# Cells and tissues of the immune system

# Where can we find immune cells in our body?

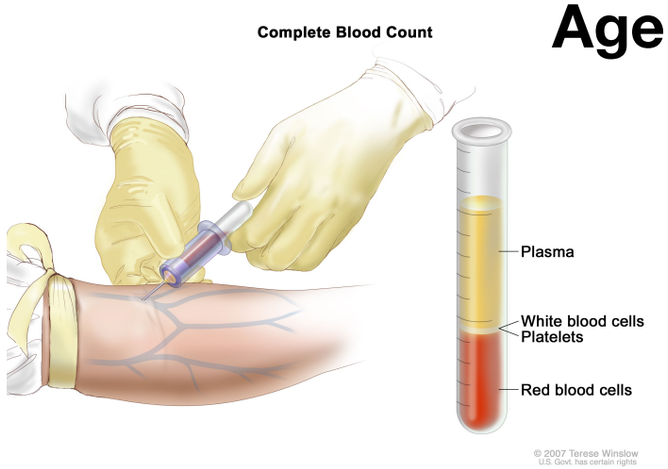
As circulating cells in blood, lymph and lymphoid organs

As scattered cells in **all tissues**

**Identification by expression of different markers**
**CD or cluster of differentiation**

# Complete Blood Count (CBC)

**CBC is a group of tests that evaluate the cells circulating in your blood, including red blood cells (RBCs), white blood cells (WBCs), and platelets (PLTs). The CBC can evaluate your overall health and detect a variety of diseases and conditions, such as infections, anemia and leukemia (cancer of the blood-forming tissues).**




## Age and Sex dependent

**Adult normal ranges:**

| Parameter | Male | Female |
|---|---|---|
| Haemoglobin g/L | 135 - 180 | 115 - 160 |
| WBC $x10^9/L$ | 4.00 - 11.00 | 4.00 - 11.00 |
| Platelets $x10^9/L$ | 150 - 400 | 150 - 400 |
| MCV fL | 78 - 100 | 78 - 100 |
| PCV | 0.40 - 0.52 | 0.37 - 0.47 |
| RBC $x10^{12}/L$ | 4.5 - 6.5 | 3.8 - 5.8 |
| MCH pg | 27.0 - 32.0 | 27.0 - 32.0 |
| MCHC g/L | 310 - 370 | 310 - 370 |
| RDW | 11.5 - 15.0 | 11.5 - 15.0 |
| Neutrophils | 2.0 - 7.5 | 2.0 - 7.5 |
| Lymphocytes | 1.0 - 4.5 | 1.0 - 4.5 |
| Monocytes | 0.2 - 0.8 | 0.2 - 0.8 |
| Eosinophils | 0.04 - 0.40 | 0.04 - 0.40 |
| Basophils | < 0.1 | < 0.1 |

**Red blood count (RBC).** This is the number of red blood cells in a certain amount of blood, usually a microliter (mcL). For reference, one drop of blood is about 40 mcL to 50 mcL.

**Hemoglobin (Hb).** This is the amount of hemoglobin in your blood.

**Hematocrit (Hct).** This is the percentage of your blood made up of red blood cells.

**Mean corpuscular volume (MCV).** This is the average size of your red blood cells.

**Mean corpuscular hemoglobin (MCH).** This is the average concentration (weight) of hemoglobin in each red blood cell.

**Mean corpuscular hemoglobin concentration (MCHC).** This is the average concentration (weight) of hemoglobin in a certain amount of blood.

**Red cell distribution width (RDW).** This is the degree of difference in red blood cell size. In other words, if the number is low, all of your blood cells are close to the same size. If it's high, there's a big difference between your largest and smallest red blood cells.

**Platelet count.** The total number of platelets in your blood sample.

**Mean platelet volume (MPV).** MPV is your average platelet size.

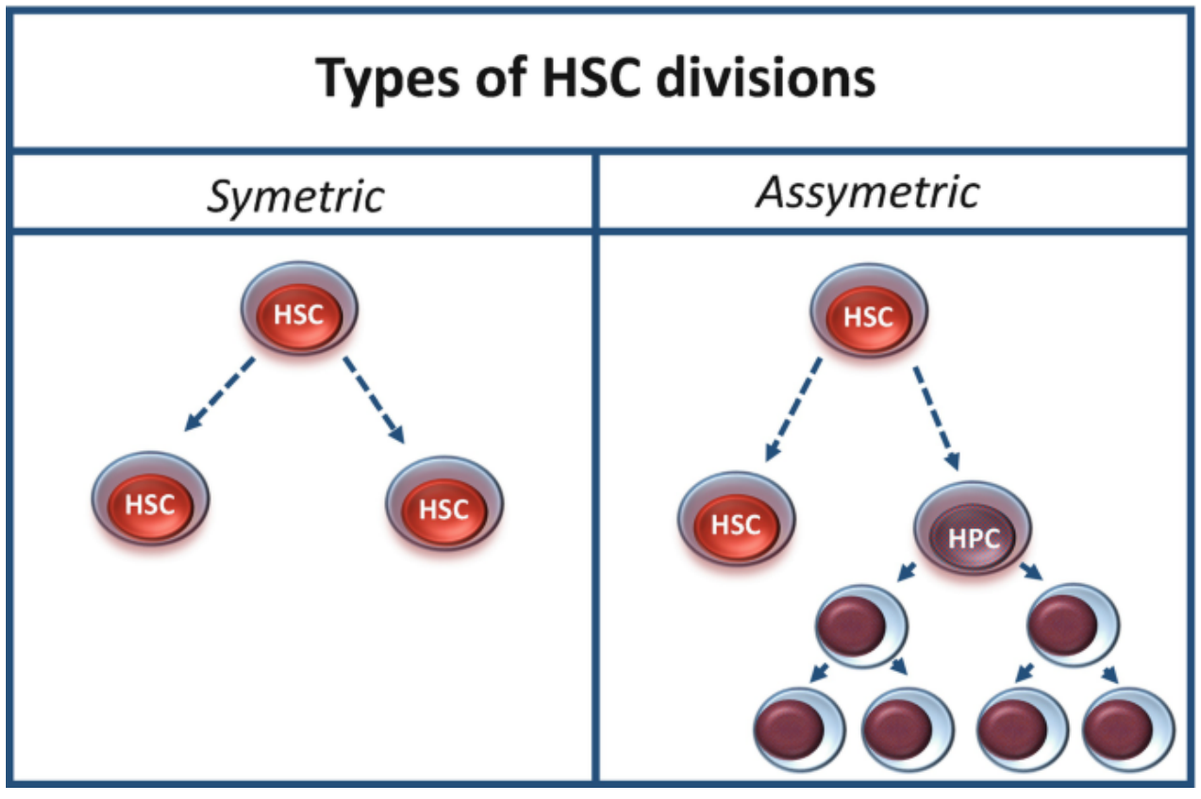
**White blood cell count (WBC).** This is a count of your total white blood cells (of all types).

# HEMATOPOIETIC STEM CELLS (HSC)

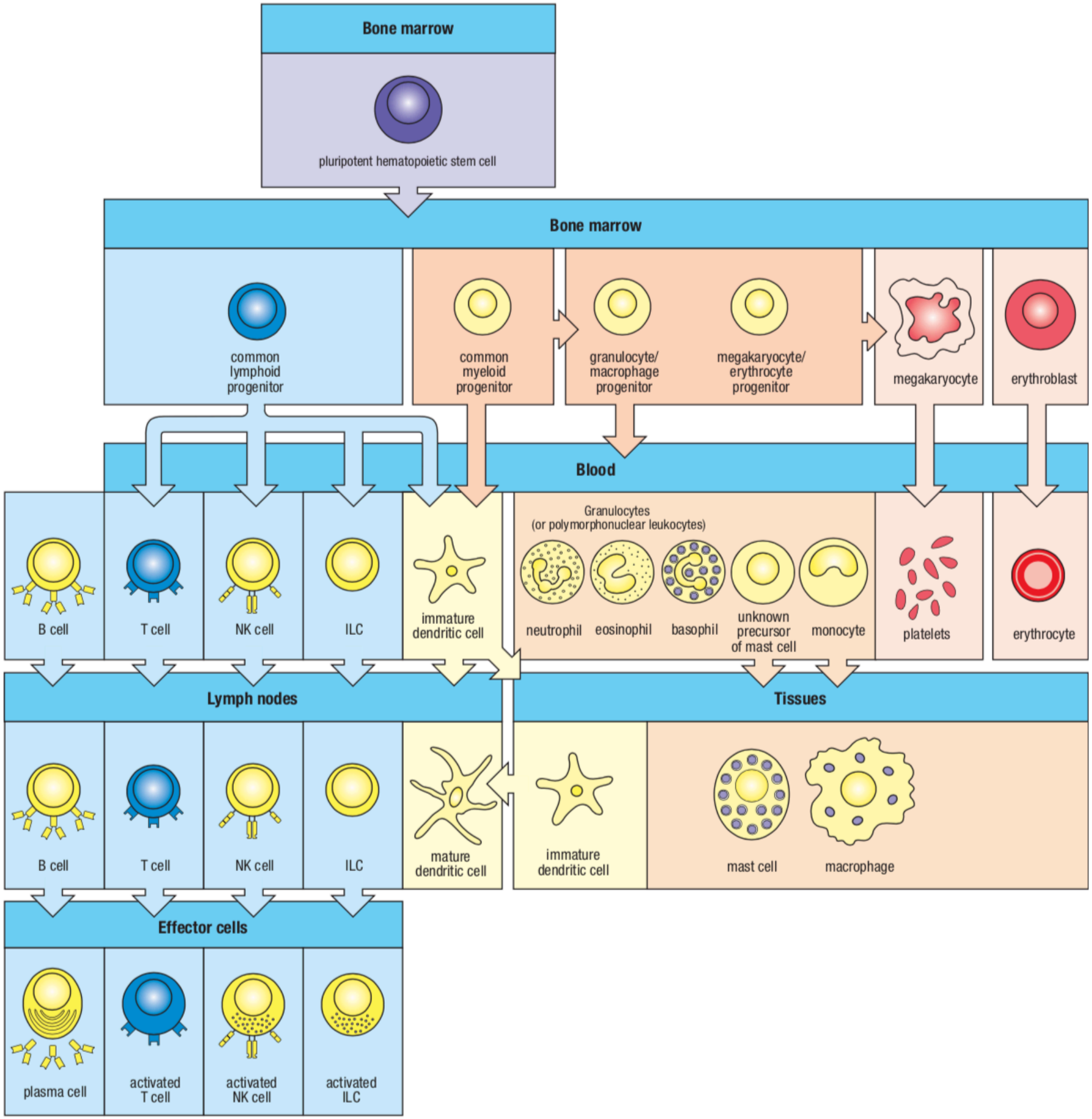
Relatively low in number ( 0,01%- ,05%) of the total marrow population.

- Two features
- 1- Self renewal
  2- Differentiation .

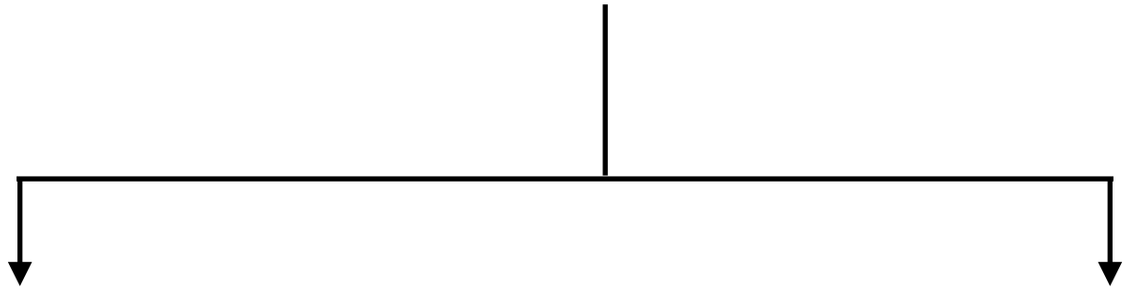
Present in : bone marrow, umbilical cord, peripheral blood.




Symmetric and asymmetric division of HSC. The most physiologically relevant is asymmetric cell division that gives rise to one HSC and one HPC. While new HSC secures constant number of HSC in BM, HPC differentiates and gives rise to clone of mature hematopoietic cells


Bone marrow
pluripotent hematopoietic stem cell
Bone marrow
common lymphoid progenitor
common myeloid progenitor
granulocyte/ macrophage progenitor
megakaryocyte/ erythrocyte progenitor
megakaryocyte
erythroblast
Blood
Granulocytes (or polymorphonuclear leukocytes)
B cell
T cell
NK cell
ILC
immature dendritic cell
neutrophil
eosinophil
basophil
unknown precursor of mast cell
monocyte
platelets
erythrocyte
Lymph nodes
Tissues
B cell
T cell
NK cell
ILC
mature dendritic cell
immature dendritic cell
mast cell
macrophage
Effector cells
plasma cell
activated T cell
activated NK cell
activated ILC

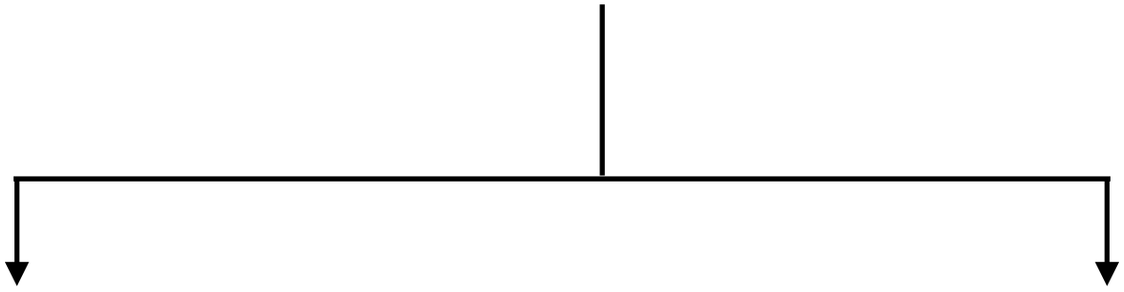
# Immune cells originate from hematopoietic stem cells (HSC) in the bone marrow



Common Lymphoid Progenitor

Common Myeloid Progenitor

# Immune cells originate from hematopoietic stem cells (HSC) in the bone marrow



## Common Lymphoid Progenitor

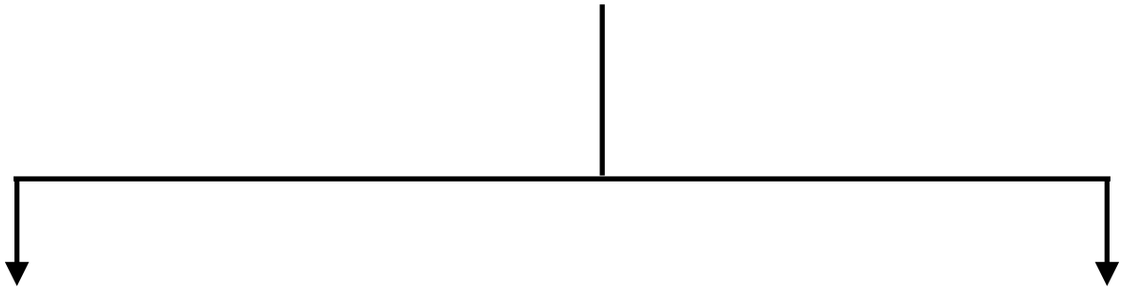
B cell  T cell  NK  ILC

## Common Myeloid Progenitor

Neutrophil  Basophil  Eosinophil

Mast cell  Monocyte

# Immune cells originate from hematopoietic stem cells (HSC) in the bone marrow



## Common Lymphoid Progenitor

B cell  T cell  NK  ILC

Dendritic cell

## Common Myeloid Progenitor

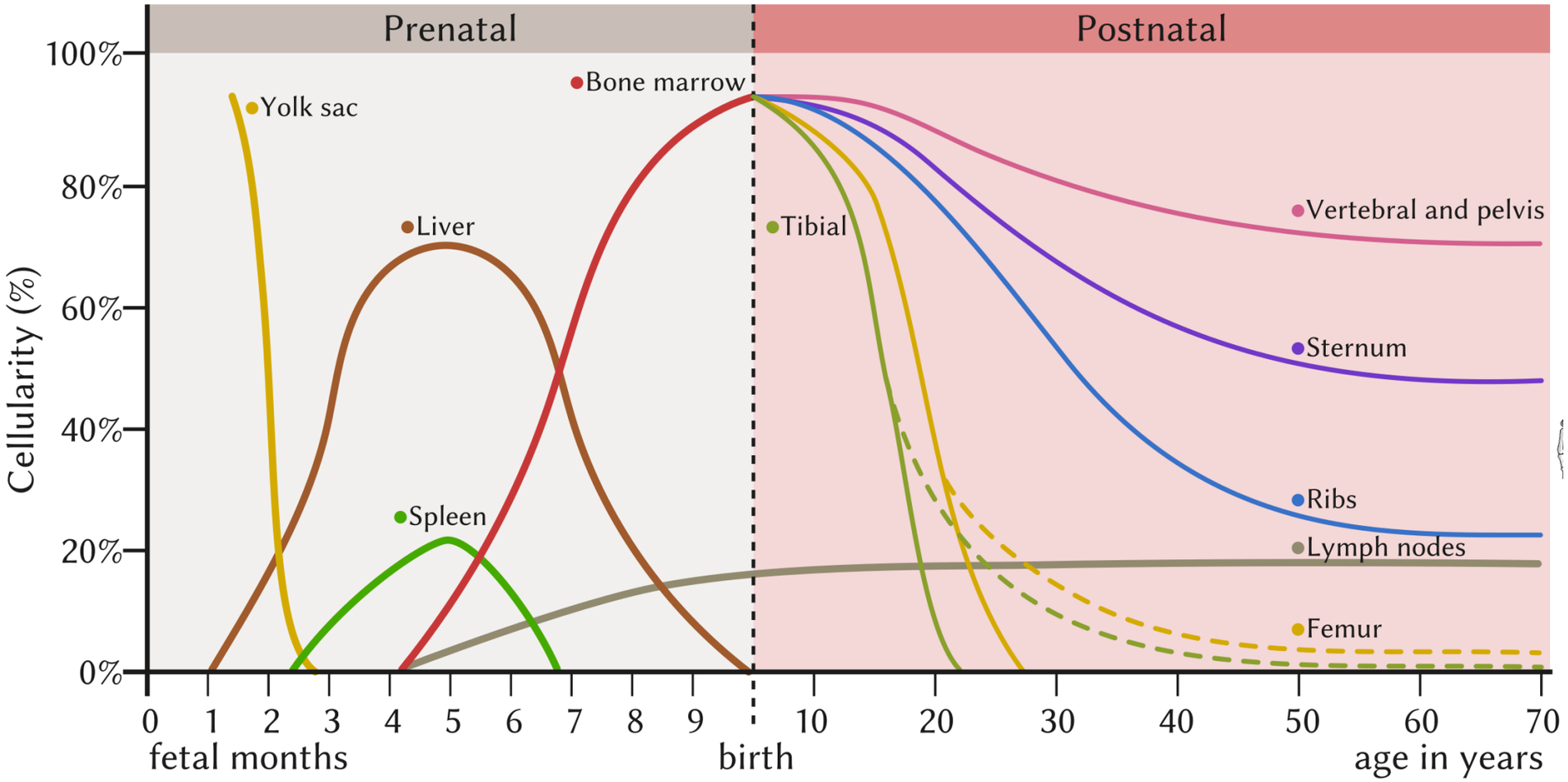
Neutrophil  Basophil  Eosinophil

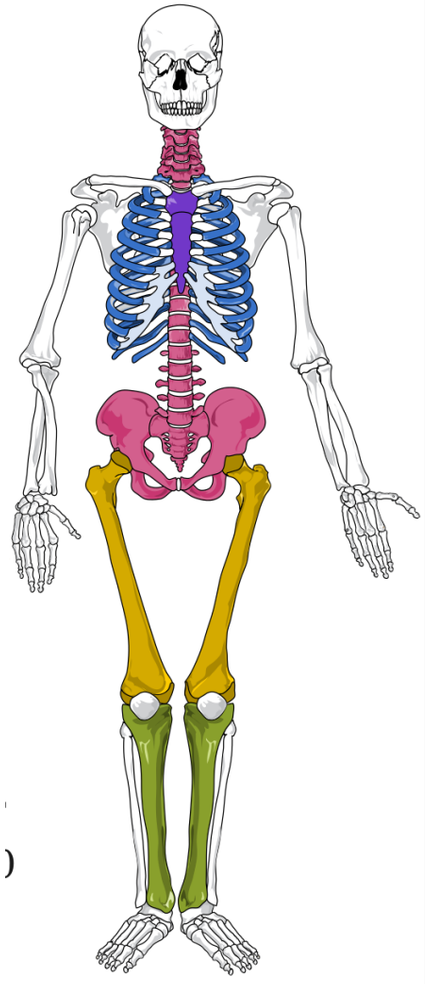
Mast cell  Monocyte

Dendritic cell

# Bone marrow

Site of generation of all blood cells (hematopoiesis)



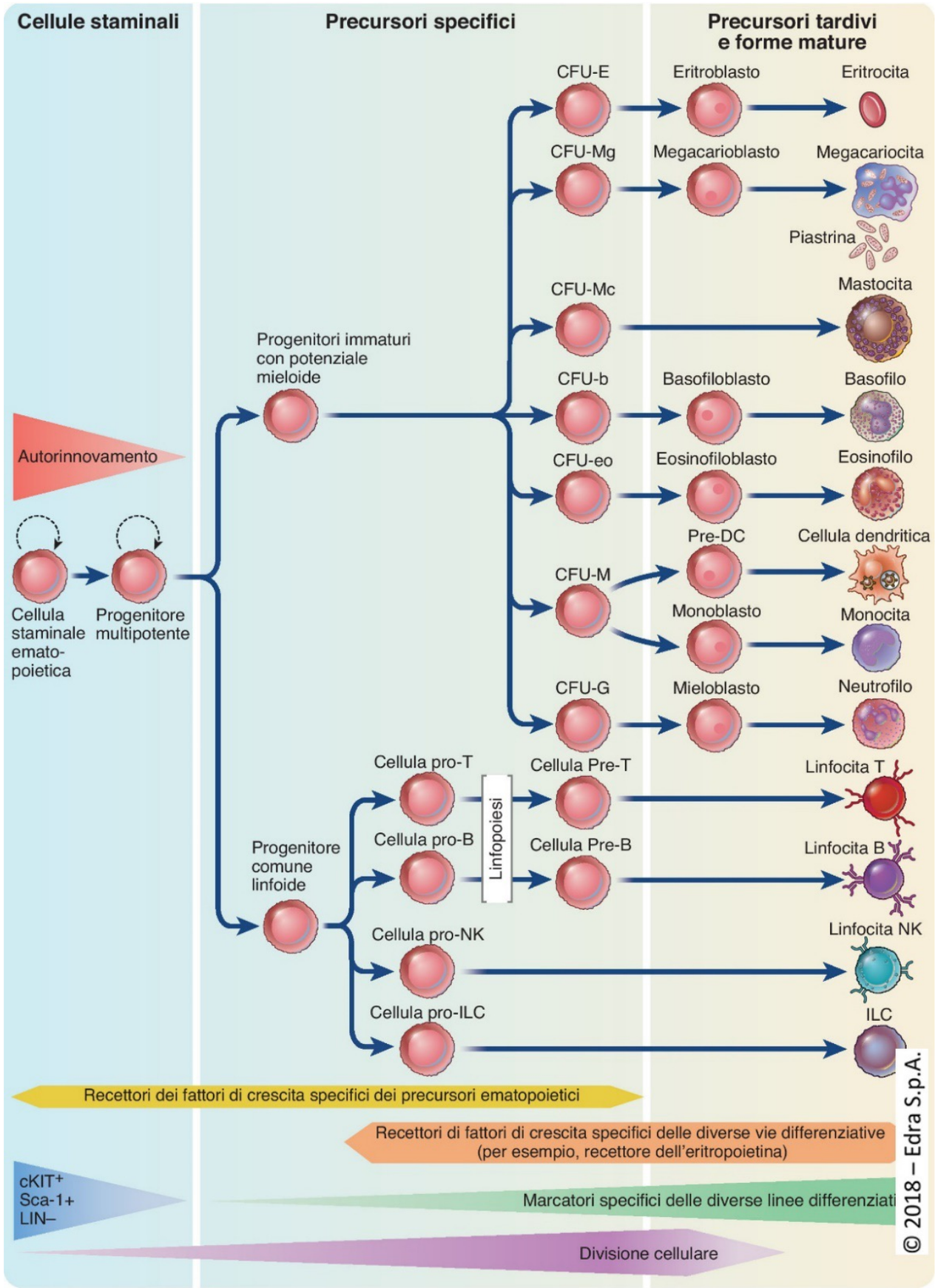
In case of exceptional demand, liver and spleen can become sites of extra-medullary hematopoiesis

**BM contain also plasmacells and memory T cells at long survival**

# Hematopoiesis

**Generation of red cells, granulocytes, monocytes and maturation of B cells**

**HSC**
**Multipotency and self renewal**
**Express CD34 and c-Kit**
**Localized in specific niches**
**Maintained  by CSFs**



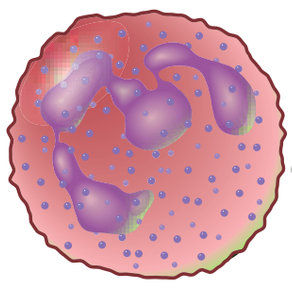
# Maintenance and differentiation of HSC requires cytokines

Provided by non hematopoietic stromal cells, fibroblasts, macrophages and antigen activated T cells

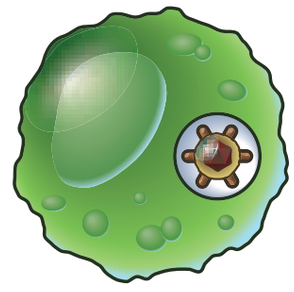
| Cytokine | Size | Principal Cellular Sources | Principal Immature Cell Targets | Principal Cell Populations Induced |
|---|---|---|---|---|
| Stem cell factor (c-Kit ligand) | 24 kD | Bone marrow stromal cells | HSCs | All |
| Interleukin-7 (IL-7) | 25 kD | Fibroblasts, bone marrow stromal cells | Immature lymphoid progenitors | T lymphocytes |
| Interleukin-3 (IL-3) | 20–26 kD | T cells | Immature progenitors | All |
| GM-CSF | 18–22 kD | T cells, macrophages, endothelial cells, fibroblasts | Immature and committed myeloid progenitors, mature macrophages | Granulocytes and monocytes, macrophage activation |
| M-CSF | Dimer of 70–90 kD; 40-kD subunits | Macrophages, endothelial cells, bone marrow cells, fibroblasts | Committed progenitors | Monocytes |
| G-CSF | 19 kD | Macrophages, fibroblasts, endothelial cells | Committed granulocyte progenitors | Granulocytes |
| Flt-3 ligand | 30 kD | Bone marrow stromal cells | HSCs, DC and B cell progenitors | Classical and plasmacytoid DCs, B cells |

*DC,* Dendritic cells; *G-CSF,* granulocyte colony-stimulating factor; *GM-CSF,* granulocyte-monocyte colony-stimulating factor; *HSCs,* hematopoietic stem cell; *IL,* Interleukin; *M-CSF,* monocyte colony-stimulating factor.

# Phagocytes



Neutrophiles



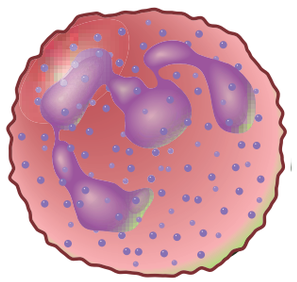
Macrophages

Ingest and destroy **microbes**

Remove **damaged tissue**

recruitment to the infection site > recognition and activation > phagocytosis

Interaction with other cells direct or by the release of cytokines



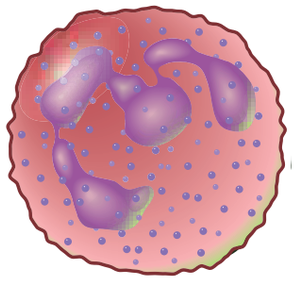
# Neutrophils

Generated in the **bone marrow**, are present in the **blood** and are recruited at the **site of infection. Reaction to acute inflammation.**

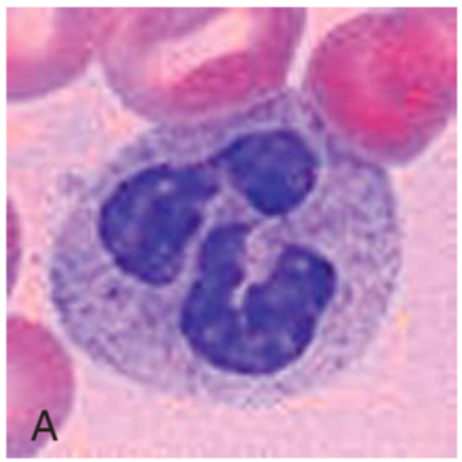
Among leukocytes, **most abundant** cell type in the blood (40-60%)

**Most rapid** responder (few hours), but also with **short-lived** (1-2 days) in tissues.

| | Mean Number Per $mm^3$ | Normal Range |
|---|---|---|
| White blood cells (leukocytes) | 7400 | 4500–11,000/$mm^3$ |
| Neutrophils | 4400 | 40–60% |
| Eosinophils | 200 | 1–4% |
| Basophils | 40 | <1% |
| Lymphocytes | 2500 | 20–40% |
| Monocytes | 300 | 2–8% |



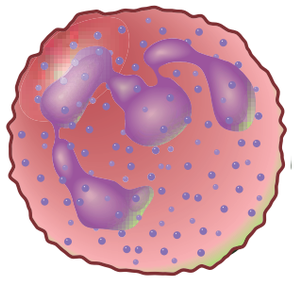
# Neutrophils




12-15 um
Segmented nucleus (3-5 lobules)
also called polymorphonuclear leukocytes (PMN)

Two types of **granules**:

- azurophilic granules (defensins and cathelicidins)
- specific granules (lysozyme, collagenase and elastase)



# Neutrophils

- Differentiation stimulated by GM-CSF and G-CSF
- Ingest and destroy **microbes (phagocytosis)**
- Degranulation of enzymes to kill extracellular microbes
- Production of reactive oxygen species (**ROS**),
  highly reactive oxidizing agents that destroy microbes
- Remove **damaged tissue**

# Macrophages

## Monocyte derived macrophages

(tissue)

Monocytes (blood, 2-8%)
and in the spleen
10-15um

Originate from HSC in bone marrow

**Differentiation stimulated by M-CSF**

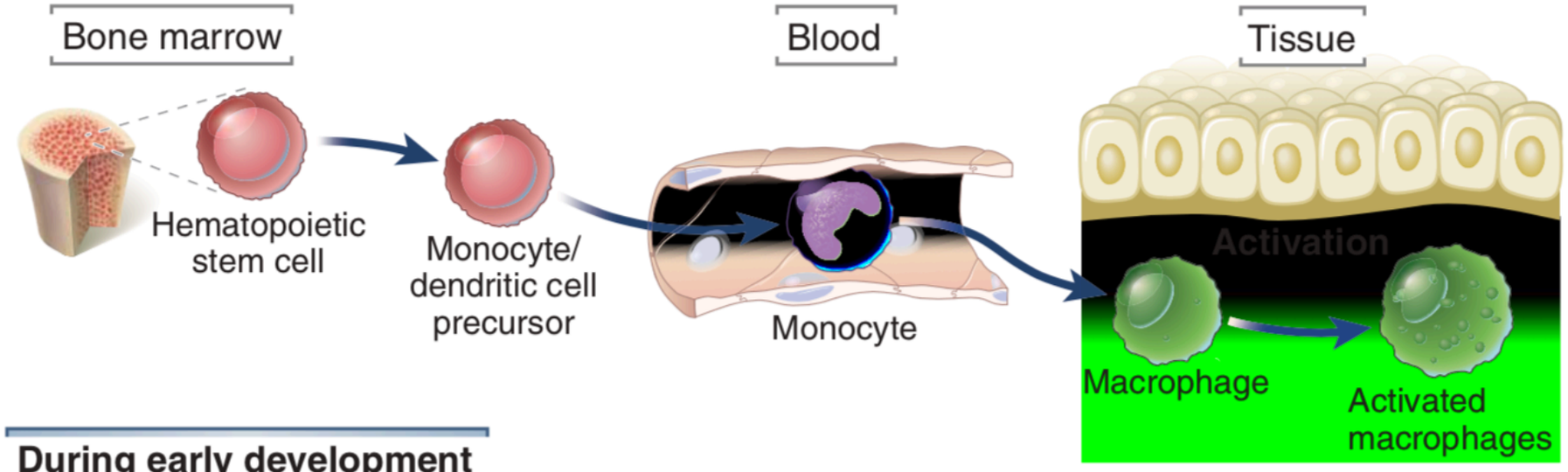
## Tissue resident macrophages

**Exception!**

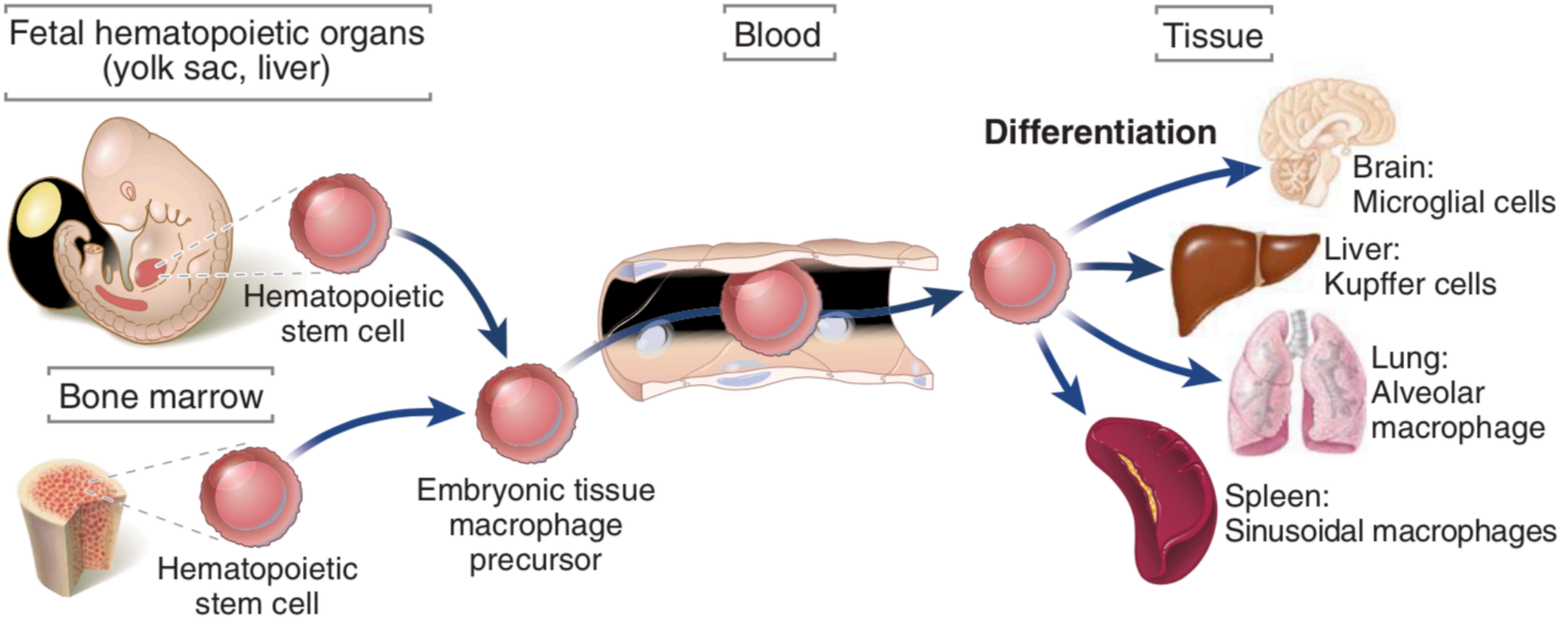
Originate from **fetal liver** and **yolk sac**

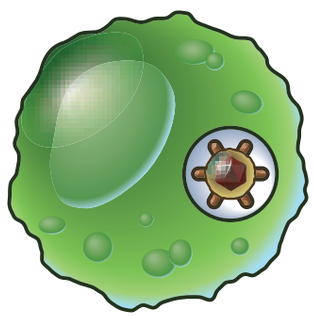
Organ specific phenotypes

## In adult homeostasis and inflammatory reactions



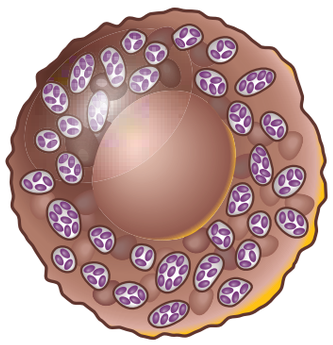

## During early development



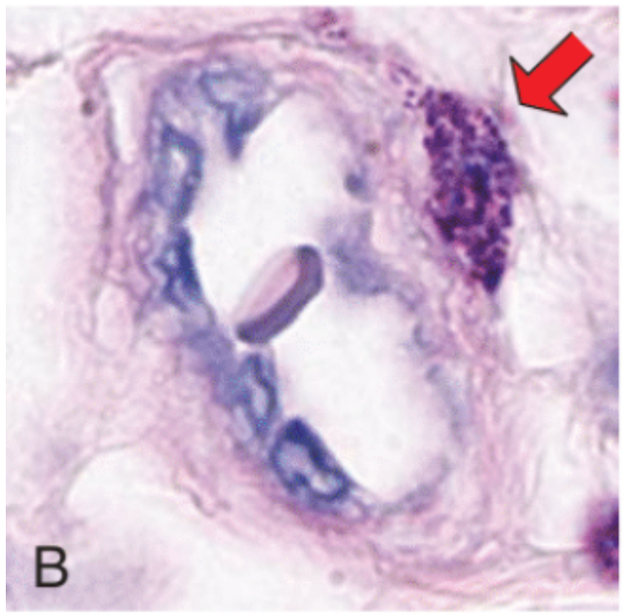


# Monocyte derived macrophages

- Ingest and destroy **microbes** (phagocytosis)
- Secrete several different **cytokines**
- Promote tissue repair inducing **angiogenesis** and synthesis of collagen-rich **extracellular matrix**
- Remove **necrotic cells (tissue cells, neutrophils…)**
- Remove **apoptotic cells, preventing inflammation**
- Antigen Presenting Cells (APC)
- Long lasting compared with neutrophils and can proliferate



# Mast cells



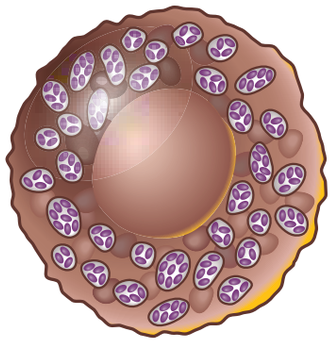

Tissue resident: **skin** and mucosal **epithelial**

Bone marrow origin

Unknown precursor (different from other granulocytes)

Cytoplasmic purple granules filled with **histamine, potent mediator of inflammation**

- Stimulated by SCF (stem cell factor)
- Parasitic infection
- Allergy

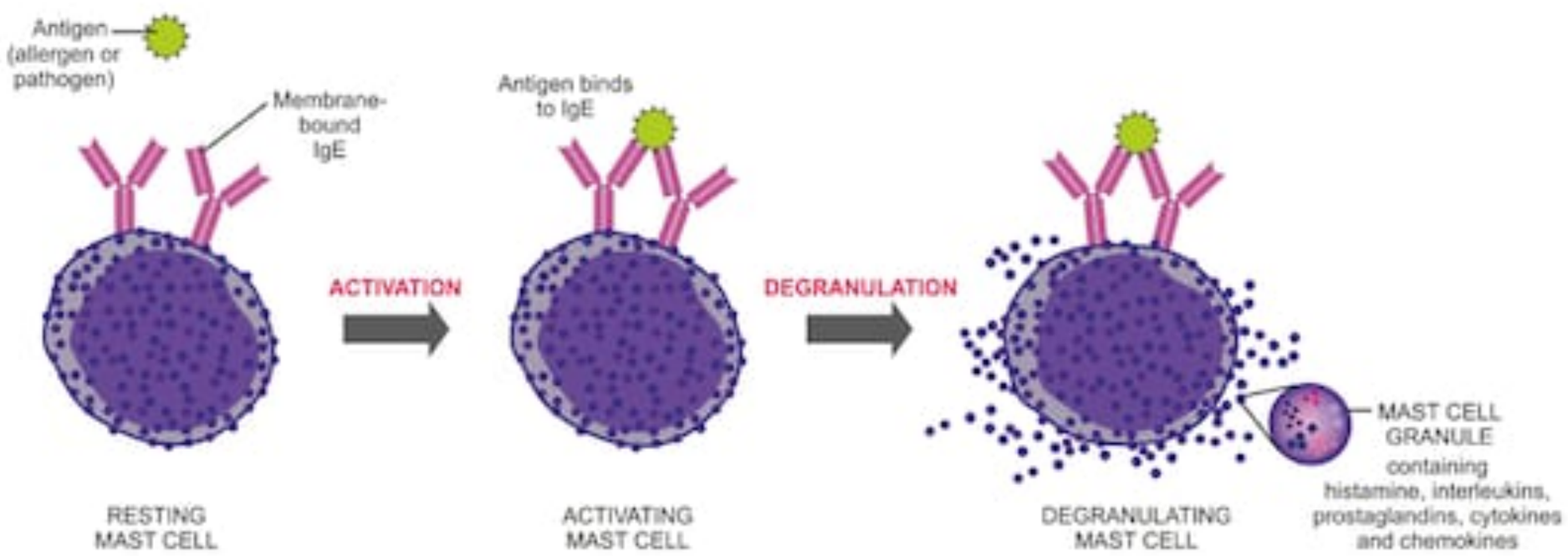


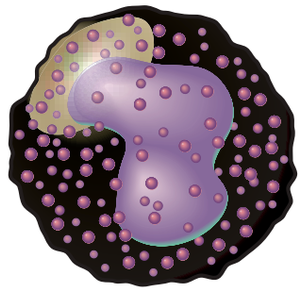
# Mast cells

## IgE dependent and independent activation

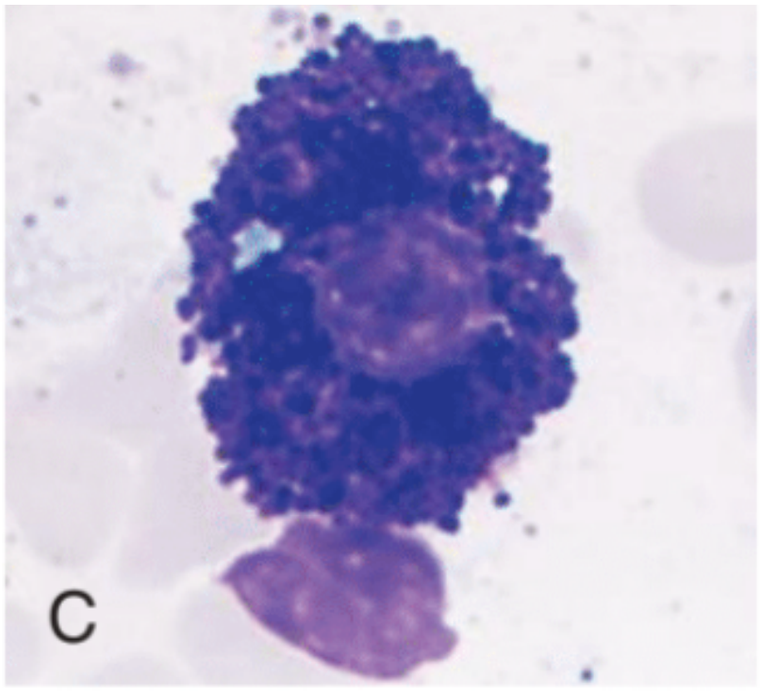
Mast cell express **high affinity receptors for IgE** (a type of antibody)

When antigen is recognised by IgE bound on mast cell surface, degranulation occurs





# Basophils

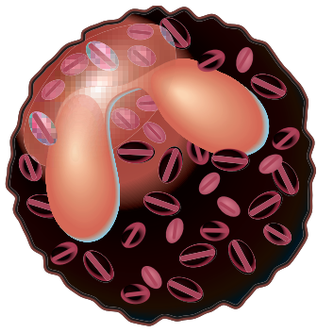



Rare cells, found most often in **blood**, can be recruited to sites of inflammation

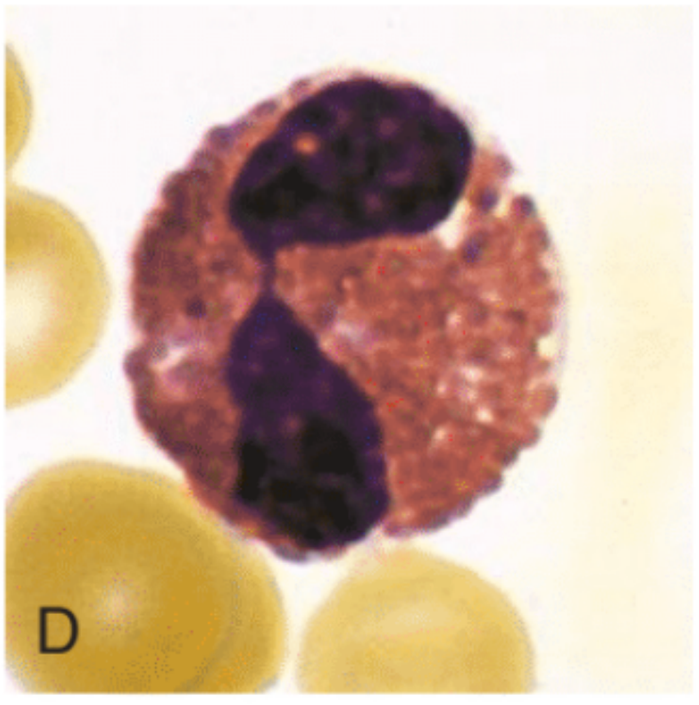
Bone marrow origin

<1% of blood cells

Similar to mast cell (but different precursor): express **high affinity IgE receptor** and can release **histamine**



# Eosinophils




Eosinophils circulate in **blood**,

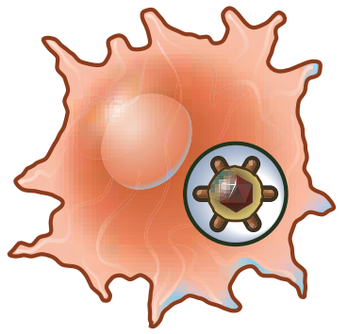
Origin from bone marrow

Physiologically present at **mucosal sites** (respiratory, gastrointestinal and genitourinary tracts)

Can be recruited to other tissues, sites of inflammation

**Maturated by  GM-CSF,  IL3 and IL-5**

Contain basic granules carrying **enzymes** capable of destroying the cell wall of **parasites**

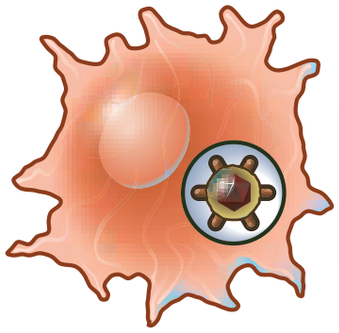


# Dendritic Cells

Tissue resident and circulating

Rapid innate response (TLR) a mechanism for the adaptive response promotion

| | |
|---|---|
| Classical DCs<br>cDCs | Capture and present antigens to **T cells**, orchestrating **T cell activation**.<br>Link between innate and adaptive immunity |
| Plasmacytoid DCs<br>pDCs | Largest producer of **type I interferon** (IFN), a cytokine critical for the **antiviral response.** Capture microbes in the blood and transport antigens to spleen to activate T cells. |



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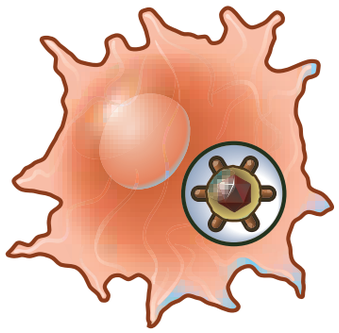
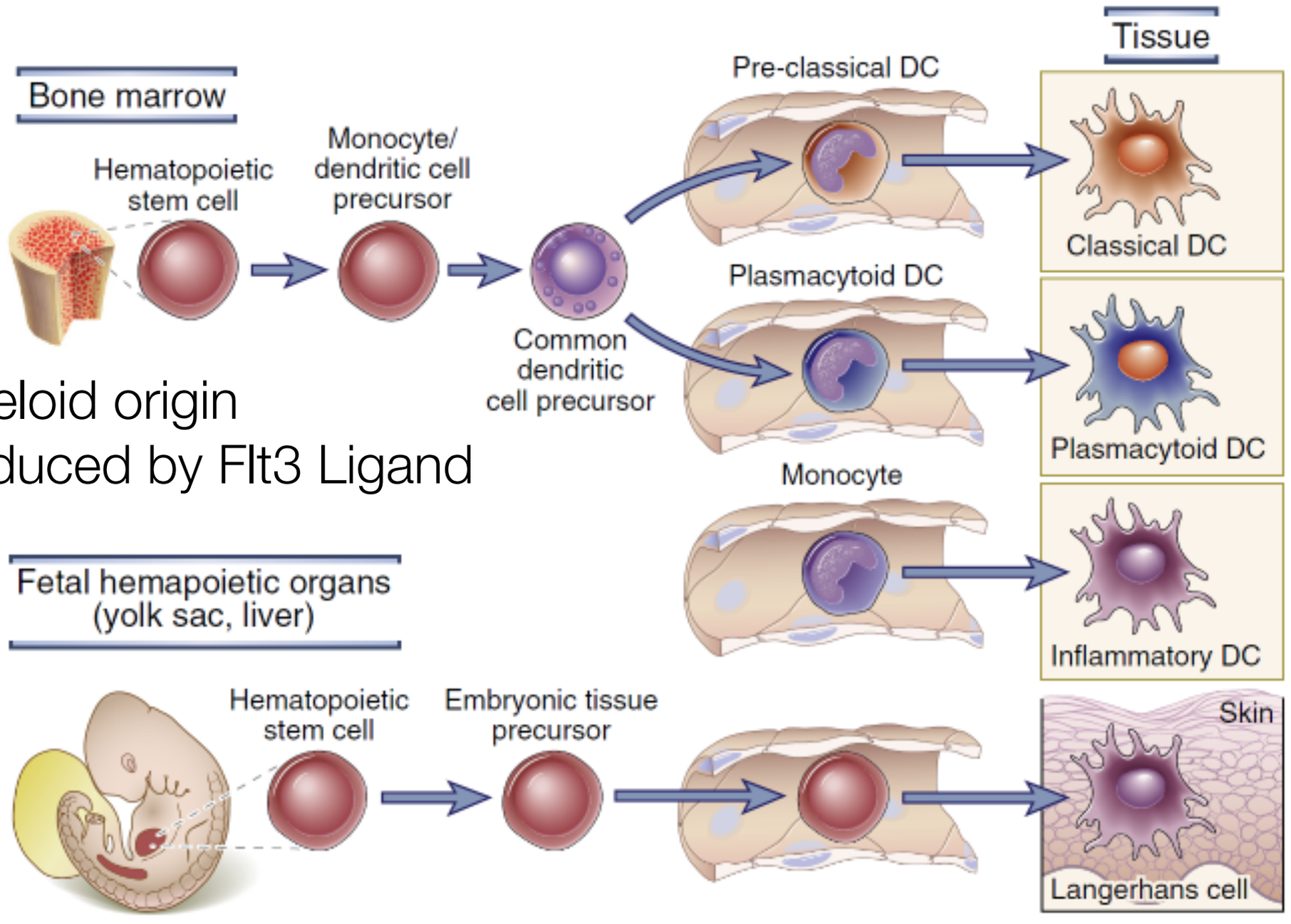
| Plasmacytoid DCs<br>pDCs | Largest producer of **type I interferon** (IFN), a cytokine critical for the **antiviral response.** Capture microbes in the blood and transport antigens to spleen to activate T cells. |
| Monocyte derived DCs<br>mDCs | Differentiate from monocytes **upon inflammation** |



# Dendritic Cells

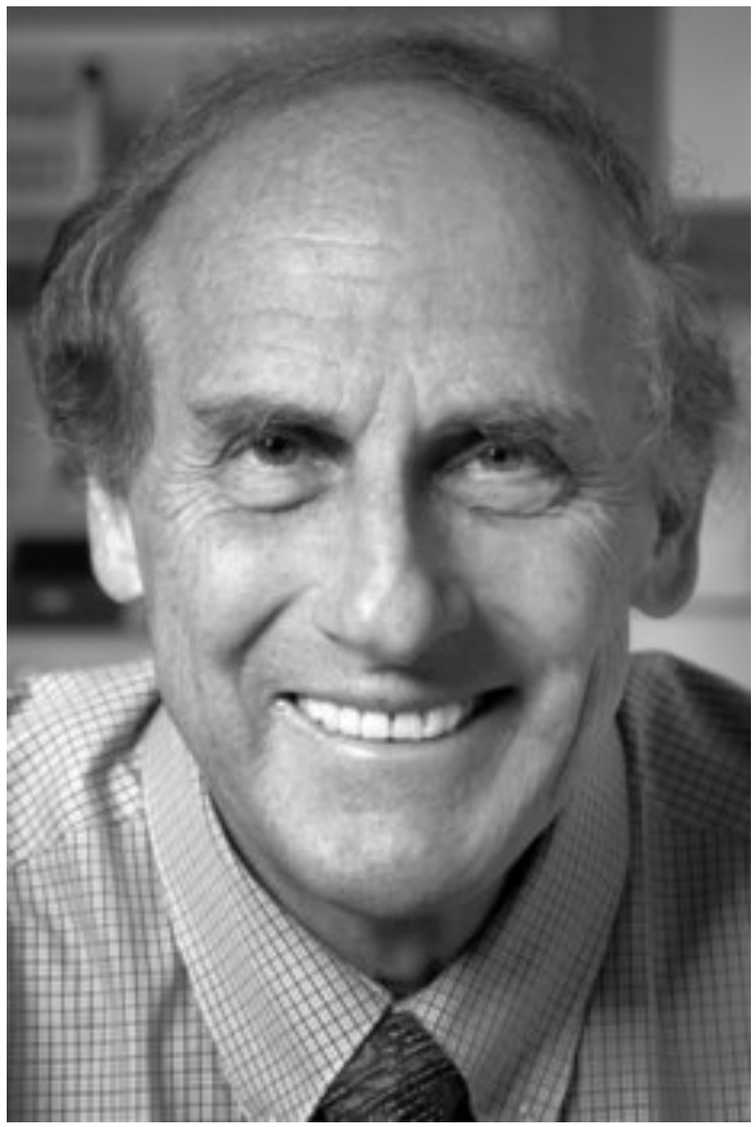



Myeloid origin

Maturation induced by Flt3 Ligand

# Dendritic Cells were worth a Nobel prize!

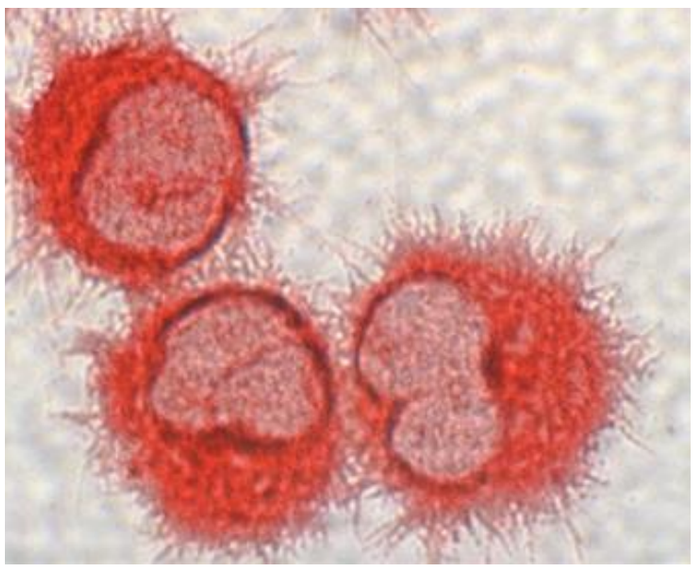
Ralph Steinmann



**The Nobel Prize in Physiology or Medicine 2011**

Long membrane projections and phagocytic capabilities

Lymphoid tissues, mucosal epithelium and organ parenchima

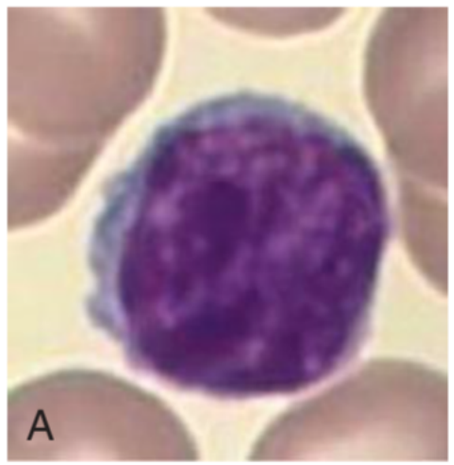


**MHCI and MHCII**

**TABLE 2.3** Human Dendritic Cell Subsets

| | Classical (Conventional) Dendritic Cells | | |
|---|---|---|---|
| **Distinguishing Feature** | **Major** | **Cross-Presenting** | **Plasmacytoid Dendritic Cells** |
| Surface markers | CD11c<br>BDCA-1 (CD1c)<br>Dectin 1 (CLEC7A)<br>Dectin 2 (CLEC6) | CD11c<br>BDCA-3 (CD141) CLEC9A<br><br>$XCR1^+$ | BDCA-2 (CD303)<br>BDCA4 (CD304)<br><br>CD123 |
| TLRs expressed | Various | Various | High levels of TLR7, TLR9 |
| Transcription factors | IRF4 | IRF8 | E2-2 |
| Major cytokines produced | IL-12, others | IL-23 | Type I IFN |
| Major postulated functions | Innate immunity: source of inflammatory cytokines<br>Adaptive immunity: capture and presentation of antigens mostly to $CD4^+$ T cells | Adaptive immunity: capture and cross-presentation of antigens to $CD8^+$ T cells | Antiviral immunity: early innate response; priming of antiviral T cells |

# B and T lymphocytes




**naïve o resting**

Small 8-10um

Large nucleo

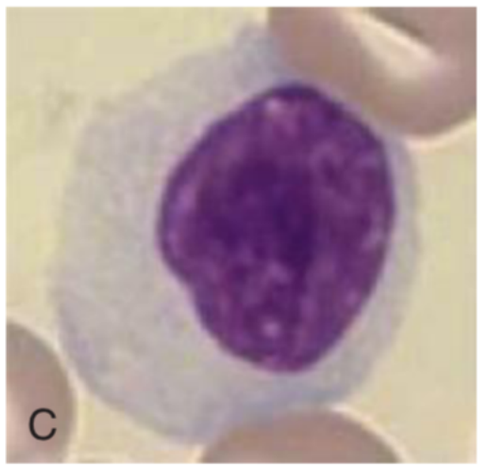
With dense heterochromatin

G0 of cell cycle

Thin rim of cytoplasm

no specialized organelles

1-3 month




**activated**
**or lymphoblats**

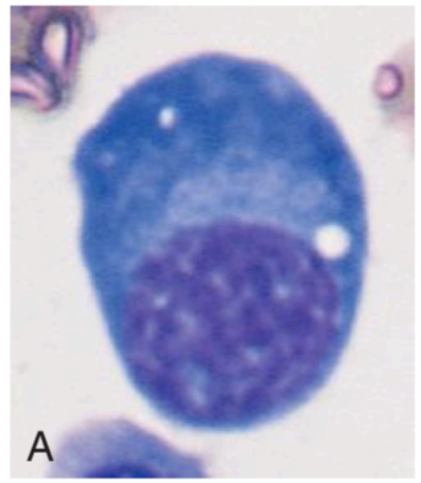
10-12 um

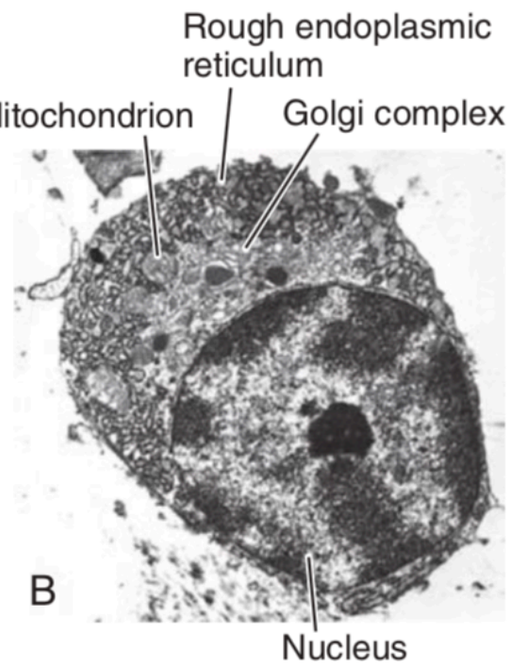
Proliferating

More cytoplasm

specialized organelles

**plasmacell**

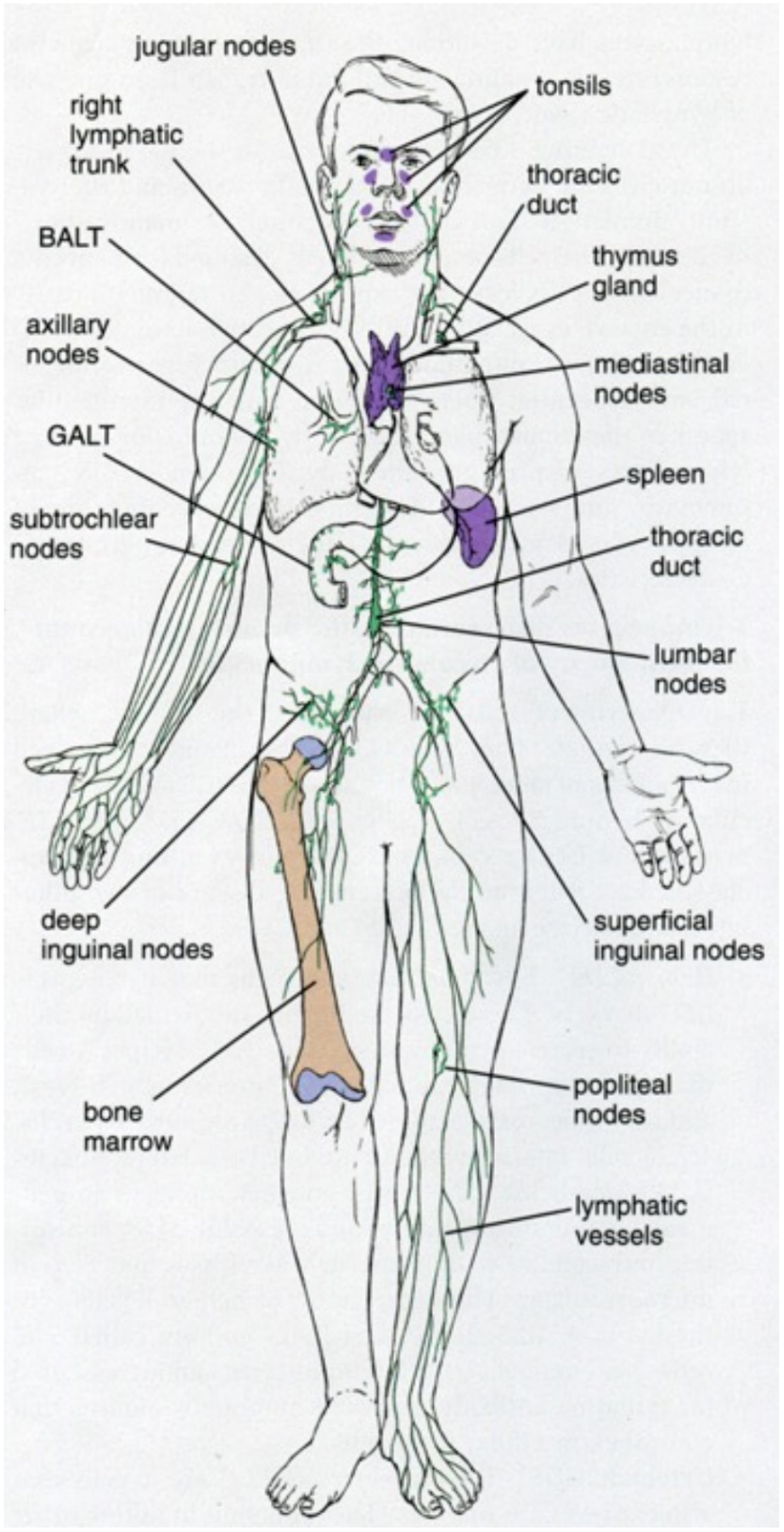


# Lymphoid tissues

Identity

Function




## Lymphoid organs are classified as:

Primary lymphoid organs

- Thymus
- Bone marrow
- Lymphatic nodules of the distal intestinal tract (e.g. ileum and appendix)

Secondary (effector) lymphoid organs/tissues

- Spleen & lymph nodes (organs)
- Mucosal associated lymphoid tissue (MALT), e.g. lymphocytes and lymphatic nodules in the lamina propria

# Lymphoid tissues

## Primary

Sites of lymphocyte **generation** and **receptor diversification and maturation and selection for non self**

Bone marrow

Thymus

## Secondary

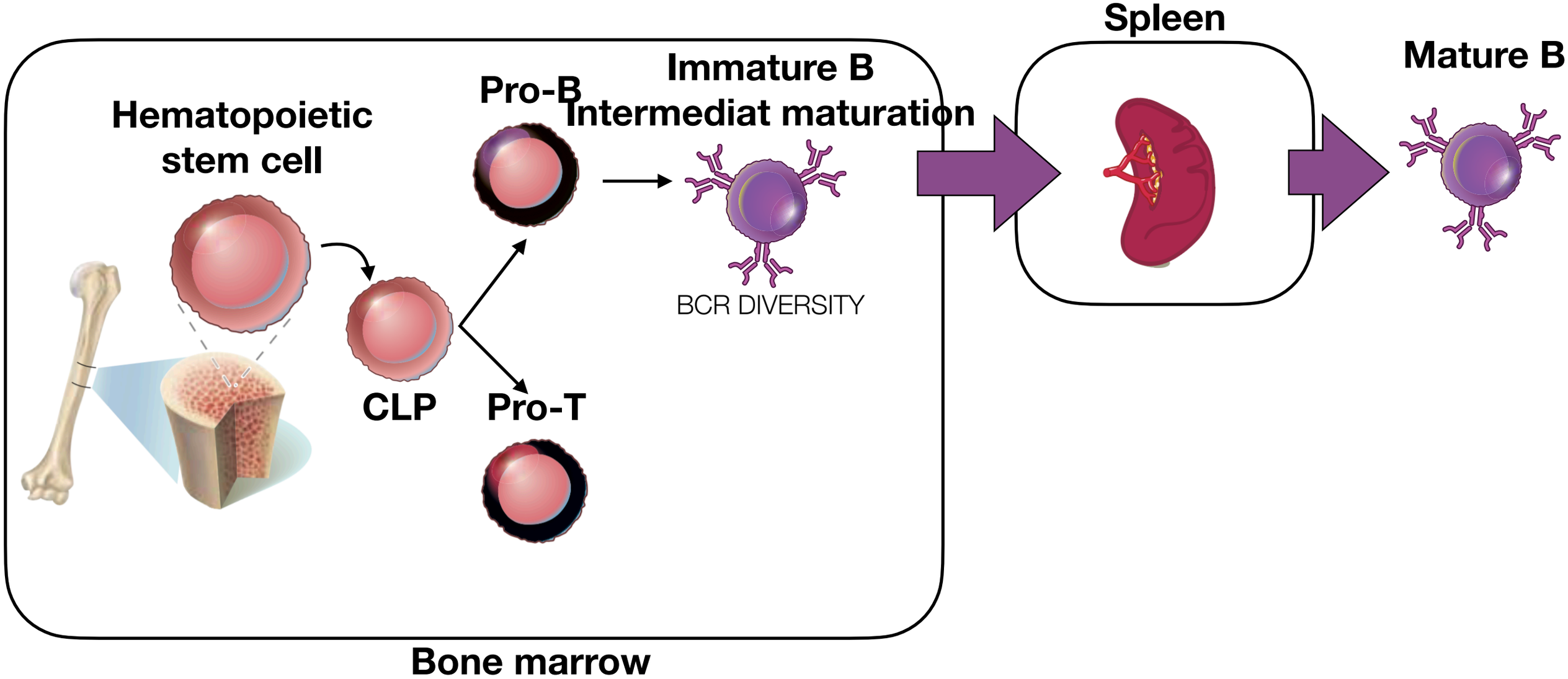
Sites of lymphocyte **activation** by foreign antigens and proliferation. Interaction between T and B.

Lymph nodes

Spleen

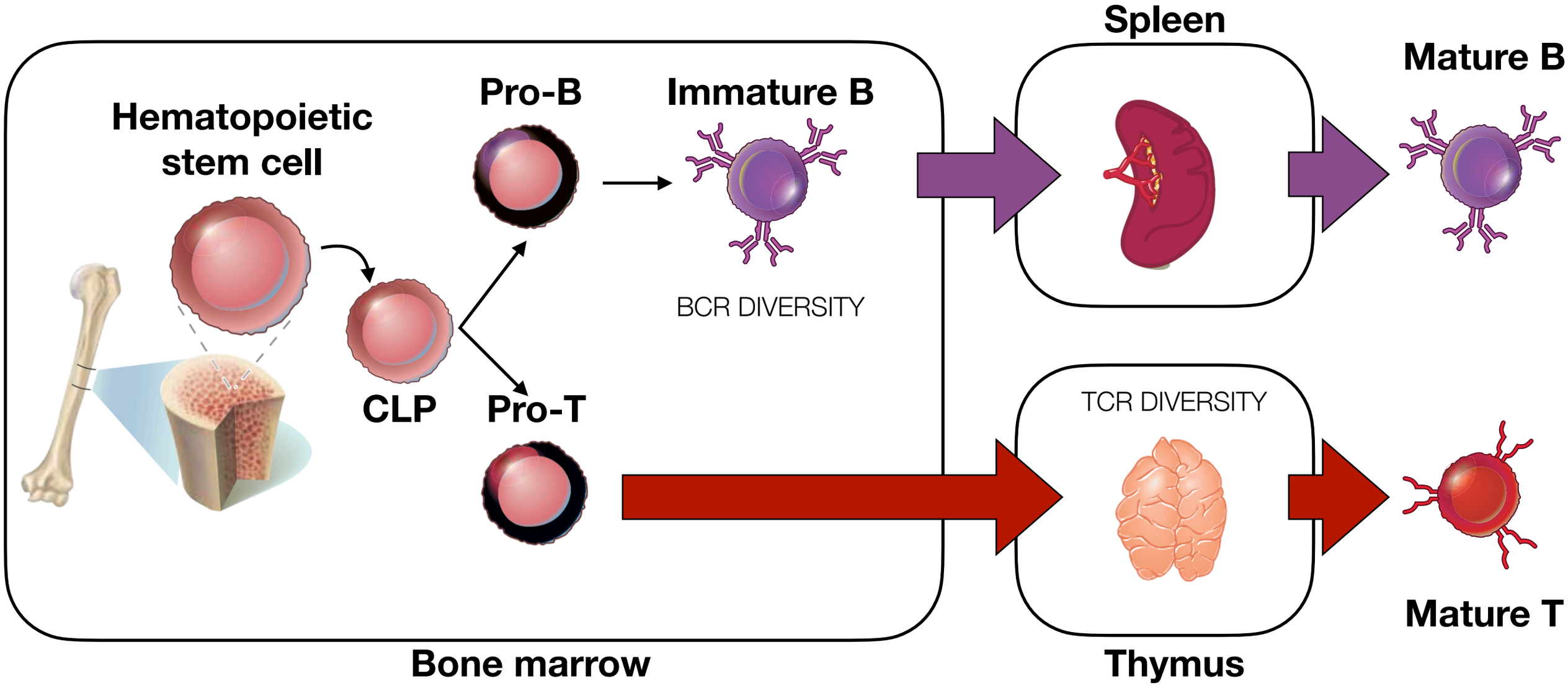
Mucosal associated lymphoid tissues (MALT)

# Lymphocyte generation and maturation




Mature lymphocyte: lymphocyte capable to respond upon antigen exposure

# Lymphocyte generation and maturation

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