Basic Immunology
(Dentistry)

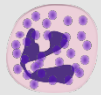
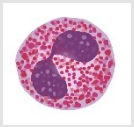
Lecture 3.-4.

Development and characteristics of the cells of the immune system.

Ferenc Boldizsar MD, PhD

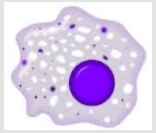
Cells of the innate and adaptive immune system

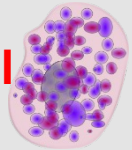
Innate:

1. **Granulocytes:**   

   neutrophil, eosinophil, basophil

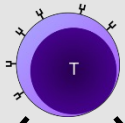
2. **Monocyte (blood), macrophage (tissues)**

3. **Dendritic cell (DC), follicular dendritic cell (FDC)** 
4. **Mast cell** 
5. **NK cell (natural killer)** 

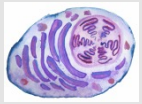
Adaptive:

T cell



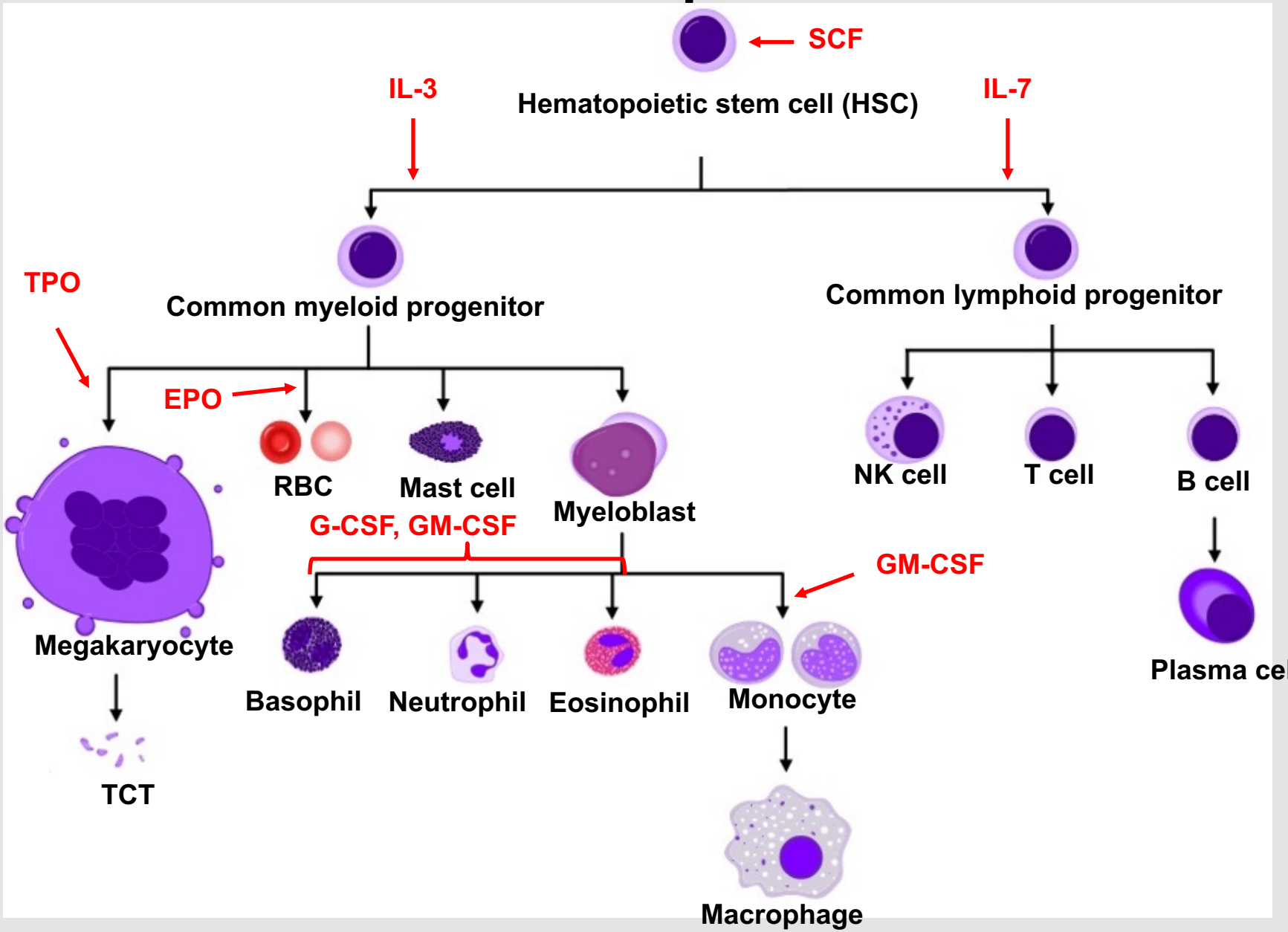
Cytotoxic **Helper**

B cell

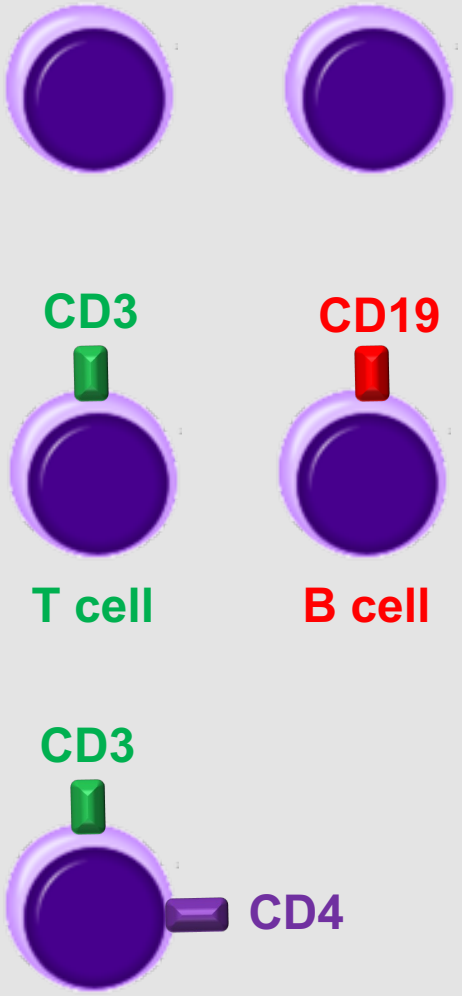


Plasma cell

Hematopoiesis



CD markers



Certain cells (e.g. lymphocytes) cannot always be distinguished based on their morphology.

Different cells can be identified and distinguished by the molecules they express on the cell surface or in the cytoplasm.
IMMUNOPHENOTYPE: The characteristic molecular pattern of a cell type determined with the use of antibodies.

Such SURFACE MOLECULES were given a standardized nomenclature:

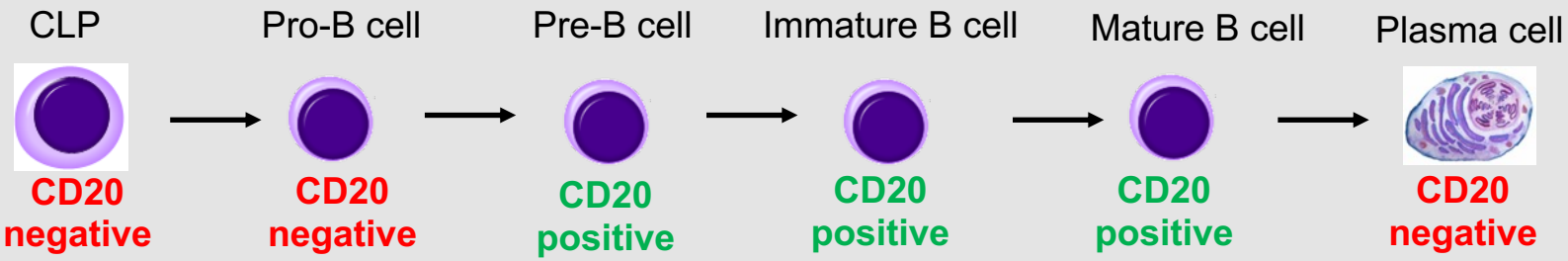
CD = **Cluster of differentiation**, usage: CD+number, e.g.:
CD1, CD2, CD3, CD4, etc…

The structure and function of CD marker **varies**!

Example for immunophenotype:
CD3+/CD4+/CD8- → Helper T cell

Types of CD markers

- **Lineage markers**: Molecules expressed exclusively on certain cell lineages.
  - E.g.: CD3 → found on all T cells CD19 → found on all B cells
- **Maturation markers:** The immunophenotype might differ in the phases of cell maturation, certain molecules are only expressed on immature cells, others on mature, fully functioning cells, etc.
  - E.g.: CD20 (It is also a lineage marker of B cells, cannot be found on any other cells)

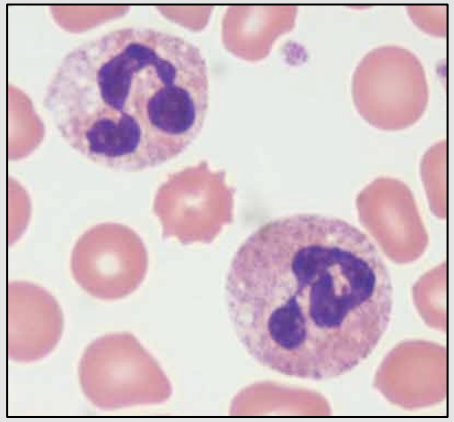


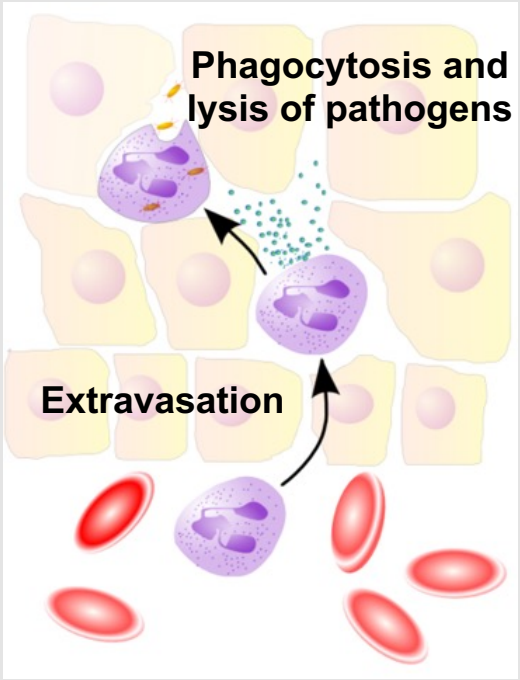
- **Activation markers:** Molecules expressed by activated cells, whereas resting cells either lack them completely or express them at low levels, e.g.:
  - CD25 (The alpha chain of the interleukin-2 receptor, IL-2Rα, see later)
  - CD80 and CD86 (B7-1 and B7-2, so-called costimulatory molecules expressed by activated antigen presenting cells, see later)

Neutrophil granulocyte

Leukocyte %	55-70
Main function:	Elimination of pathogens, removal of tissue debris
Recognition:	PRR, Fc receptor, Complement receptor
Content of granules:	Digesting enzymes
Elimination of pathogens:	Phagocytosis, respiratory burst, degranulation
Produced mediators:	Inflammatory cytokines
Fc receptor:	FcγR (binds IgG)
Role in diseases:	Inflammatory reactions

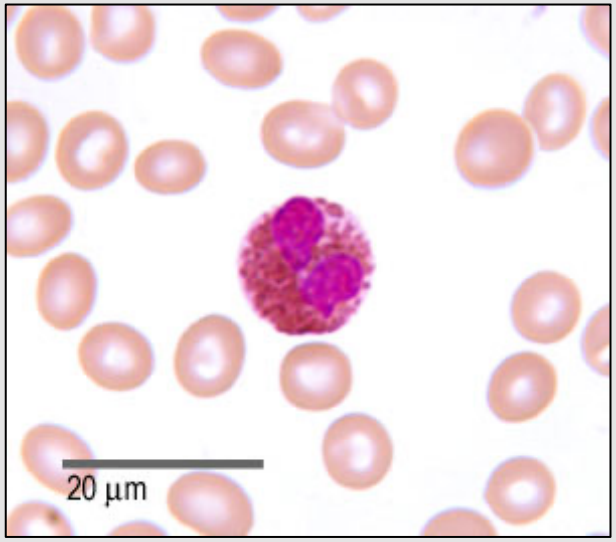
Red: Only possible after the activation of the adaptive immunity

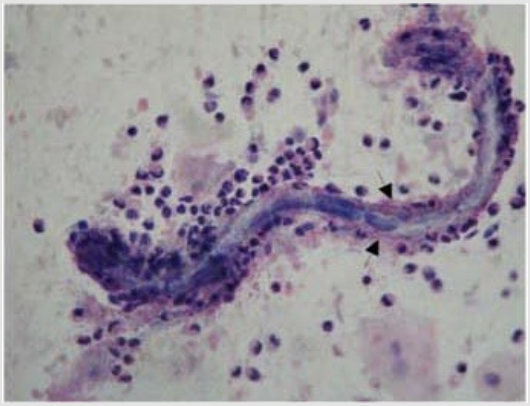




Eosinophil granulocyte

Leukocyte %	2-4
Main function:	Defense against multicellular parasites
Recognition:	PRR, Fc receptor
Content of granules:	Toxic proteins, enzymes
Elimination of pathogens:	Degranulation
Produced mediators:	Prostaglandins, Leukotrienes, Inflammatory cytokines
Fc receptor:	FcεR (binds IgE)
Role in diseases:	Allergic reactions



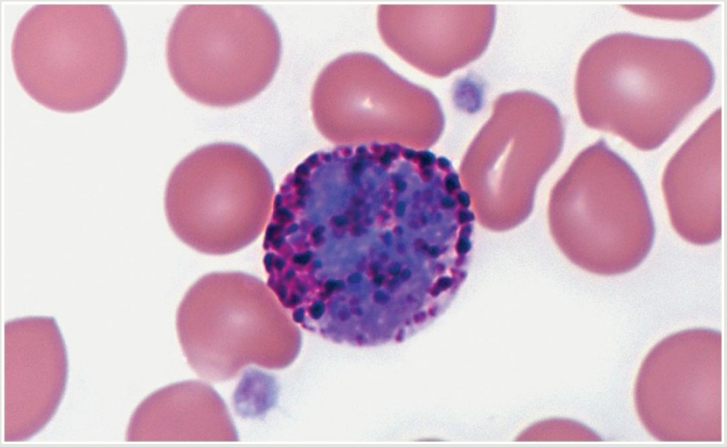


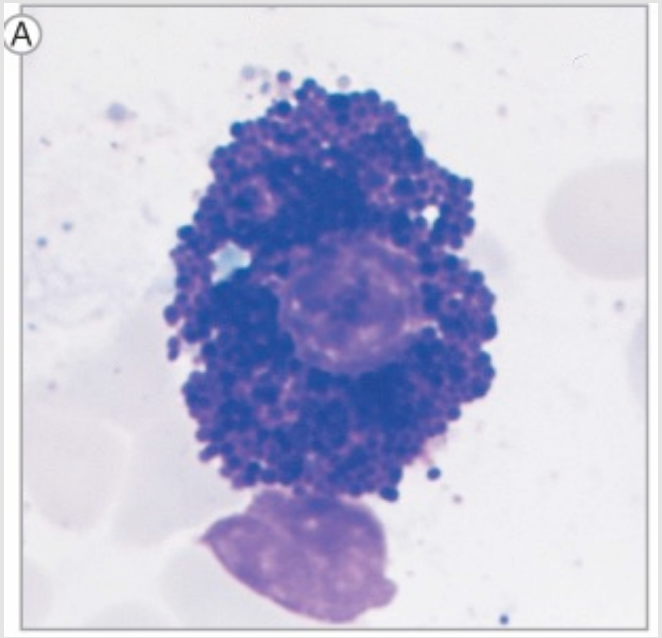
Eosinophils surrounding a *Strongyloides stercoralis* larva. (sputum from a parasitic pneumonia case)

Red: Only possible after the activation of the adaptive immunity

Basophil granulocyte

Leukocyte %	0-1
Main function:	Defense against multicellular parasites
Recognition:	PRR, Fc receptor
Content of granules:	Histamine, heparin
Elimination of pathogens:	Degranulation
Produced mediators:	Cytokines (e.g. IL-4), Leukotrienes
Fc receptor:	FcεR (binds IgE)
Role in diseases:	Allergic reactions



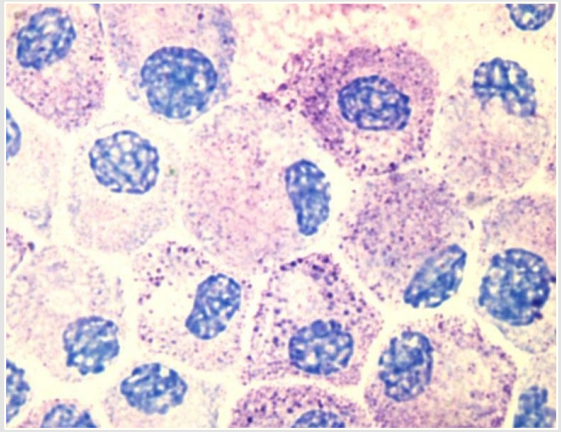


Red: Only possible after the activation of the adaptive immunity

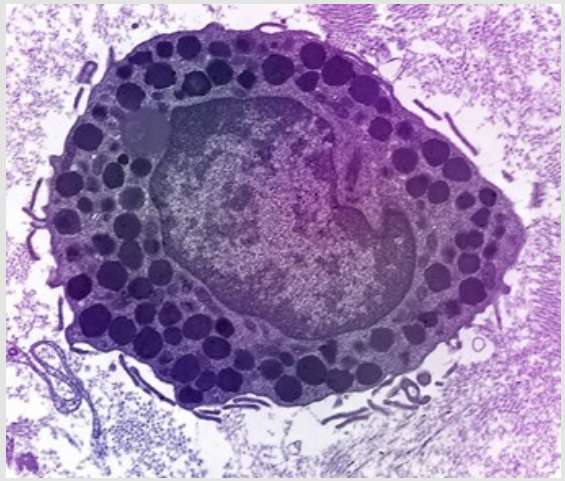
Mast cell (mastocyte)

Found in:	Tissues
Main function:	Defense against multicellular parasites
Recognition:	PRR, Fc receptor
Content of granules:	Histamine, heparin, enzymes
Elimination of pathogens:	Degranulation
Produced mediators:	Cytokines, Leukotrienes
Fc receptor:	FcεR (binds IgE)
Role in diseases:	Allergic reactions

Red: Only possible after the activation of the adaptive immunity

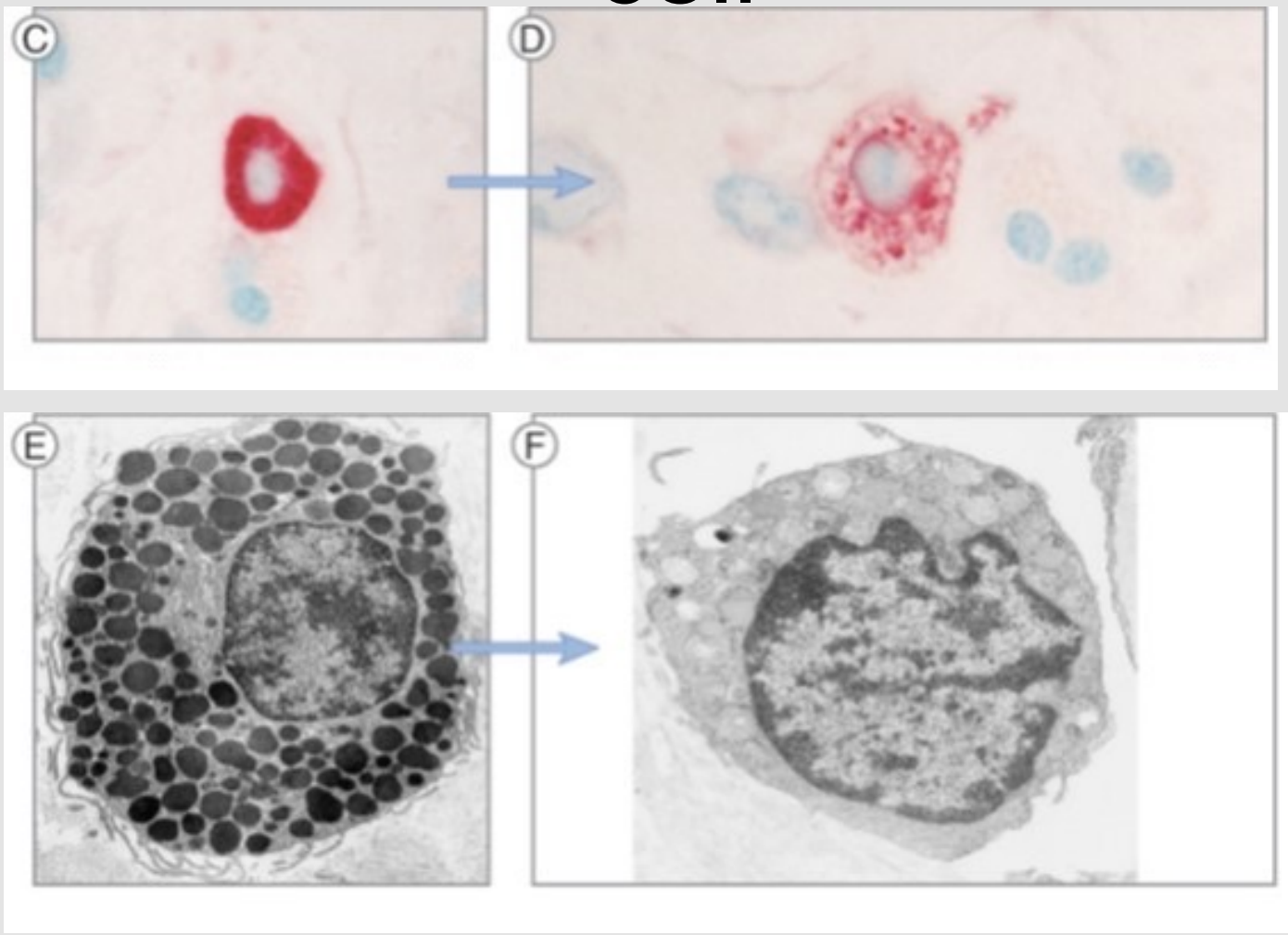


Cultured mast cells
(Toluidine blue staining)



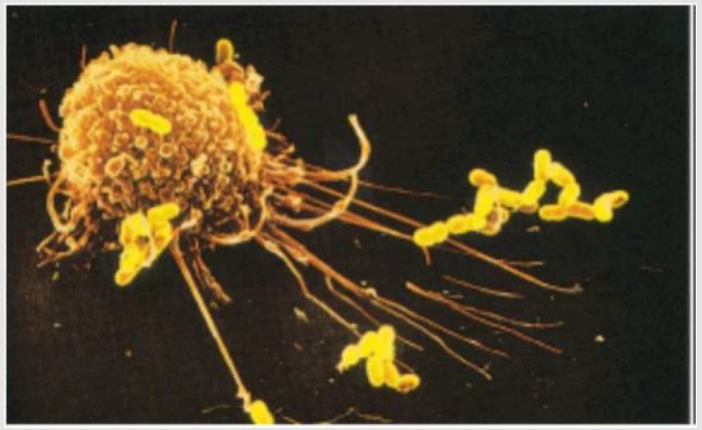
Mast cell (electron microscopy image)

Quick degranulation of a mast cell

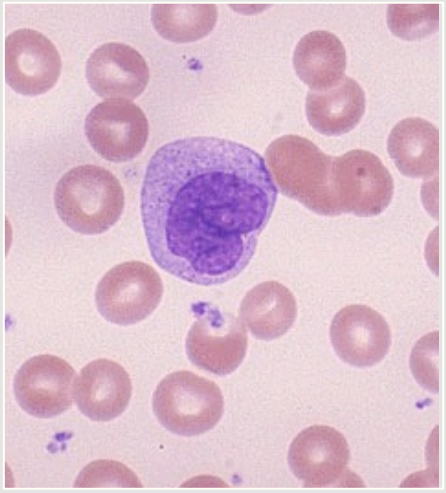


Monocyte, macrophage

Leukocyte %:	2-8
Main function:	Phagocytosis, Antigen presentation, Cytokine production,
Site of antigen presentation:	Locally, in the tissues
Recognition:	PRR, Fc receptor, Complement receptor
Elimination of pathogens:	Phagocytosis, Respiratory burst
Produced mediators:	Cytokines
Fc receptor:	FcγR (binds IgG)
Role in diseases:	Type IV. hypersensitivity



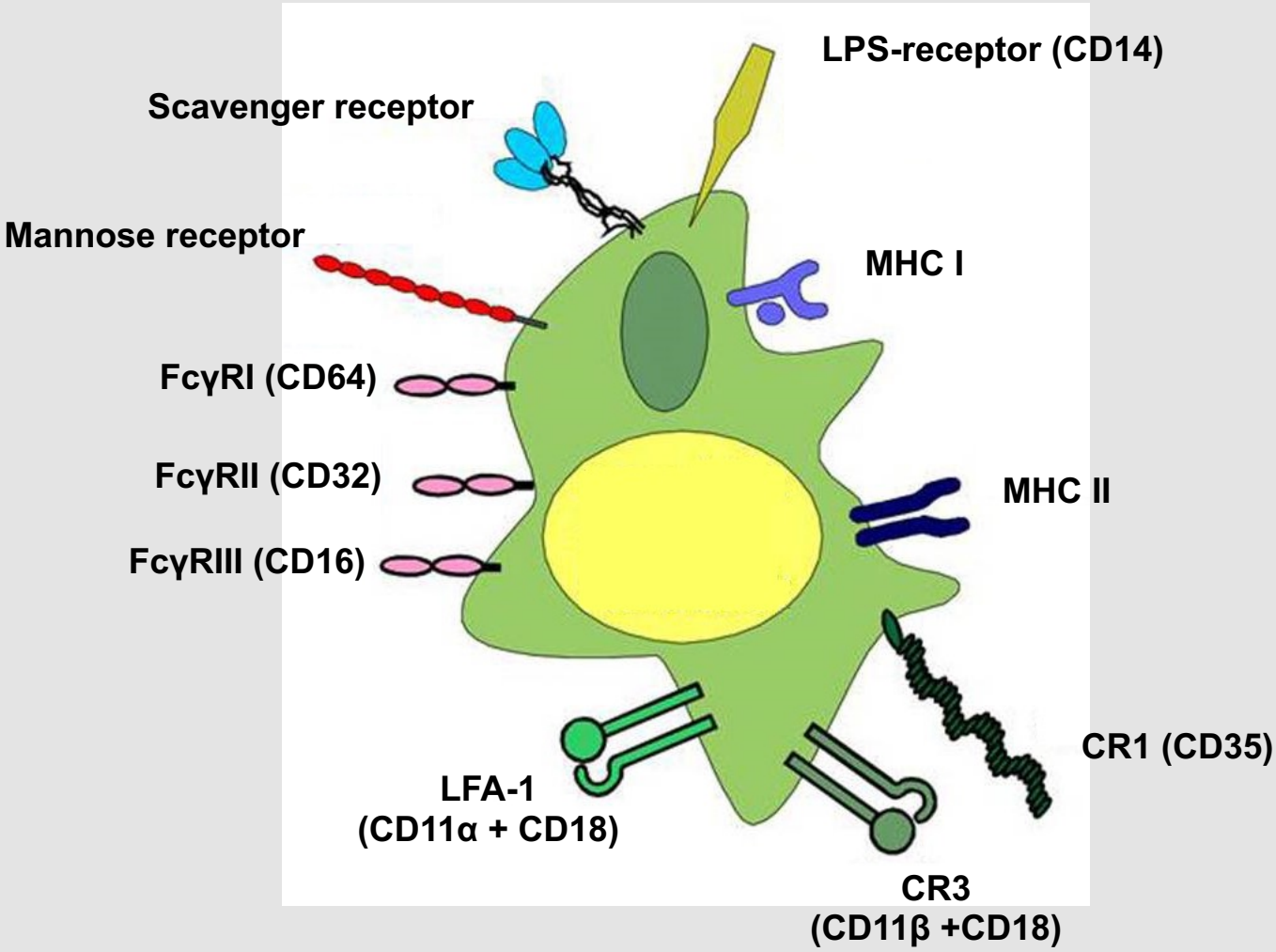
A macrophage ingesting (phagocytosing) bacteria (SEM image)



A monocyte in a blood smear

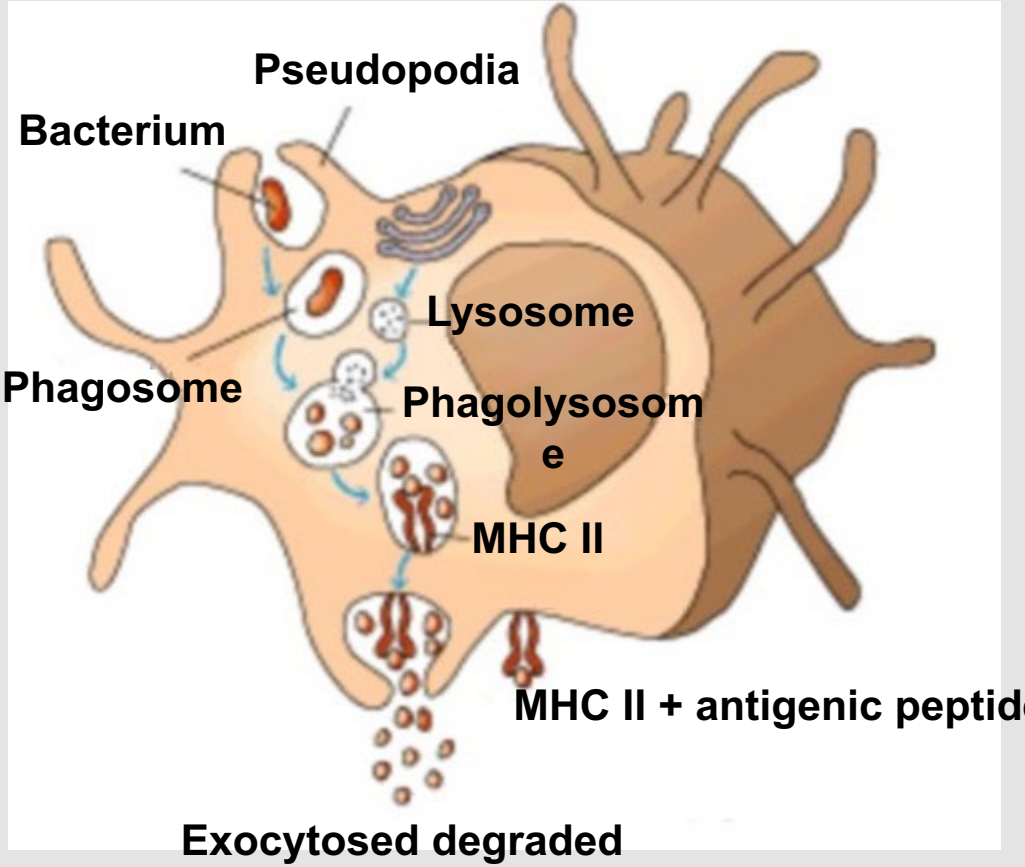
Red: Only possible after the activation of the adaptive immunity

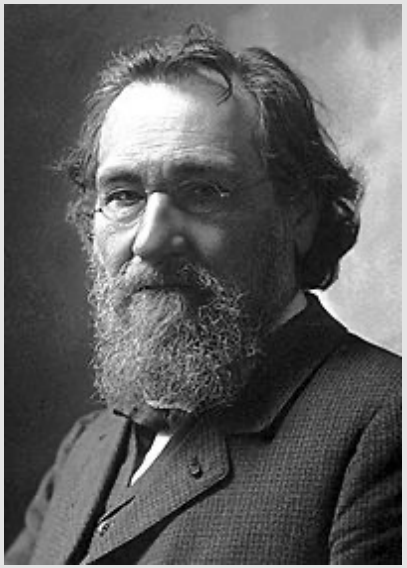
Surface molecules of macrophages



Phagocytosis

Phagocytosis and antigen presentation of macrophages:





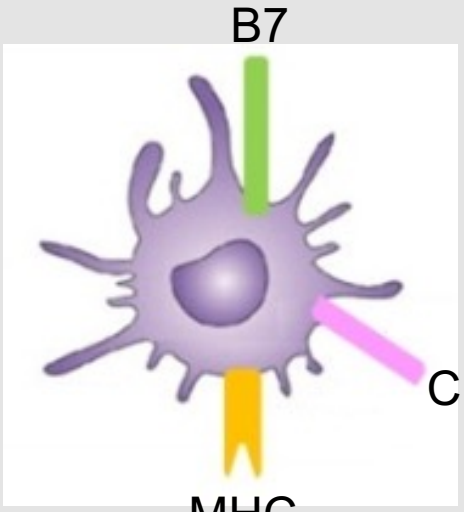
Ilya Ilyich Mechnikov who discovered macrophages and the phenomenon of phagocytosis.

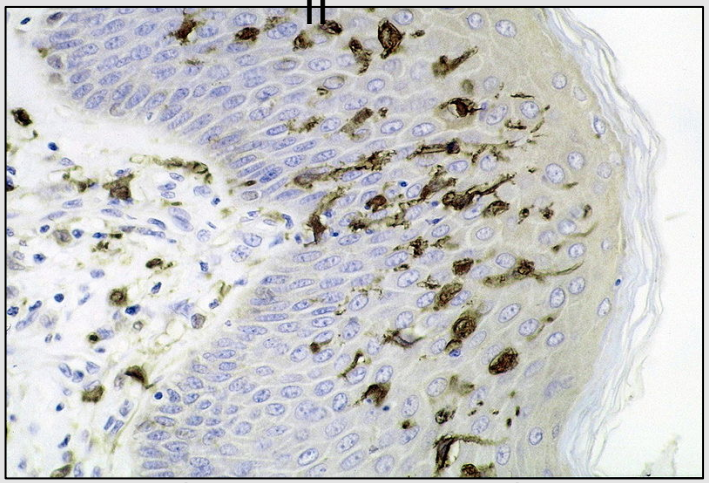
Was awarded the 1908 Nobel Prize in Physiology or Medicine jointly with Paul Ehrlich „in recognition of their work on immunity”.

Dendritic cell (DC)

Found in:	Tissues
Main function:	Antigen presentation
Site of antigen presentation:	In the secondary lymphoid organs
Recognition:	PRR, Fc receptor
Produced mediators:	Cytokines
Fc receptor:	FcγR (binds IgG)
Role in diseases:	Autoimmunity, HIV infection

Red: Only possible after the activation of the adaptive immunity

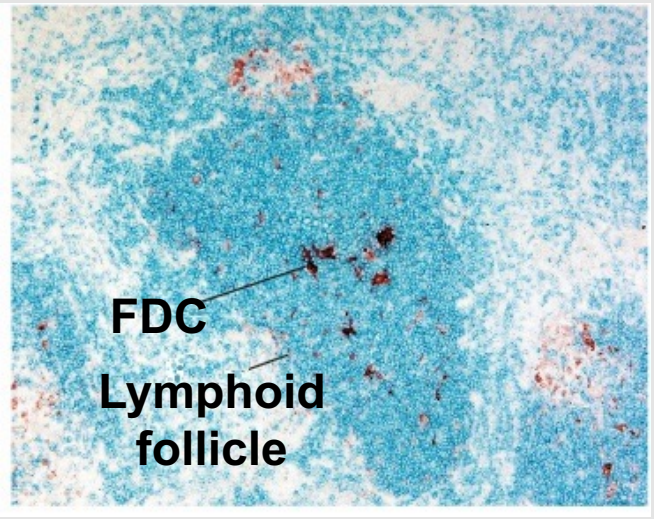




Dendritic cells (Langerhans cells) in the skin of a *Mycobacterium ulcerans* infected patient. (immunohistochemistry)

Follicular dendritic cell (FDC)

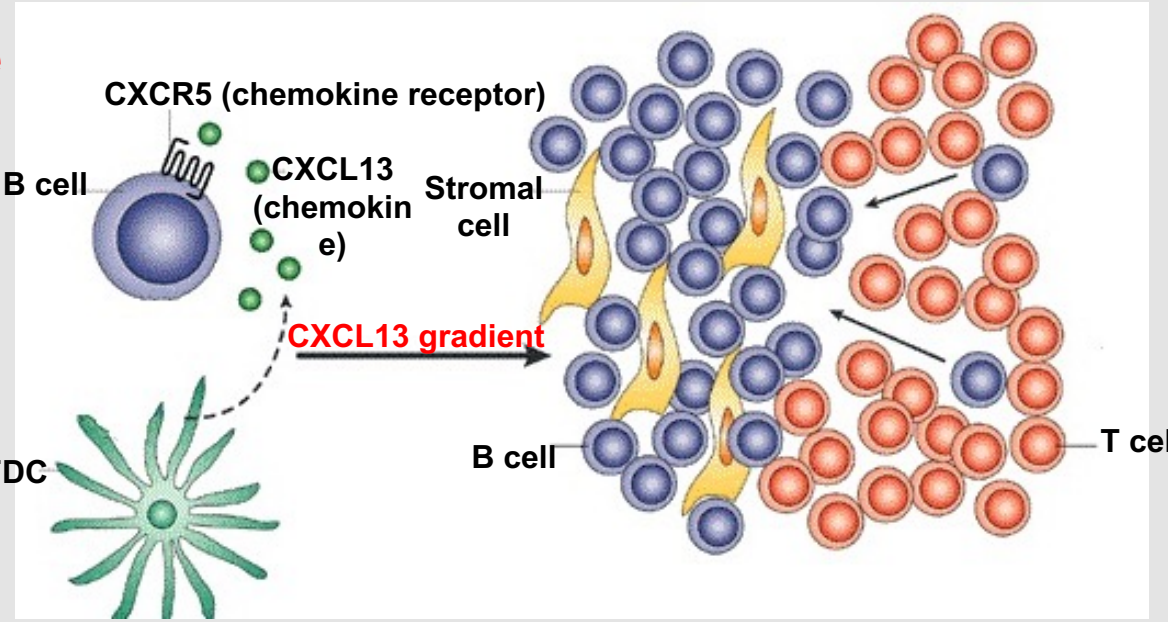
Found in:	Lymphoid follicles
Main function:	Formation of follicles, Keeping the antigen in the follicle for B cells
Recognition:	Fc receptor, Complement receptor
Produced mediators:	Cytokines
Fc receptor:	FcγR (binds IgG)



Red: Only possible after the activation of the adaptive immunity

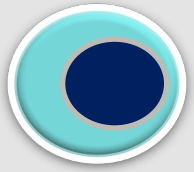
Iccosome:

- Antigen
- Antibody + Fc receptor
- Complement + Complement receptor



Cells of the lymphoid lineage

Innate lymphoid cells (ILC)



HAVE NO ANTIGEN-RECOGNTIION RECEPTORS

There is no difference in the morphology!

Lymphocyte

HAVE ANTIGEN-RECOGNITION RECEPTORS

NATURAL

LYMPHOCYTES

ADAPTIVE

γδ T cell

T cell (CD3+)

αβ T cell

Helper T cell (CD4+)

B1 B cell

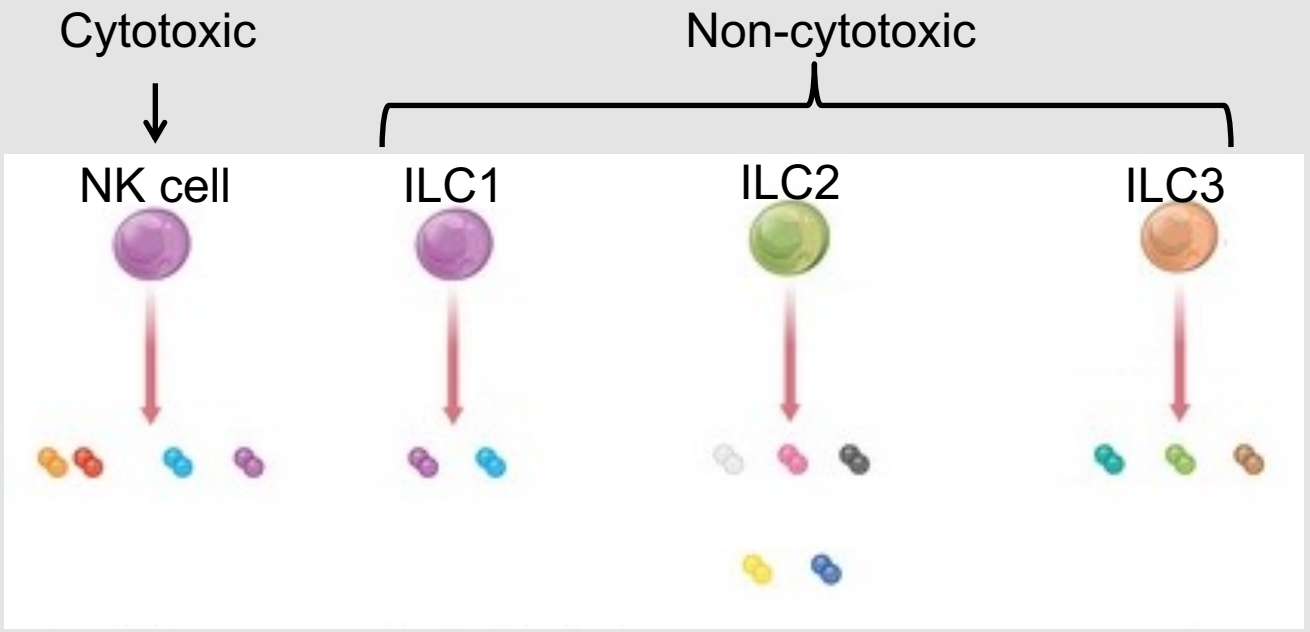
B cell (CD19+)

B2 B cell

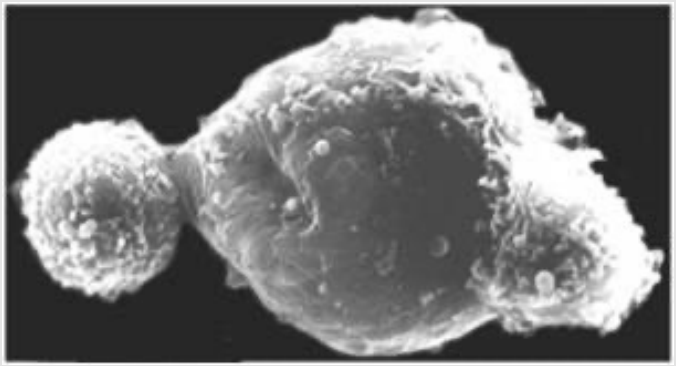
Cytotoxic T cell (CD8+)

Innate lymphoid cells (ILC)

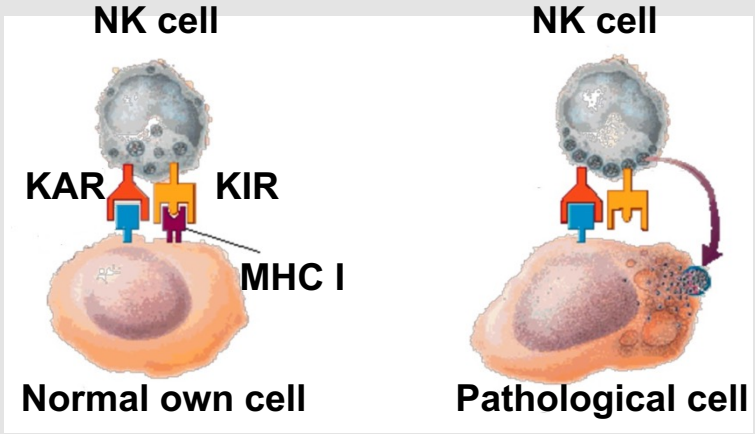
- They cannot be distinguished from lymphocytes based on their morphology but unlike adaptive lymphocytes they cannot recognize antigens. → **They have no antigen recognition receptors.**
- They are classified based on the cytokines they produce and the transcripition factors that are necessary for their formation. (see in the lectures):
  - Group 1 ILCs:
    - **NK cells**
    - ILC1
  - Group 2 ILCs:
    - ILC2
  - Group 3 ILCs:
    - ILC3/LTi



Natural killer cells (NK cells)



Two NK cells kill a cancerous cell. (Scanning electron microscopy image)



CELL IS LEFT ALIVE

CELL IS KILLED

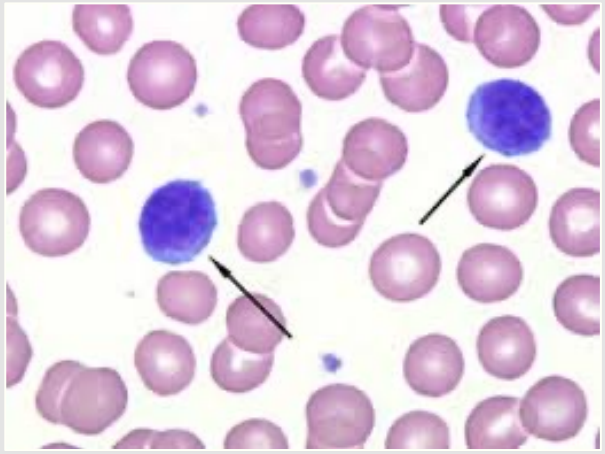
Blood lymphoid cells %:	**≈ 10**
Main function:	**Killing cells infected with intracellular pathogens, Killing cancer cells**
Recognition:	**KAR → killing the target KIR → sparing the target Fc receptor, Complement receptor**
Cytotoxicity:	**Fas-FasL, Perforin, Granzymes**
Produced mediators:	**Cytokines**
Fc receptor:	**FcγR (binds IgG)**

Red: Only possible after the activation of the adaptive immunity

Lymphocytes

Leukocyte %:	25-40*
Main function:	ADAPTIVE IMMUNITY
Recognition	Antigen-specific receptors (TCR, BCR)

* Including NK cells



B cell (CD19+)

↓

Antibody production

Cytotoxic T cell (CD8+)

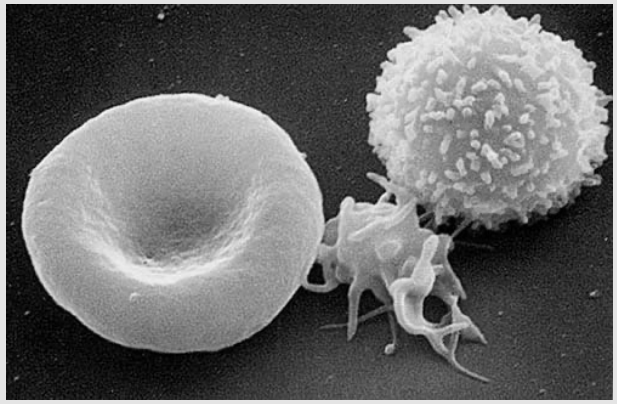
↓

Direct killing of target cell (infected or cancerous)

Helper T cell (CD4+)

↓

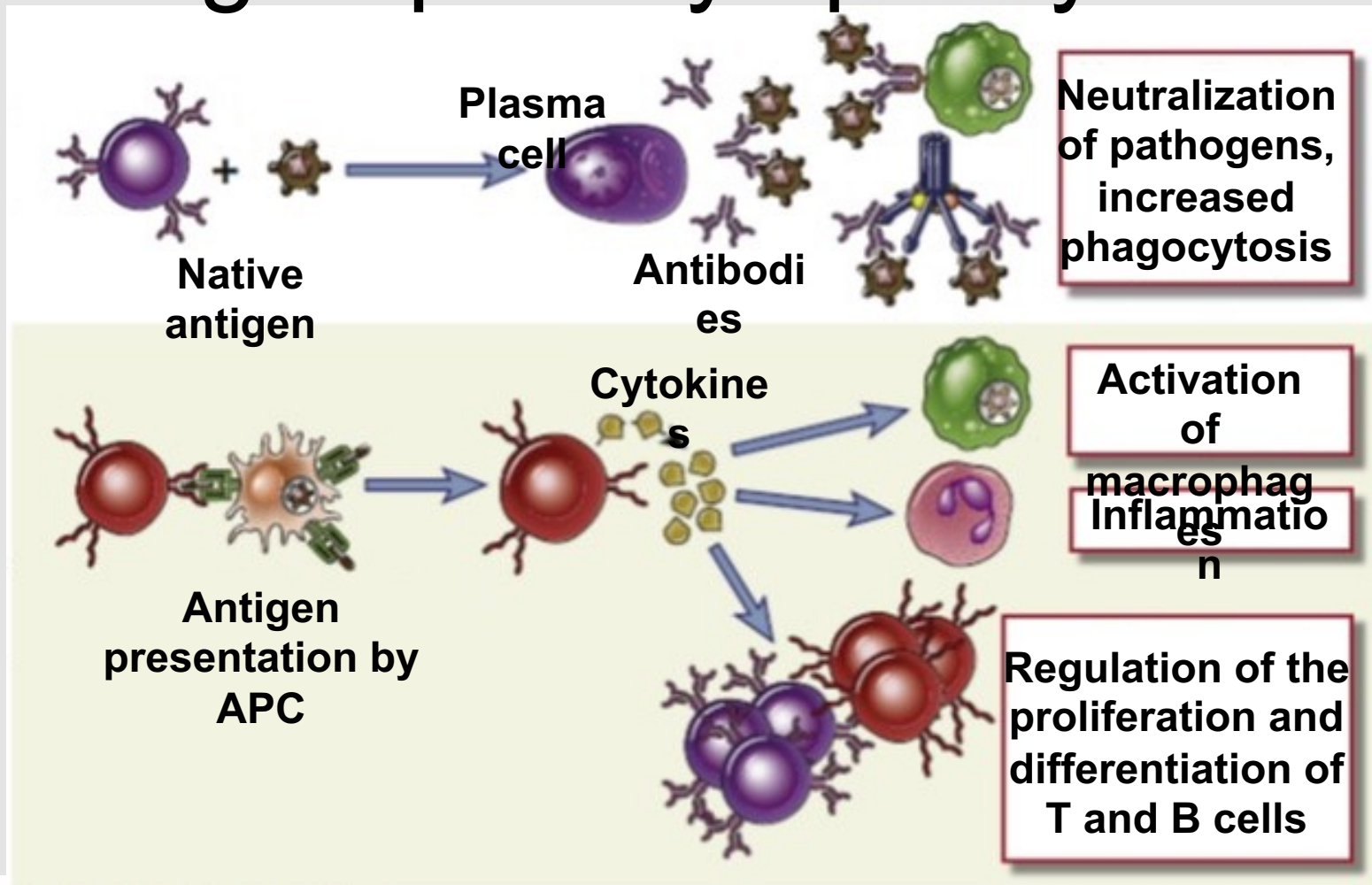
Regulation of the immune response



A red blood cell, a platelet and a lymphocyte (SEM image)

All of the above are done in an ANTIGEN-SPECIFIC manner!

Main groups of lymphocytes

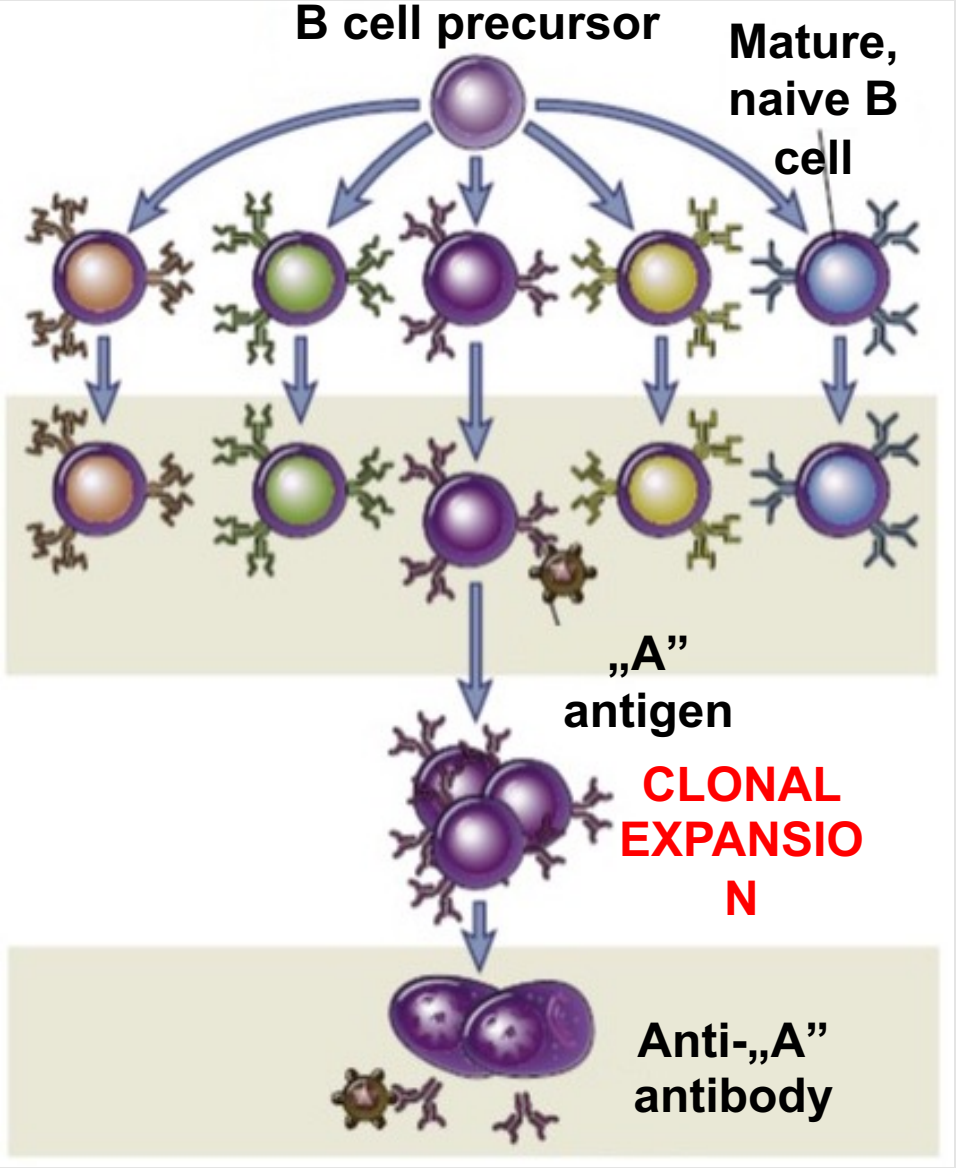


Clonality

1. Each newly produced lymphocyte expresses a **unique antigen-binding receptor**.

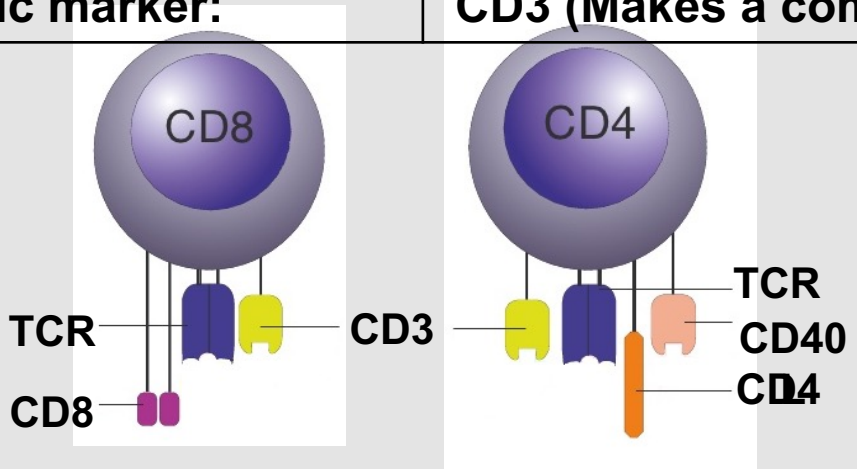
2. **Only those lymphocytes will become activated which recognize an antigen**. These selected cells will proliferate and produce **clones** of themselves with each sister cell having the same antigen-recognition receptor.

3. These clones will differentiate into **effector cells** which will participate in the immune response. (e.g. effector plasma cells produce antibodies)



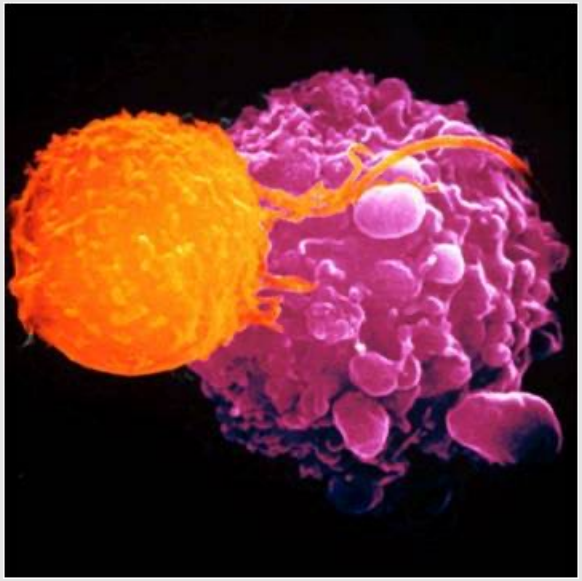
T cells

Main function:	**Antigen-specific killing of target cell (CD8+), Regulation of the immune response through cytokines (CD4+)**
Recognition:	**Through MHC, antigen-specific TCR**
Possible type of TCR:	**αβ and γδ**
Produced mediators:	**Cytokines**
Main types of αβ T cells:	**CD4+ Helper CD8+ Cytotoxic**
Site of production:	**Bone marrow, thymus**
Characteristic marker:	**CD3 (Makes a complex with the TCR)**



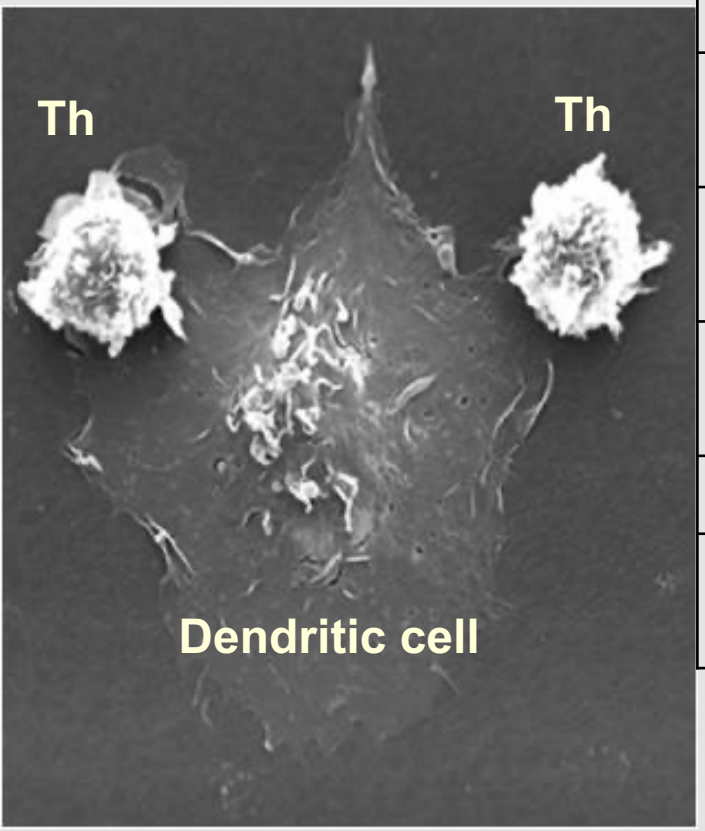
Cytotoxic T cells (Tc or CTL)

Blood T cells:	**1/3**
Main function:	**Effector cell of the cellular immunity**
Recognition:	**Through MHC I, antigen-specific TCR**
Target cells to kill:	**Infected with IC pathogens, Cancerous, Foreign (transplantations!)**
Recognized antigens:	**Endogenous (from the cytoplasm of the target cell)**
Cytotoxicity:	**Fas-FasL, Perforin, Granzyme**
Immunophenotype:	**CD3+/CD8+/CD4-**



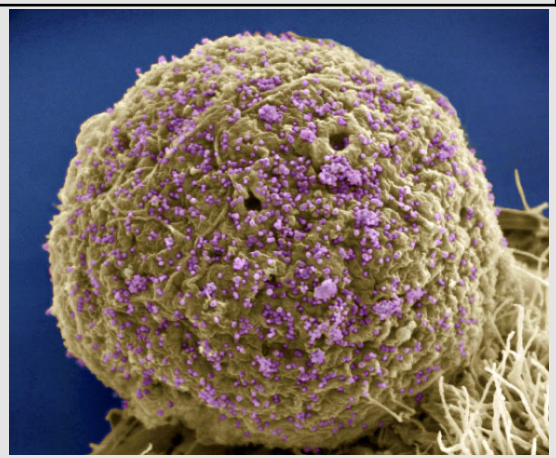
A cytotoxic T cell kills a cancer cell. (SEM image)

Helper T cells (Th)



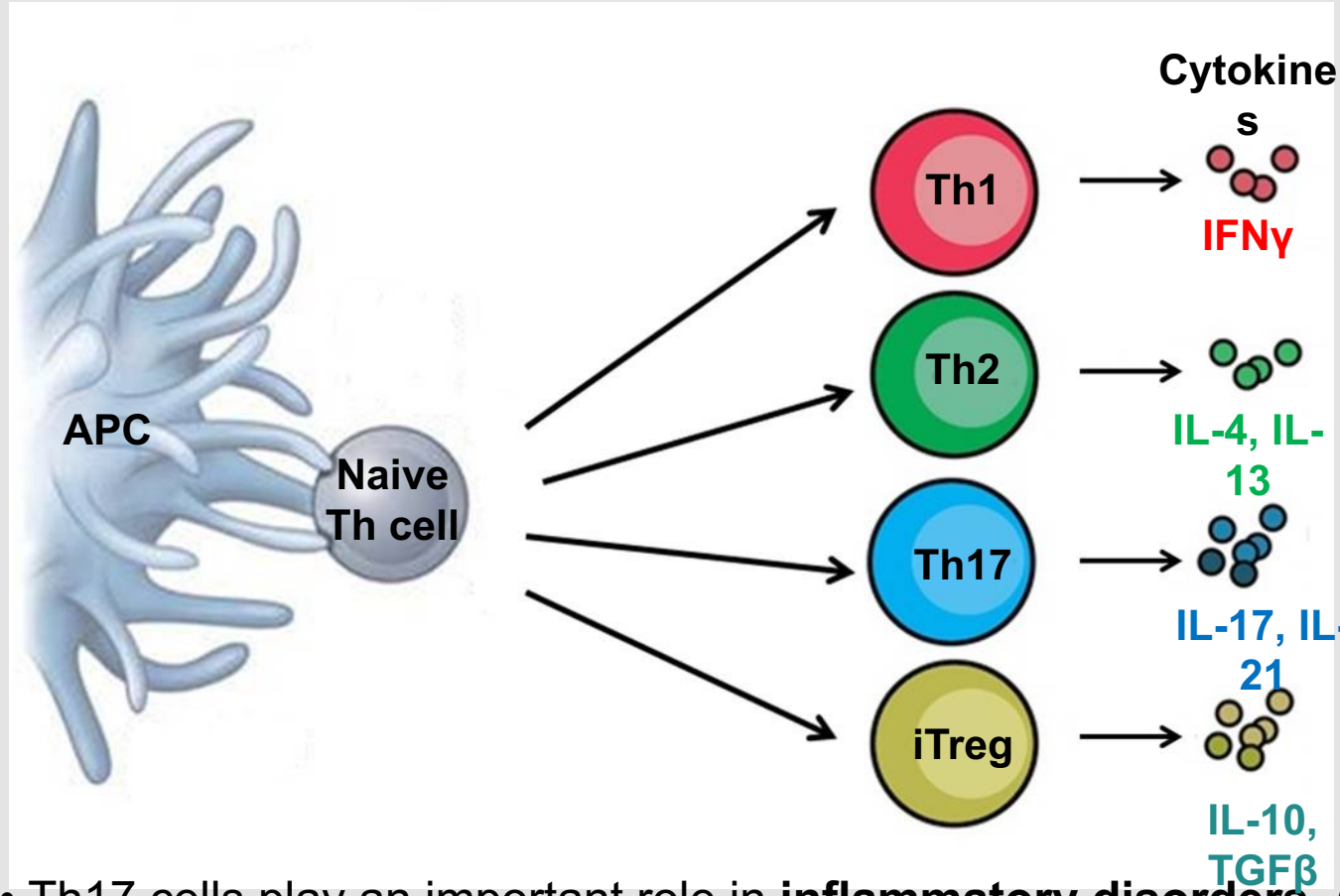
Two helper T cells attached to a dendritic cell. (Scanning electron microscopy image)

Blood T cells:	**1/3**
Main function:	**Regulation of immune response**
Recognition:	**Through MHC II, antigen-specific TCR**
Recognized antigens:	**Exogenous (degraded in phagolysosomes)**
Immunophenotype:	**CD3+/CD4+/CD8-**
Role in diseases:	**Autoimmunity, HIV infection**



Yellowish-brown: Th cell
purple: **HIV** virions (SEM image)

Main subtypes of Th cells



Cellular immune response (intracellular pathogens)

Humoral immune response (extracellular pathogens)

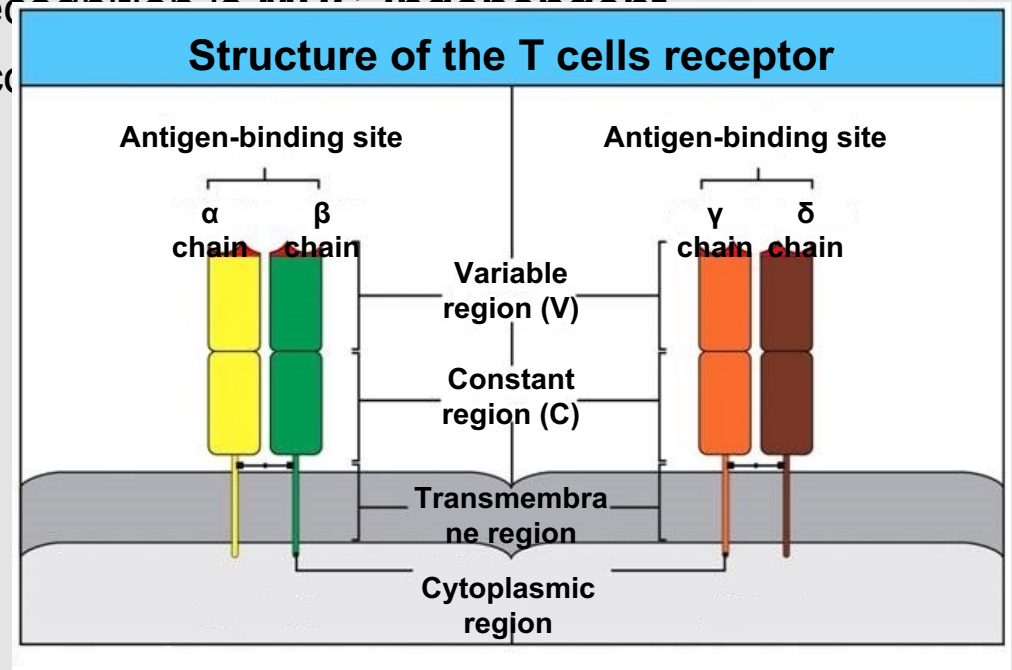
Extracellular pathogens, fungi

Antigen-specific suppression (see later)

- Th17 cells play an important role in **inflammatory disorders**. (see later)
- **Regulatory T cells** (Treg): They can inhibit other immune cells (**suppression**, see later), their immunophenotype is: **CD4+/CD25+/Foxp3+**

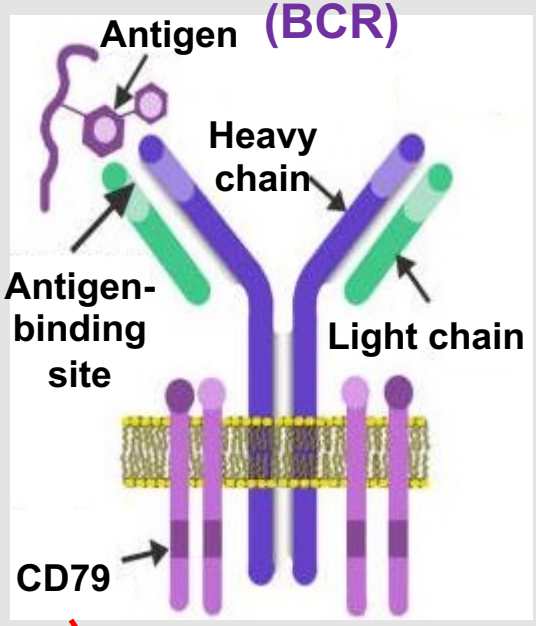
γδ T cells

- They express TCRs that consist of γ and δ chains.
- They are **innate-like lymphocytes**, they are not as well-characterized as αβ T cells.[17.]
- They are mainly found in the **skin** and the **mucosa**; usually as intraepithelial lymphocytes (IELs). They can be detected in the peripheral blood in low numbers.
- They participate in the early phases of the immune response against invasive pathogens.
- Their antigen-rec
- They mainly rec



B cells

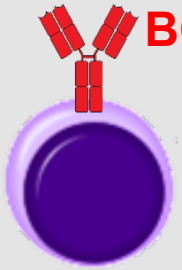
B cell receptor (BCR)



Signal transduction in the case of antigen binding

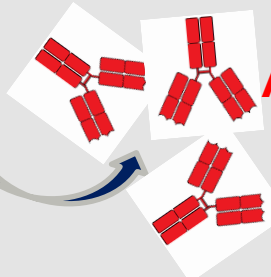
Blood lymphoid cells %:	**10-15**
Main functions:	**Antibody production, Antigen presentation**
Recognition:	**Native antigens with antigen-specific BCR**
Main types:	**B1 and B2**
Site of production:	**Bone marrow**
Characteristic marker:	**CD19 (makes a complex with BCR)**

BCR = surface immunoglobulin



B cell

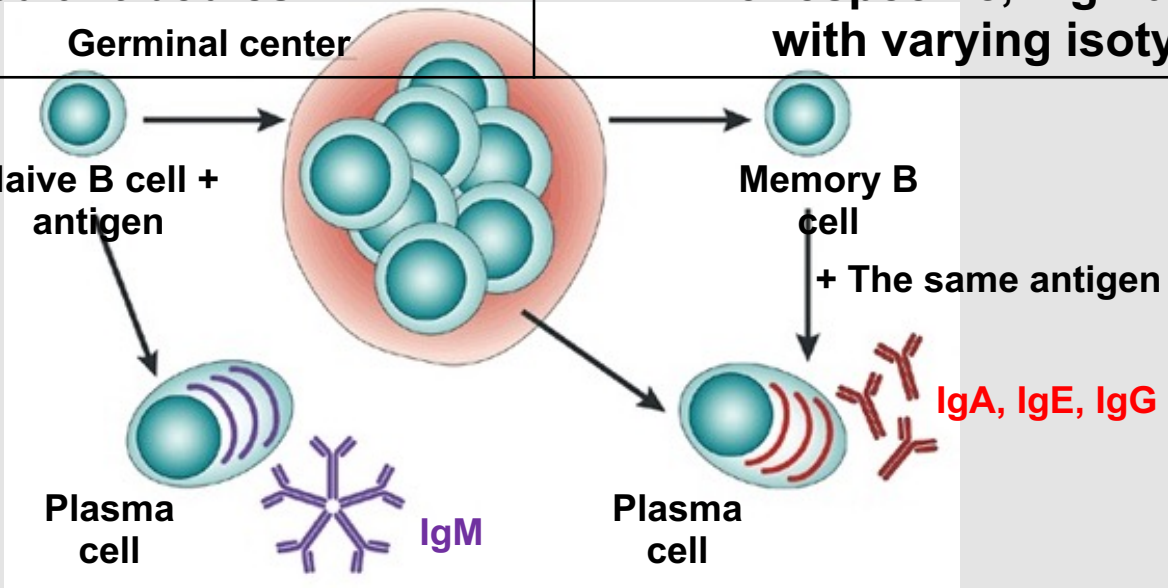
Plasma cell



Antibody against the same antigen recognized by the BCR (secreted immunoglobulin)

B2 B cells

Found in:	**Follicles in secondary lmyphoid organs, blood**
Main functions:	**Antibody production, Antigen presentation**
Recognition:	**Native antigens with antigen-specific BCR**
Site of primary maturation:	**Bone marrow**
Site of antigen-dependent maturation:	**Germinal center**
Produced antibodies:	**Monospecific, high-affinity, with varying isotype**



B1 B cells

- Only few can be found in the peripheral blood.
- **They are innate-like lymphocytes**, most of them reside on serous membranes. (e.g. peritoneum, pleura, pericardium)
- They are first produced in the fetus and later undergo self-renewal in the periphery, not in the bone marrow, as B2 cells do.
- They produce **natural autoantibodies** that can bind that can bind evolutionarily **conserved self-antigens**.
- They were first described as CD5+ B cells in mice.
- The immunophenotype of the human B1 cells is still controversial.

	B1 cells	B2 cells
Spontaneous antibody production	Significant	Minimal
Isotype of produced antibodies	**IgM**	IgM/IgG/IgA/IgE
Affinity and specificity of antibodies	**Polyspecific with low affinity**	Monospecific with high affinity
Affinity maturation, memory	No	Yes

Thank you for your attention!