised 2° lymphoid organ
- fully committed to regulating immune response
- encapsulated, bean-shaped str. → lymphocytes, macrophages, dendritic cells
- connected to both blood & lymph vessels, first str. to encounter antigens that enter through blood.

Ideal microenvironment for antigens - lymphocyte interaction

Lymph node

Cortex	Paracortex	Medulla
contains B lymphocytes, macrophages & dendritic cells arr. in follicles	• T cells + dendritic cells	• plasma cells + site where lymphocy exit lymph nodes

Antigen in infected tissue → cortex →
- presented as peptides on APC
- passed on to B cells
- presented as antigen-MHC complexes to T cells in paracortex.

T cells in lymph node

- 16-24 hours for a naive T cell to browse all MHC-peptide combinations on the surface of dendritic cells on paracortex
- How are T cell-movements in the lymph node controlled?

Fibroblast reticular cell conduit system (FRCC) – fibroblast reticular cells form web of processes that guide T-cell movements via associated cell-adhesion molecules & cytokines.
↳presence of this network increases the probability that T cells will meet their specific MHC-peptide combination.

- after TCR binds to MHC peptide → stops migrating
  ↓
  proliferate, & depending on cues from APC, differentiate into effector cells
- $CD8^+$ T cells → ability to kill target cells
- $CD4^+$ cells → effector cells that can activate B cells, macrophages, T_C cells.

B cells in lymph node

- B cells activated & diff. into plasma cells here
  - requires antigen engagement with BCR & direct contact with $CD4^+$ T_H cells
- different from T cells in that they can sense soluble or free antigen
- Binds to antigen → partially activated → engulfs & processes antigen → present it to T_H in paracortex → fully activated & proliferates
- Some B cells on activation → move to follicle to establish germinal center
- Germinal center → facilitates affinity maturation of B cells
  - B cell undergoes somatic hypermutation of genes coding for antigen receptors
  - ↓
  - those with highest affinity survive
  - ↓
  - differentiate into plasma cells
    - stay and release antibodies in blood stream
    - take up residence in the bone marrow

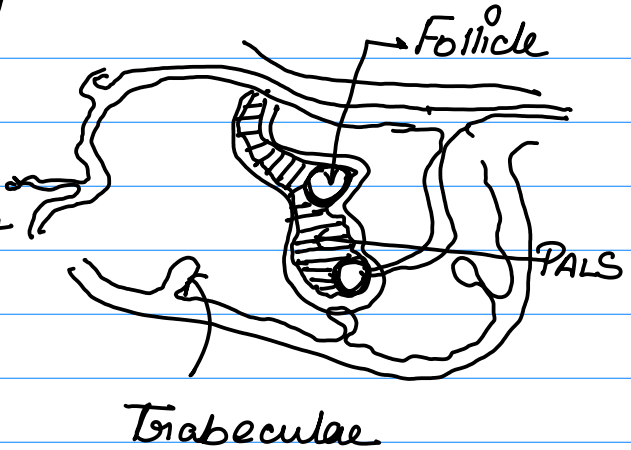
How are memory T & B cells in the lymph node?

Interactions b/w T_H & APC, & b/w T_H & B cells → results not only in proliferation of antigenic-specific lymphocytes, but also, generation of memory T and B cells

↳ reside in 2° lymphoid organs (Central memory cells)

Spleen

- high on left side of abdominal cavity
- filters blood and traps blood-borne antigens
- spleen is not affected by lymphatic vessels
- Trabeculae - no. of projections of capsule that provides structural support to the spleen



- Spleen → red pulp
  ↓
  white pulp, separated by marginal zone
- White pulp → surrounds the splenic artery, PALS (Periarteriolar lymphoid sheath)
  ↙ T cells ↘ B cell follicles

- Marginal zone - has B cells & specialised macrophages
  → first line of defense against blood-borne pathogens

MALT

- Mucosa-associated lymphoid tissue (MALT)
- major sites of entry for most antigens