

Cells and tissues

Course	 Immunology
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Reading	<input type="checkbox"/>

Haemopoetic system

- The great majority of cells involved in mammalian immunity are derived from precursors in the bone marrow and circulate in the blood, entering and sometimes leaving the tissues when required.
 - A very rare stem cell persists in the adult bone marrow (at a frequency of about 1 in 100,000 cells), and retains the ability to differentiate into all types of blood cell.
 - Stem cell marker CD34+ (multipotent)
- Haemopoiesis has been studied either by injecting small numbers of genetically marked marrow cells into recipient mice and observing the progeny they give rise to (*in vivo* cloning) or by culturing the bone marrow precursors in the presence of appropriate growth factors (*in vitro* cloning).
- Proliferation and differentiation of all these cells is under the control of soluble or membrane bound growth factors produced by the bone marrow stroma and by each other.
- Within the cell these signals switch on specific transcription factors, DNA-binding molecules which act as master switches which determine the

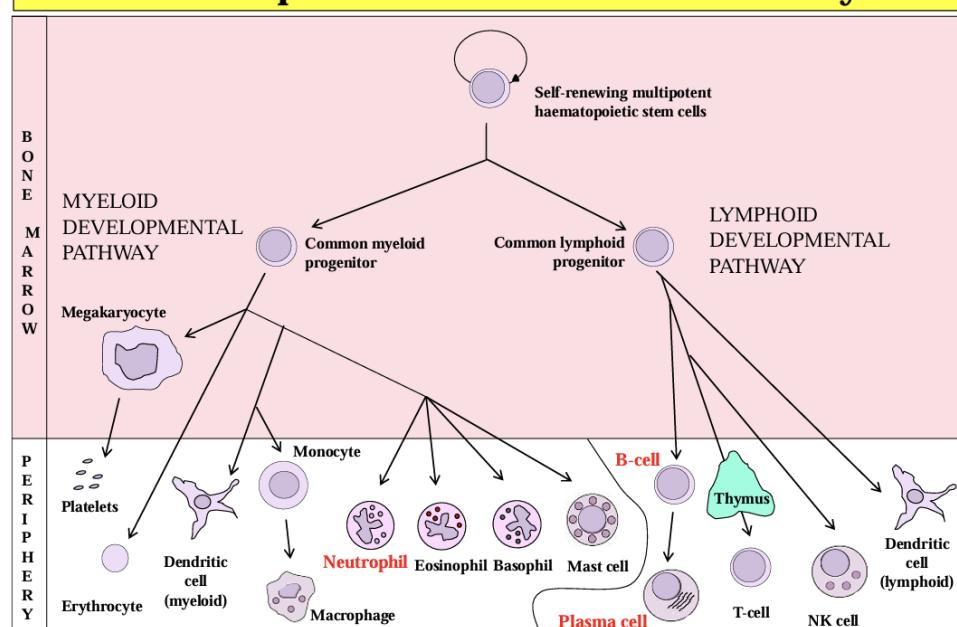


Only a small proportion of immune cells are found in blood because the circulation serves as a mean of transportation. The cells are either in its place of departure or destination most of the time.

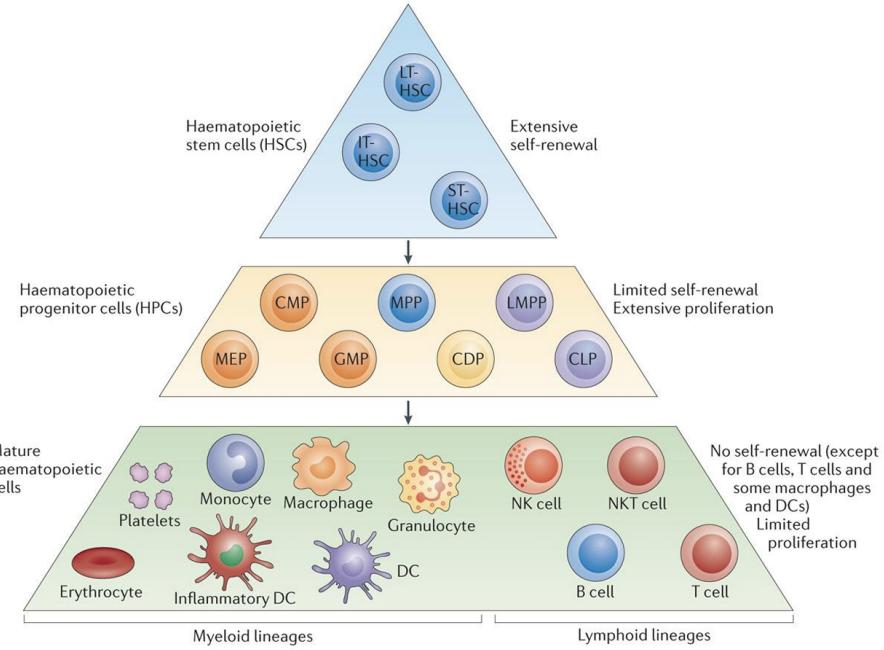
subsequent genetic programme which gives rise to development of the different cell types (known as lineages).

- Remarkably, recent studies have suggested that it may even be possible to turn one differentiated cell type into another by experimentally introducing the right transcription factor into the cell.
- This finding has important therapeutic implications, for example in curing genetic immunodeficiencies.

Figure 1 -Differentiation of haematopoietic stem cells into the specialised cells of the immune system



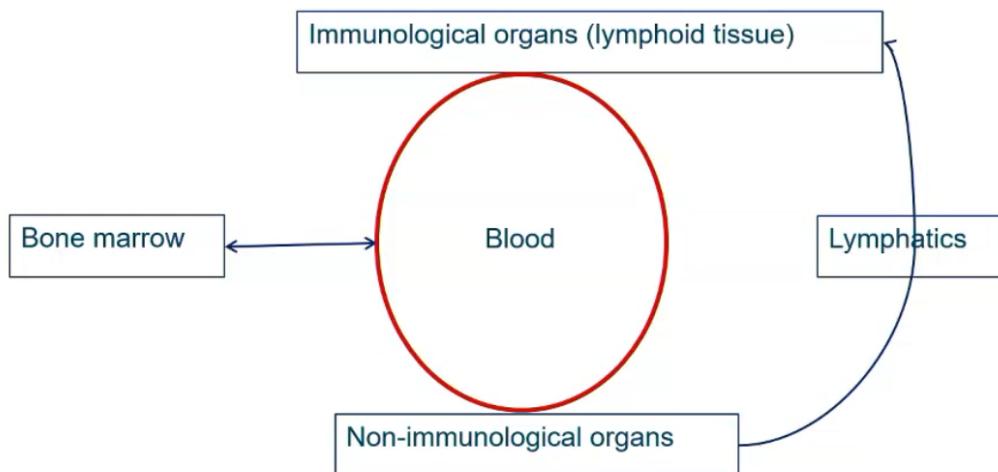
Note that there are both myeloid and lymphoid origin DC.



The immune system is part of the haemopoietic system.

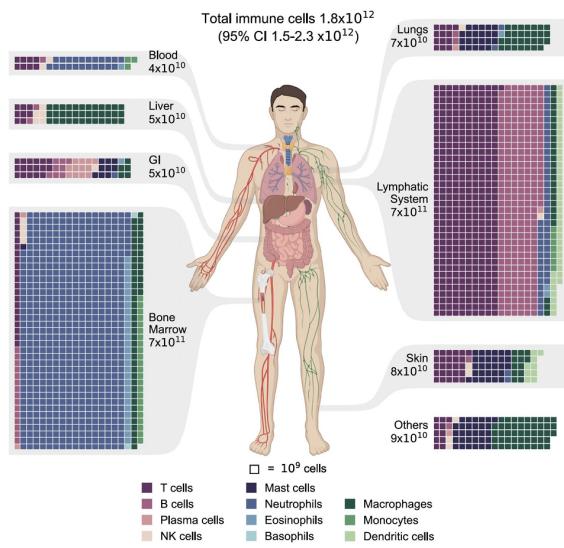
- It is large, plastic, movable and renewable
 - It is the largest physiological system of the human body
- This combination sets it apart from other anatomical systems of the body
 - Large: $10E12/13$ cells
 - Weights the same as a pineapple
 - Dynamic: $10E9$ lymphocytes per day, $10E10$ granulocytes per day (granulocytes: neutrophils, basophils, eosinophils)
 - Number of immune cells vary depend on whether an individual is diseased
 - Vs. other organs: the total number of cells remain largely unchanged although there are dying and renewing
 - Movable: needed throughout the body as there is never sufficient residual cells when infected
 - Thus the correct amount of cells needs to be moved to infected tissue
 - Renewable
 - **One** cell is enough to repopulate the whole immune system
 - haematopoietic stem cell transplantation (HSCT)

Geography of the immune system: the major compartments and their interactions



- Cells derived from the bone marrow (T cells to thymus, B cells remain)
- Travel through blood, which connects the immunological organs and non-immunological organs
- Lymphatics are in all tissue which drains tissue fluid to the lymphoid organs (lymphoid tissue)
 - If blocked, swelling
- Lymph nodes: 200-300
 - Lots near gut and lungs as there are more exposure to foreign substances

The total mass, number and distribution of immune cells in the human body



- Note that the large majority of immune cells are in the **lymphatic system** and **bone marrow**
 - Lymphatic system consists of: lymphatic vessels, lymph nodes, lymphoid organs, lymphoid tissues and lymph
- Bone marrow: largely neutrophils
- Lymphatic system: T and B cells
- Liver: Macrophages (tissue resident)
- Blood: Neutrophils
- Lungs: macrophages and mast cells
- Other: Macrophages, mast cells

Innate immunity and Adaptive immunity

- Innate immunity come first and activates the adaptive immunity
 - Usually not sufficient to manage pathogens thus supplemented with adaptive
 - Communications between the two arms

Major cell types of the immune system

Innate	Adaptive	Broderlands
Granulocytes	T cells	Innate lymphoid cells
Macrophage	B cells	NK cells
Dendritic cells		NK T cells $\gamma\delta$ T cells (GD)

Stem cell

- Totipotent and self-renewing marrow cell

- Found in low numbers in blood as well as bone marrow
 - Numbers can be boosted by treatment with appropriate growth factors (e.g. G-CSF **Granulocyte colony-stimulating factor**), which greatly facilitates the process of 'bone marrow' transplantation.

Granulocytes: Neutrophils, Eosinophils, Basophils

Neutrophils

Bone marrow → blood → Non-immunological organs (site of infection) → Death

- Most commonest leucocyte in the human blood
 - Major circulating WBC
- **Short-lived** phagocytic cell whose granules contain numerous **bactericidal substances**
 - Major function is **rapid defence** against infection by phagocytosis and killing
 - Autoregulation of apoptosis
- First cells to be recruited to the sites of infection from blood

Eosinophils

- A leucocyte whose large refractile granules contain a number of highly **basic or cationic proteins**, possibly killing larger **parasites** including worms
- Low number in healthy individual

Basophils

- A leucocyte whose large basophilic granules contain **heparin** and **vasoactive amines**, important in the inflammatory response
- Low number in healthy individual



Damage of tissue and symptoms of illness is usually due to the immune response to the pathogen rather than the pathogen itself. Thus the regulation of the immune response is important

Monocyte

- The largest nucleated cell of the blood

- Develop into a macrophage when migrates into tissues

Macrophages

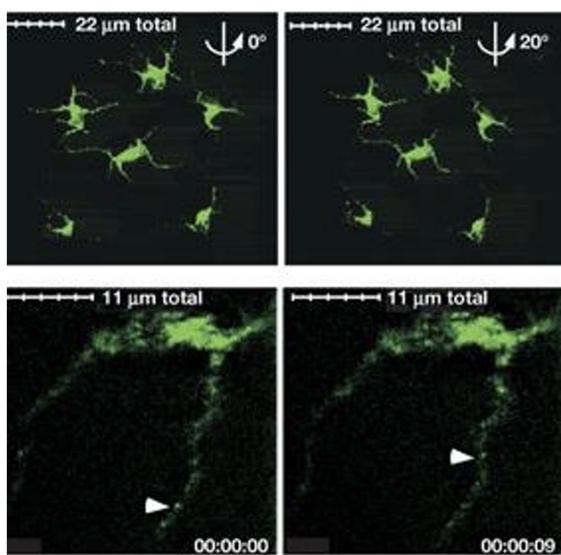
Bone marrow → Blood (monocytes) → Immunological and non-immunological organs (Long lived)

- Principal resident phagocyte of the tissues and serous cavities such as the pleura^{胸膜} and peritoneum^{腹膜}
- Tissue resident and long lived
 - Also sentinel cells
- Different kinds: Kuppfer cells (liver and spleen macrophages efficiently drain blood)
- Major scavenger of dying cells / cellular debris (key role in homeostasis to keep tissue healthy)
 - Although better at clearing some types of bacteria than neutrophils e.g. TB

Dendritic cells (DCs)

Bone marrow ↔ Non-immunological organs → via lymphatics → Lymph nodes

- Found in all tissues of the body
 - Langerhans' cells: skin and mucous membrane - picks up samples
 - Veiled cell: Lymphatic system (afferent lymph) - becomes less dendritic
 - Interdigitating: T cell areas of lymphoid tissues (thymus) - antigen presenting
- Take up antigen from the periphery and then migrate to the T-cell areas of the lymph node or spleen via the lymphatics or the blood.
 - Antigen may also get into the LN by passive draining
- Their major function is to activate T cell immunity.
- Sampling the outside
 - Connects innate and adaptive immune system



- Appearance depends on the way to see, i.e. dendrites are planar like starfish on the skin

Langerhan's
cells in skin

Lymphocytes

- Small
- 25% circulating WBC
 - But only 2% of total cells in blood (RBC is a large portion)
- Major cell of adaptive immune system
 - T cells and B cells are histologically very similar
- Very long lived
- Various stages of differentiation: resting, activated, plasma cells, naive/memory
 - Different shapes between different stages
- Constantly recirculating between tissues and blood

B cells

- Bone marrow (or, in birds, bursa)-derived lymphocyte
- Precursor of antibody-forming cells (plasma cells)
- In fetal life, the liver may play the role of 'bursa'.

Plasma cell

- A B cell in its high-rate antibody-secreting state.
- Seldom seen in the blood, but are found in bone marrow, spleen, etc., whenever antibody is being made.
- Lots of ER to make antibodies

T cell

- Thymus-derived lymphocyte, develop in the thymus
- Responsible for :
 - Killing virus infected cells or tumour cells
 - Regulating antibody producing B cells
 - Regulating innate cells such as macrophages and neutrophils

Platelets

- Small cells responsible for sealing damaged blood vessels ('haemostasis') but also the source of many inflammatory mediators.

Natural killer cell (NK cell)

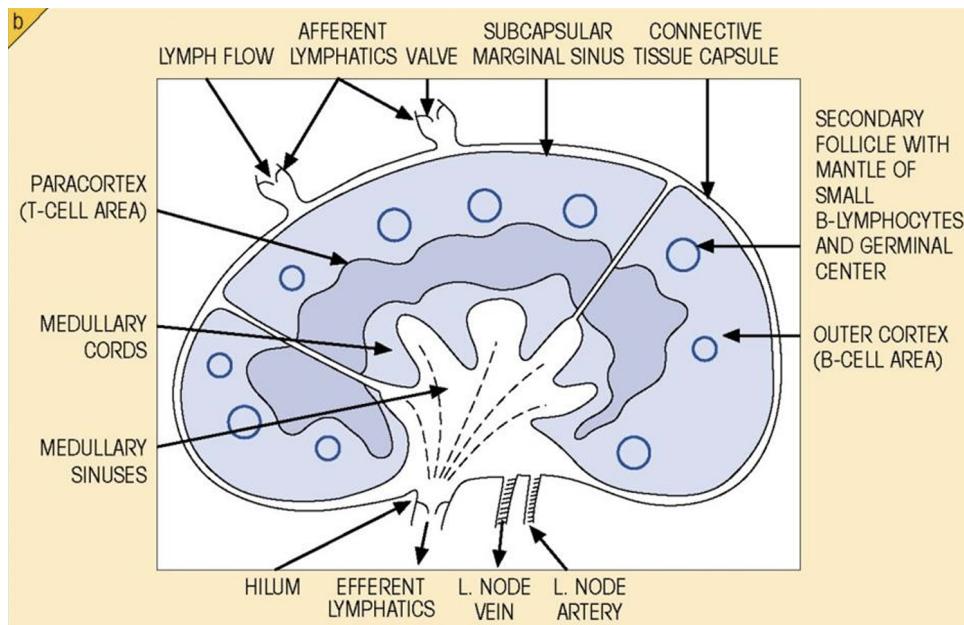
- An innate lymphoid cell, cells related to lymphocytes but not carrying antibody or the T cell receptor.
- Capable of killing some virus-infected cells and some tumour cells, but with complex sets of receptors which are quite distinct from those on true lymphocytes.

Lymphoid tissues

Lymph nodes are connected with lymphatic vessels

- Afferent: entering the LN
- Efferent: leaving the LN

Lymphoid tissue structure

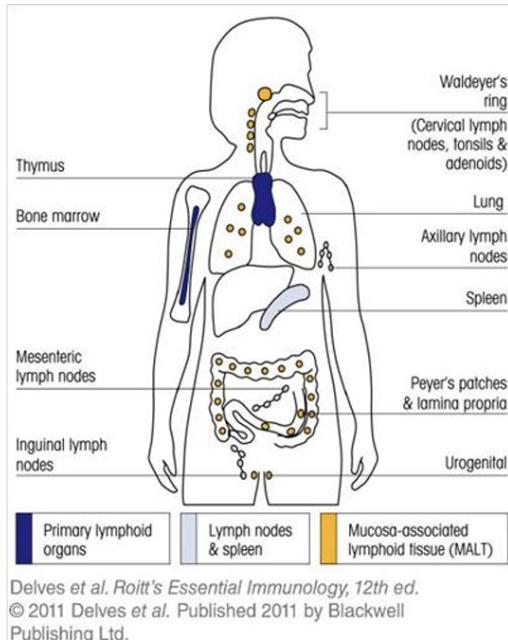


Helps efficient drainage and helps cellular communication

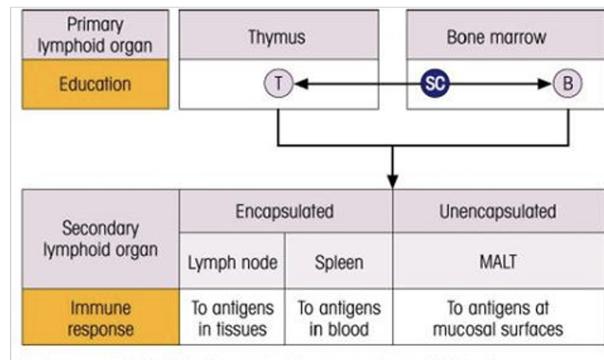
- Separate T and B cell areas
 - T cells - paracortex
 - B cells - outer cortex
- Reticular meshwork 网状
- Dendritic cell networks
- Constant cellular equilibrium with blood and tissue via the lymphatic system



Note that nothing immunologically happen in the blood or lymphatics but travelling (route)



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B and T cells are produced within primary (central) lymphoid organs

T cells

- T cells develop in the **thymus** from precursors derived from haematopoietic stem cells in the bone marrow.
- Thymus is organised into an outer cortex and inner medulla containing T lymphocytes at different stages of development.
 - T-cell development in the thymus in more detail in 'Immunological tolerance'.

B cells

- The primary lymphoid organ for B cells is the **bone-marrow**.

The specific **microenvironment** within the primary lymphoid organs is essential for the differentiation of T and B cells.

- This environment is created by epithelial and other stromal cells through lymphocyte contact and production of cytokines.
- Lymphocytes migrate from these primary organs via the blood stream to become activated within the secondary (peripheral) lymphoid organs or tissues where they respond to pathogen antigens.

Secondary lymphoid tissues

- Composed of aggregates of lymphocytes, which are either organised into discrete structures, the lymph nodes and spleen, or appear as unencapsulated tissue, the mucosa-associated lymphoid tissues (MALT), lining the respiratory, gastrointestinal and genitourinary tracts.

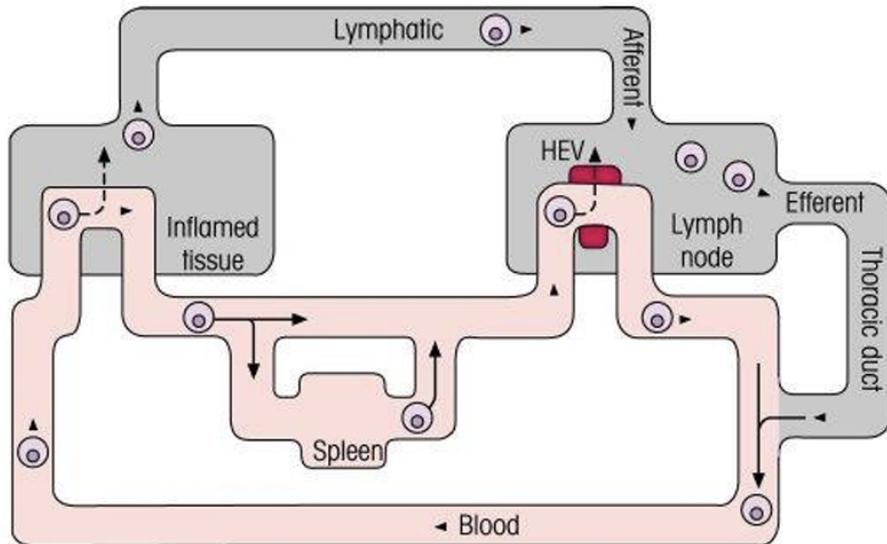
Within the lymphoid organs and tissues there are **areas** which contain predominantly either T or B cells.

- Non-lymphoid cells are also important in the generation of immune responses by the lymphocytes.
- These 'accessory' cells include **dendritic cells** which are often localised to specific areas within the lymphoid tissues
 - E.g. interdigitating dendritic cells which present antigen to T-cells in the paracortex of lymph nodes, PALS of spleen and Peyer's patches of MALT, and **follicular dendritic cells** which present antigen to B-cells in the **germinal centres**.
 - These germinal centres comprise organised structures in secondary lymphoid tissues where all the cells required to initiate an adaptive immune response (dendritic cells, helper T-cells, B-cells) can interact optimally with each other.
 - They are the sites of B-cell memory generation, of antibody class switching and somatic hypermutation, and the generation of the precursors of the antibody-secreting plasma cells.

Following migration of newly-produced lymphocytes to the secondary lymphoid tissues they do not remain sedentary but recirculate, **continuously leaving and re-entering lymphoid tissues**, transported in the blood circulation and the lymphatic system.

Lymphocytes recirculate through blood vessels and lymphatics

- Local LN where the antigen will be presented to T cells
- T cells are travelling from LN to LN to find an relevant (recognisable antigen)



- To enter lymph nodes and MALT from the circulation they leave the blood vessels through specialised areas of vascular endothelium - the **high endothelial venules (HEV)**. (Note that the spleen lacks HEV).
 - If nothing is recognised the T cells will go back to the blood via the efferent lymph and keep on searching
 - If T cells are activated, they travel back to the blood via efferent (as infection is not in the LN) and enters the inflamed tissue
 - HEV allow naive T cells and memory T cells to recirculate in the lymph nodes
- Inflamed tissue:
 - Increased permeability to allow T cells enter (as the neutrophils)?
 - Drain to the LN via the lymphatics and afferent lymph

Lymphocyte recirculation allows antigen-reactive cells to 'home' to the places where they are required, with a targeted migration of lymphocytes into the sites where infection may be present.

- This traffic is mediated through **homing molecules** on the lymphocyte surface which recognise vascular addressins on the blood vessel endothelium.