The role of anatomical/physiological barriers

- It ensures a mechanical defense against the pathogen microbes

To inhibit the proliferation of pathogen microbes:

- Production of several chemical compounds (eg. Antimicrobial peptides: defensin)

- The presence of commensal microorganisms

Elements and functions of innate immunity

- Phagocytes, soluble factors (opsonisation !)
- The role of pattern recognition molecules in the detection of pathogens (eg. TLR, NLR, RLR, CRP)
- The first line of defense against infections-local
- Localisation of microbes and inhibits their spreading
- The effector mechanisms of innate immunity aid the adaptive immunity to eliminate the pathogens

Inflammation

1. Types of inflammation: local and systemic
   acute and chronic

2. Cellular elements of acute inflammation:

cells in tissues: macrophage, mast cell, dendritic cell

cells migrating to the site of inflammation: neutrophil granulocytes, monocytes, later effector lymphocytes

inflammatory blood vessel wall changes (adhesion molecules, chemokines)

3. Molecules of inflammation: plasma mediators (complement), lipid mediators, chemokines (IL-8, C3a, C5a), cytokines (IL1, IL-6, TNFalpha)

4. Participants of systemic inflammation: CNS-fever, Liver-production of acute phase proteins, bone marrow-leukocytosis

IMMUNOLÓGIAI ÉS BIOTECHNOLÓGIAI INTÉZET

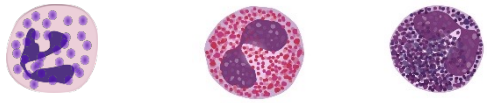
3rd practice: Types and functions of lymphoid cells, CD markers

Basic Immunology

University of Pécs, Clinical Center
Department of Immunology and Biotechnology
Pécs

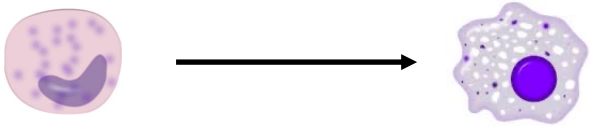
Cells of the innate and adaptive immune system

Innate:

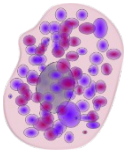
1. **Granulocytes:** 

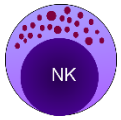
   neutrophil, eosinophil, basophil

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

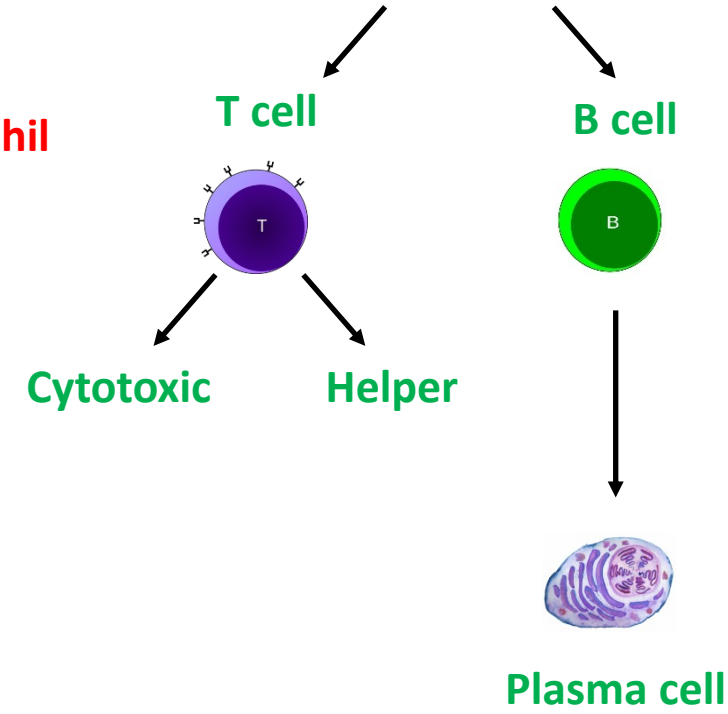


3. **Dendritic cell (DC), follicular dendritic cell (FDC)**

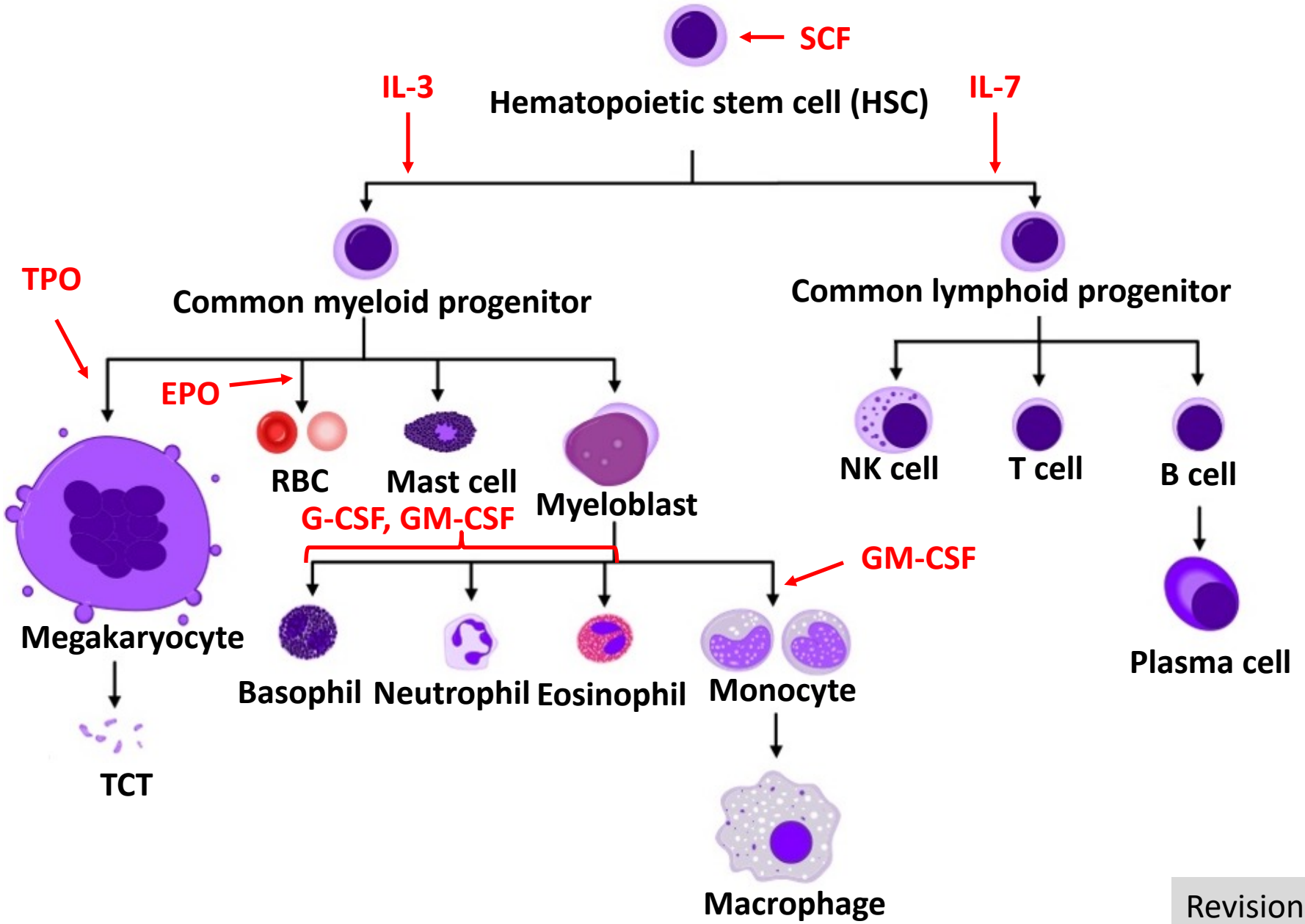
4. **Mast cell** 

5. **NK cell (natural killer)** 

Adaptive:

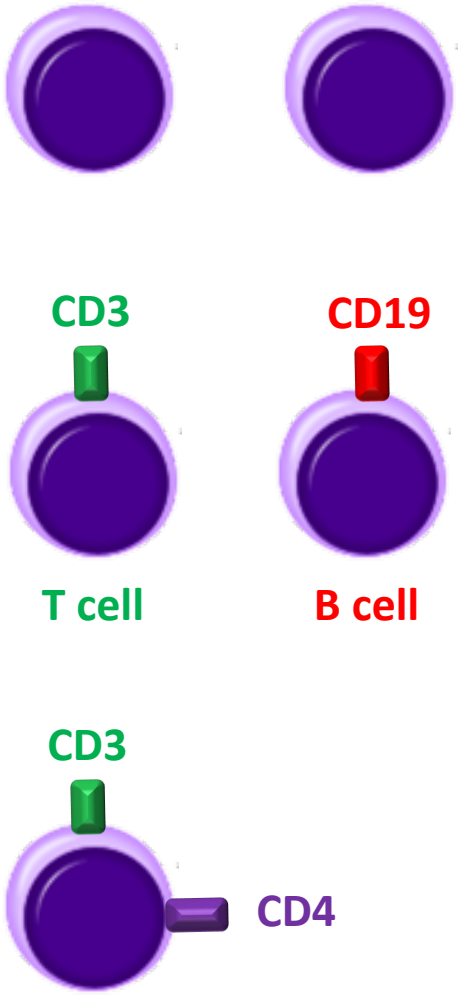


Hematopoiesis



Revision 2.

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:

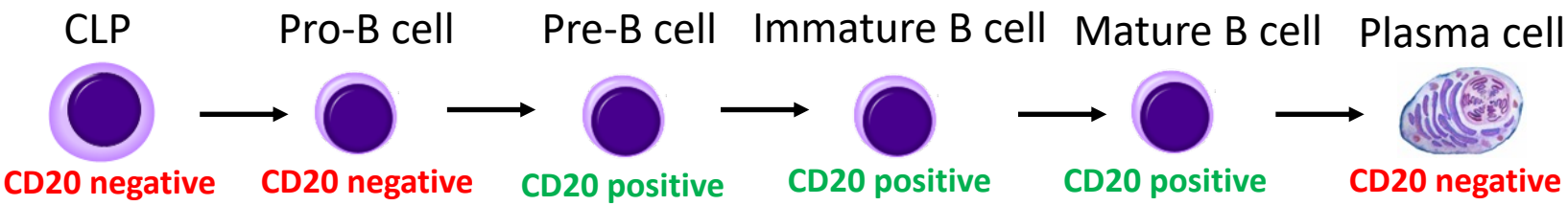
CD = **Cluster of differentiation**, usage: CD+number, e.g.: CD1, CD2, CD3, CD4, etc…

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

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

Types of CD markers

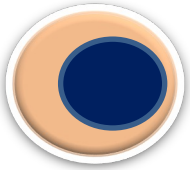
- **Lineage markers**: Molecules expressed exclusively on certain cell lineages.
  - E.g.: CD3 → found on all T cells CD19 → found on all B cells
- **Maturation markers:** The immunophenotype might differ in the phases of cell maturation, certain molecules are only expressed on immature cells, others 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)

Cells of the lymphoid lineage

Innate lymphoid cells (ILC)

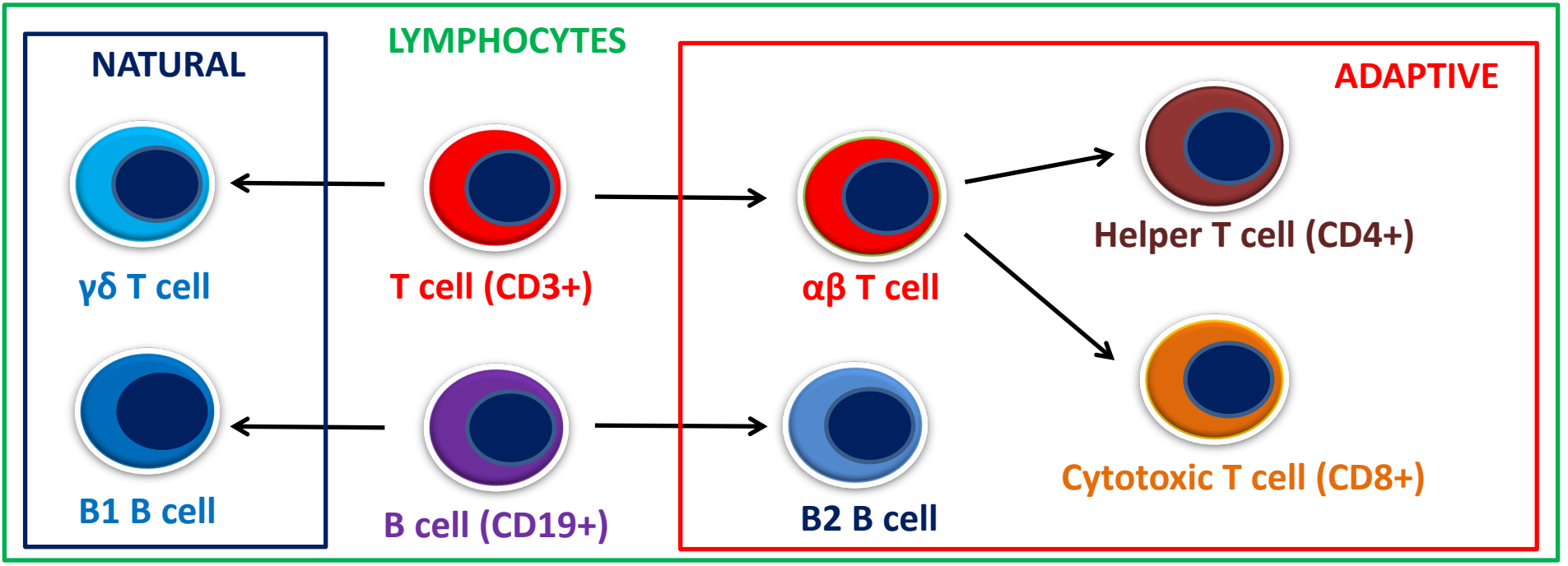


HAVE NO ANTIGEN-RECOGNTIION RECEPTORS

There is no difference in the morphology!

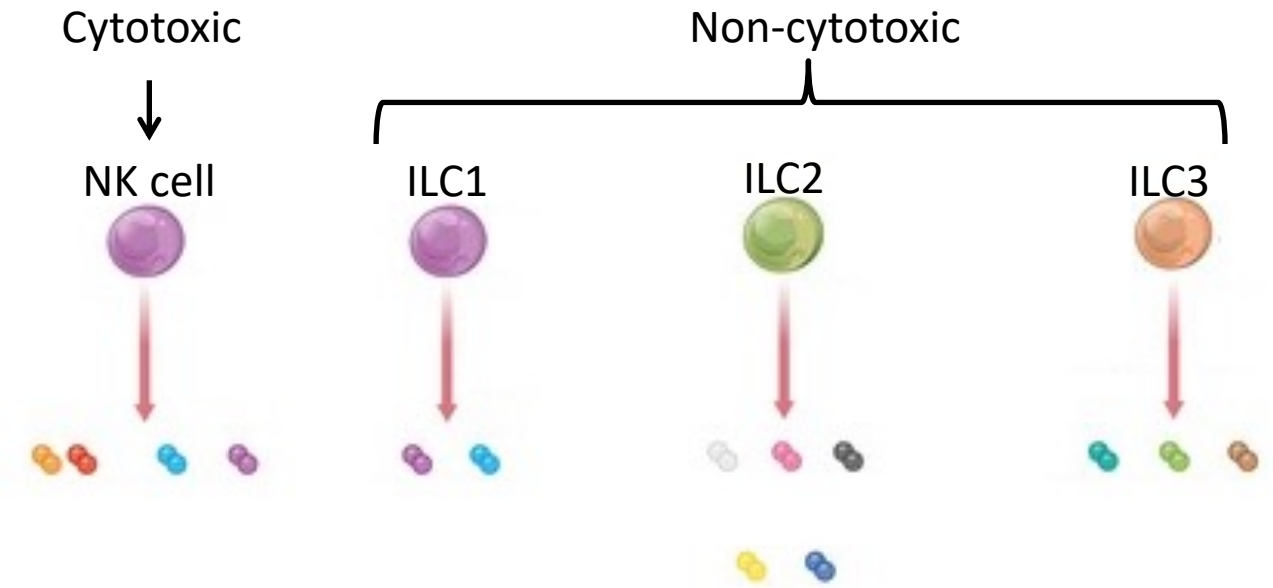
Lymphocyte

HAVE ANTIGEN-RECOGNITION RECEPTORS

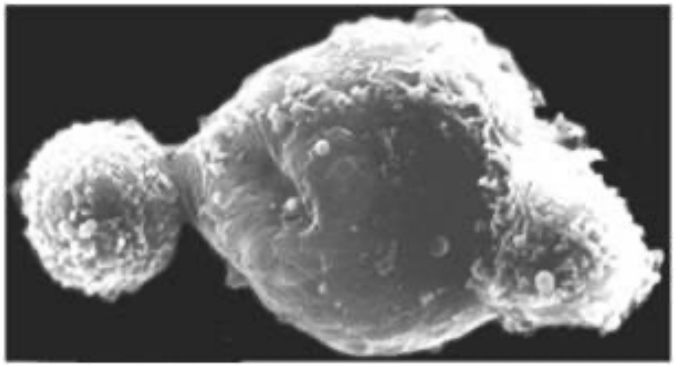


Innate lymphoid cells (ILC)

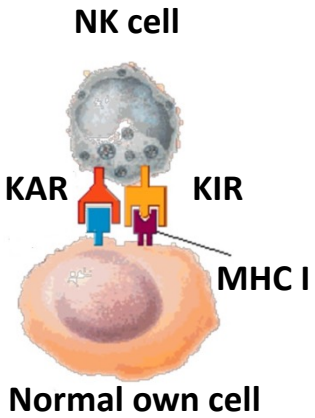
- They cannot be distinguished from lymphocytes based on their morphology but unlike adaptive lymphocytes they cannot recognize antigens. → **They have no antigen recognition receptors.**
- They are classified based on the cytokines they produce and the transcripition factors that are necessary for their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



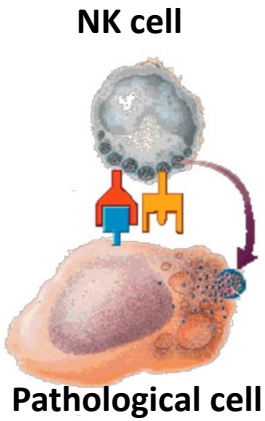
Natural killer cells (NK cells)



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



CELL IS LEFT ALIVE



CELL IS KILLED

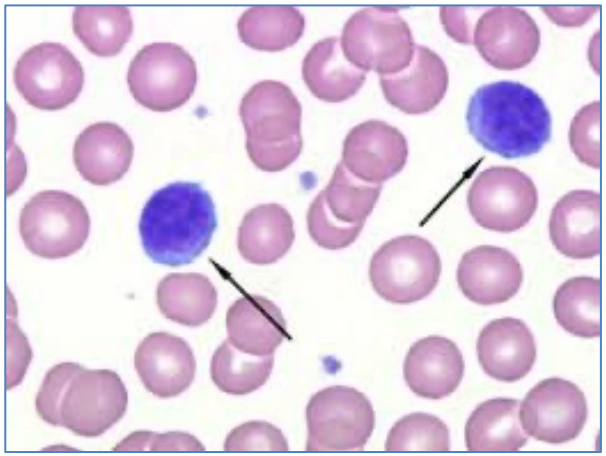
Blood lymphoid cells %:	**≈ 10**
Main function:	**Killing cells infected with intracellular pathogens, Killing cancer cells**
Recognition:	**KAR → killing the target KIR → sparing the target Fc receptor, Complement receptor**
Cytotoxicity:	**Fas-FasL, Perforin, Granzymes**
Produced mediators:	**Cytokines**
Fc receptor:	**FcγR (binds IgG)**
Characteristic marker:	**CD56**

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+)

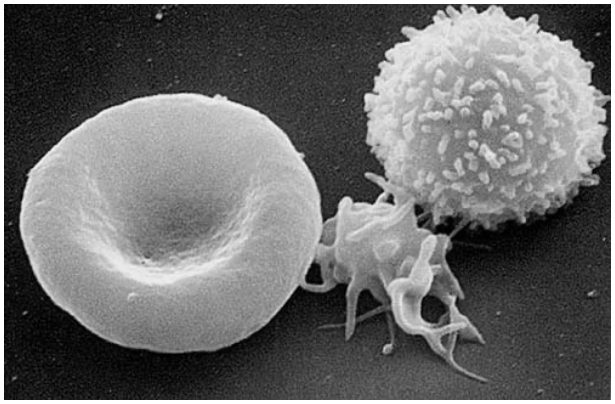
↓

Direct killing of target cell (infected or cancerous)

Helper T cell (CD4+)

↓

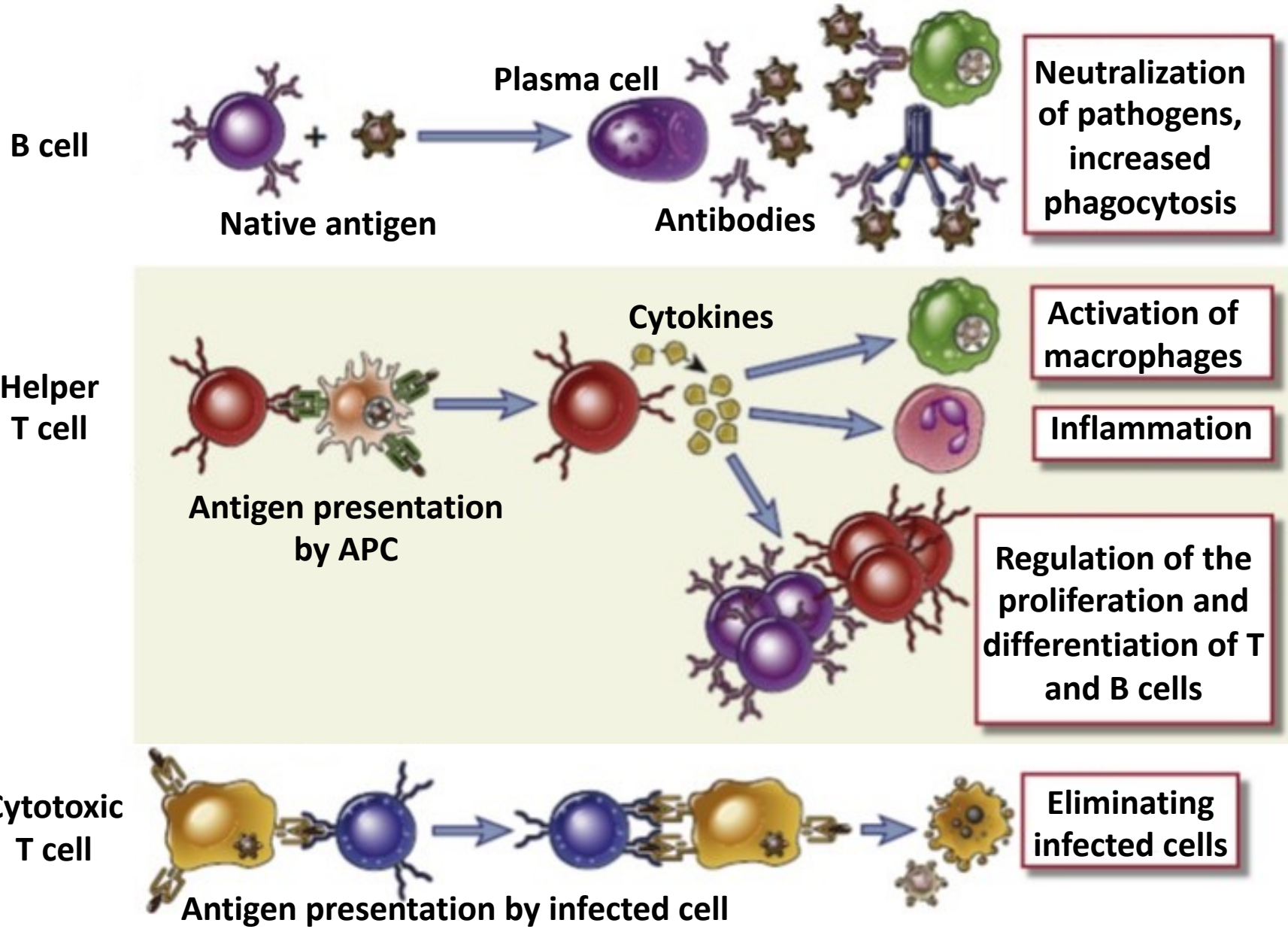
Regulation of the immune response



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

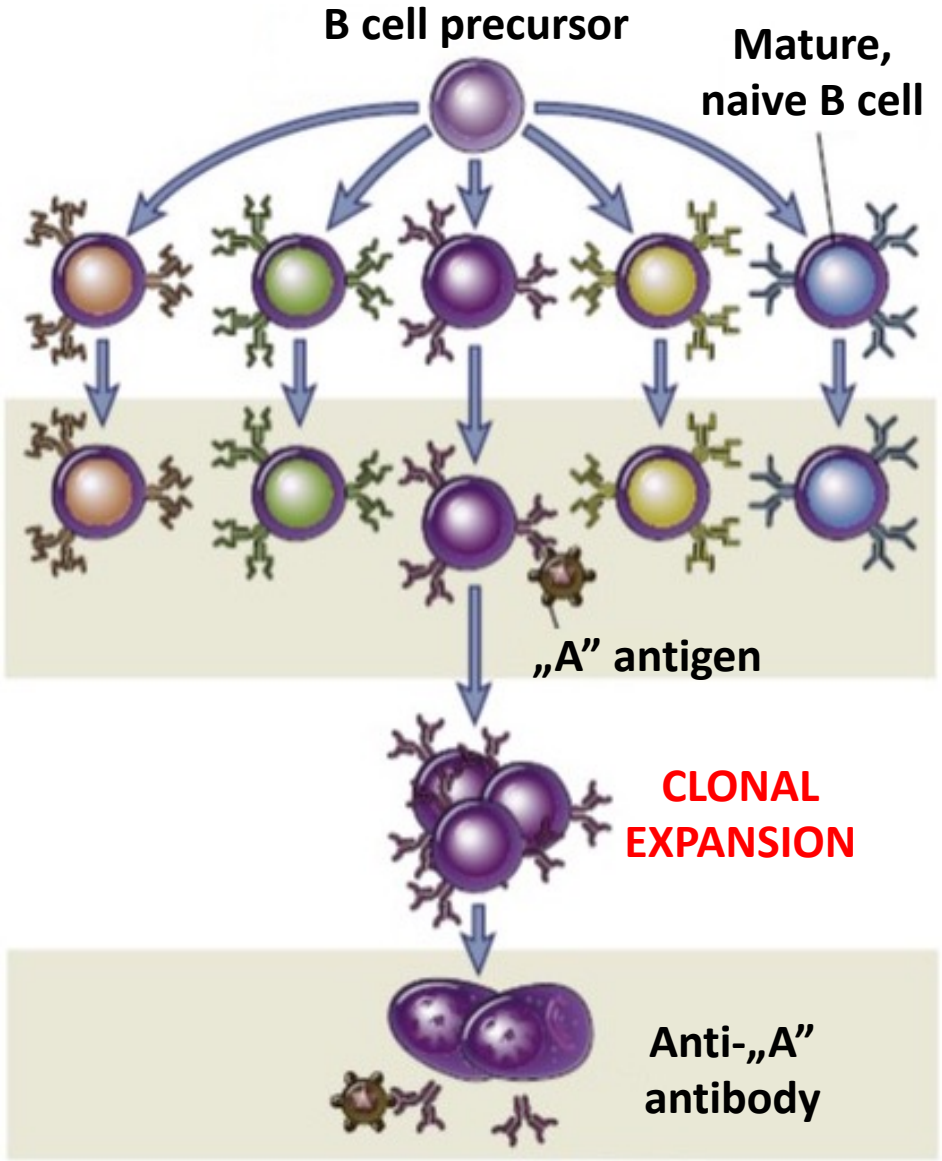


Clonality

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

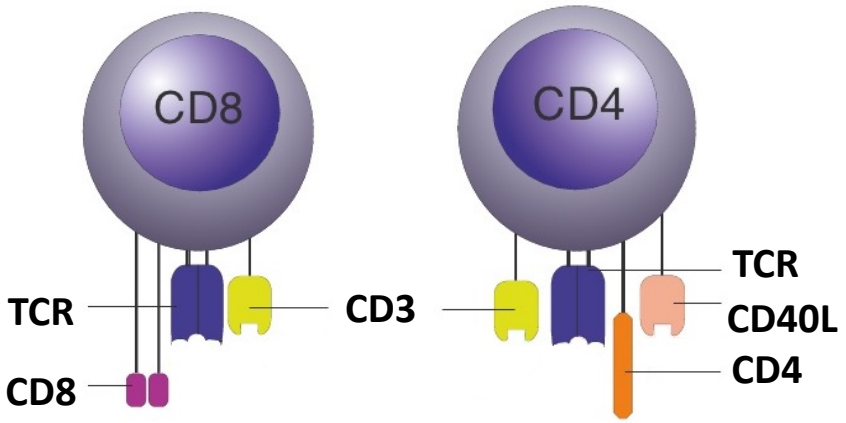
2. **Only those lymphocytes will become activated which recognize an antigen**. These selected cells will proliferate and produce **clones** of themselves with each sister cell having the same antigen-recognition receptor.

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



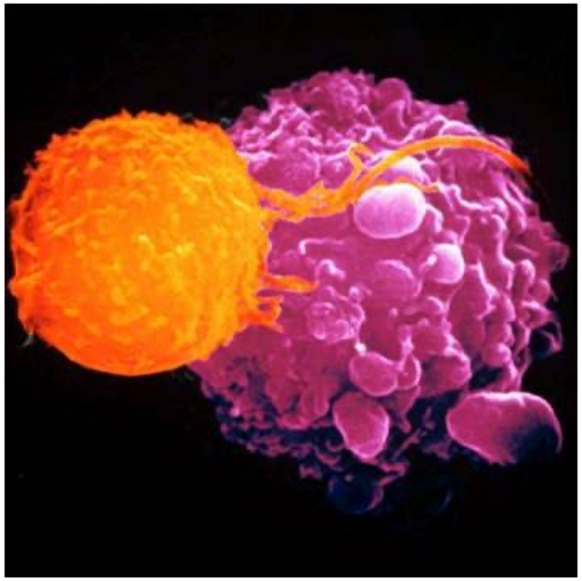
T cells

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)**



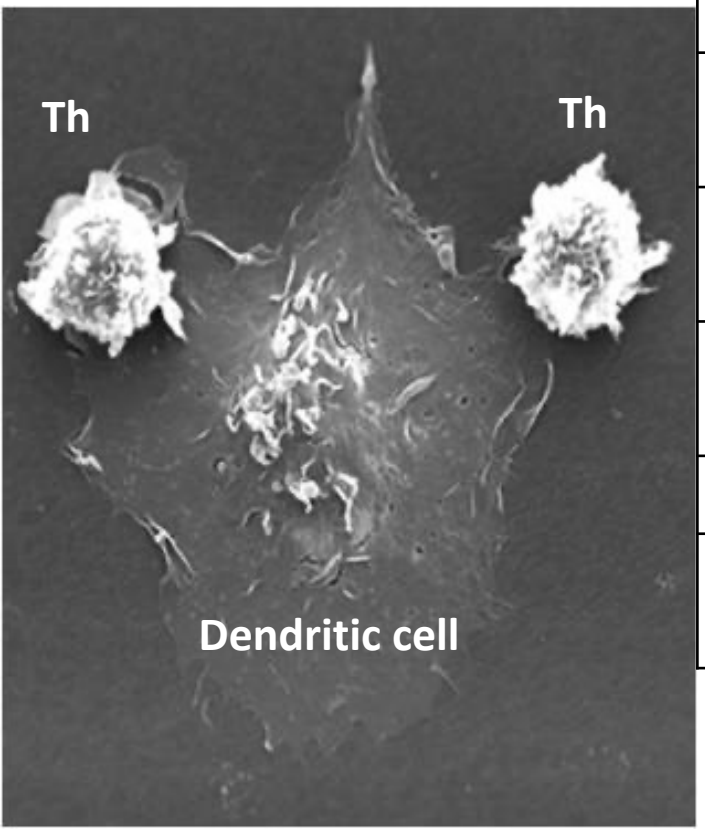
Cytotoxic T cells (Tc or CTL)

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-**



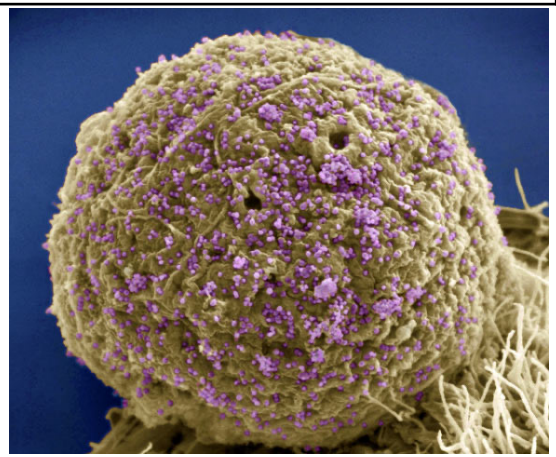
A cytotoxic T cell kills a cancer cell. (SEM image)

Helper T cells (Th)



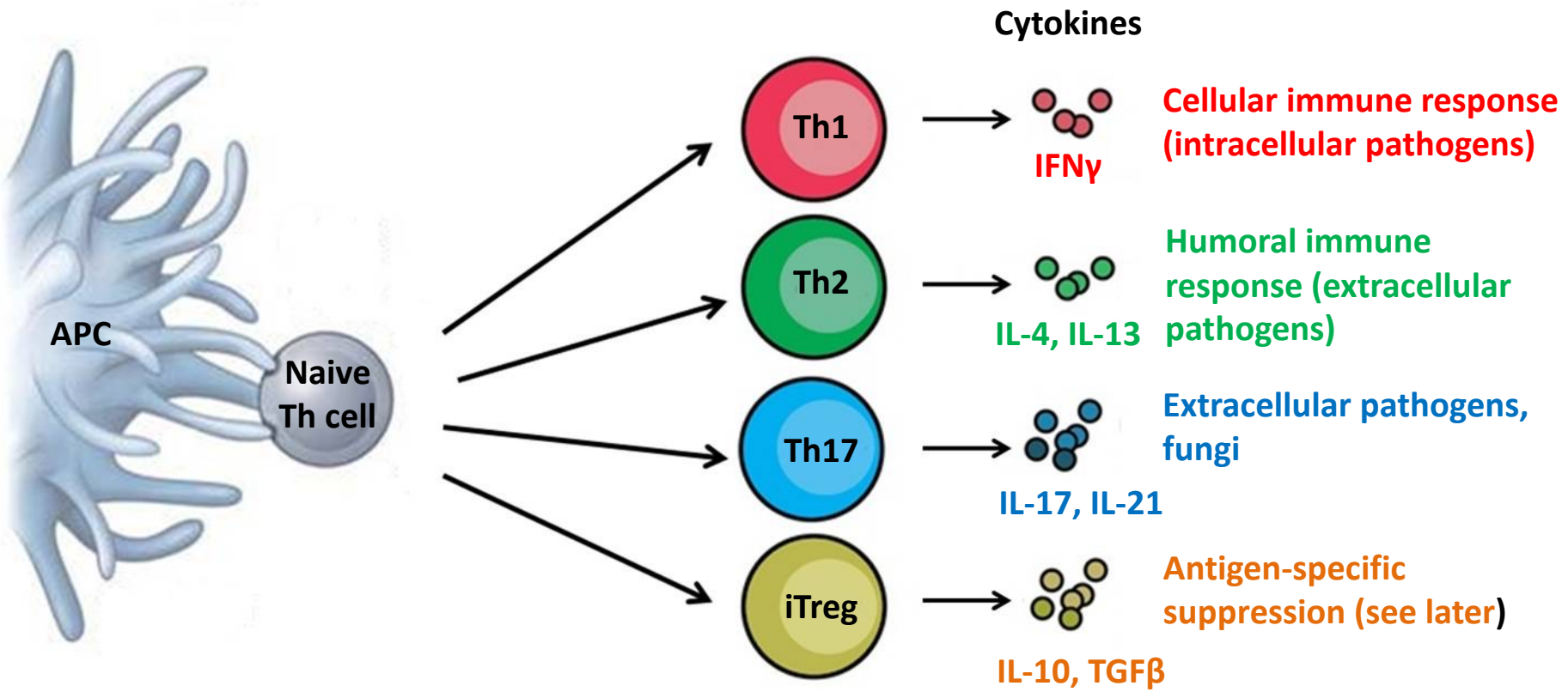
Two helper T cells attached to a dendritic cell. (Scanning electron microscopy image)

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)

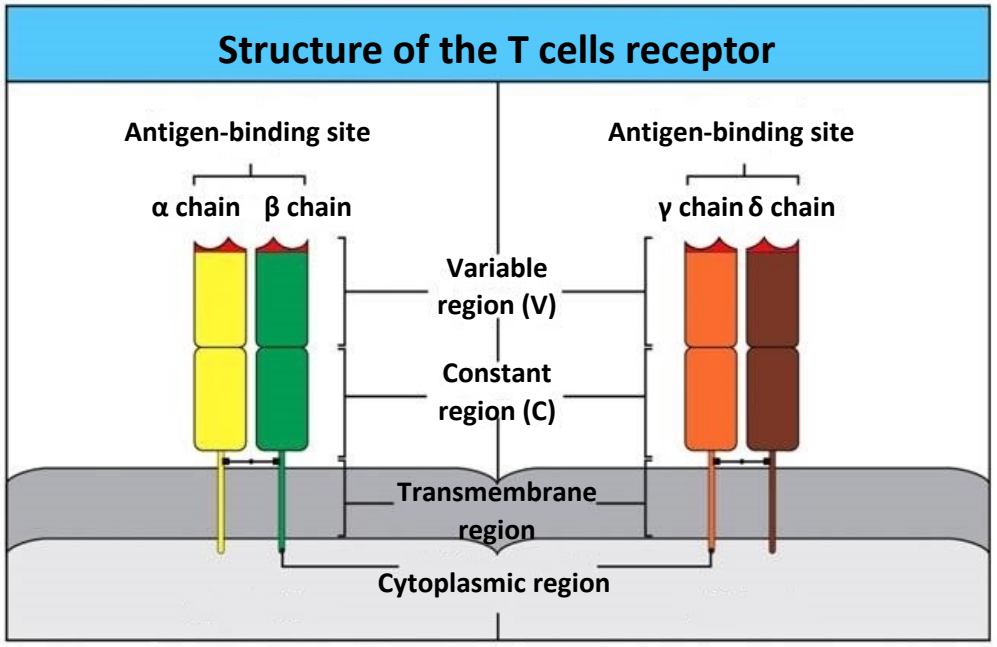
Main subtypes of Th cells



- 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+**

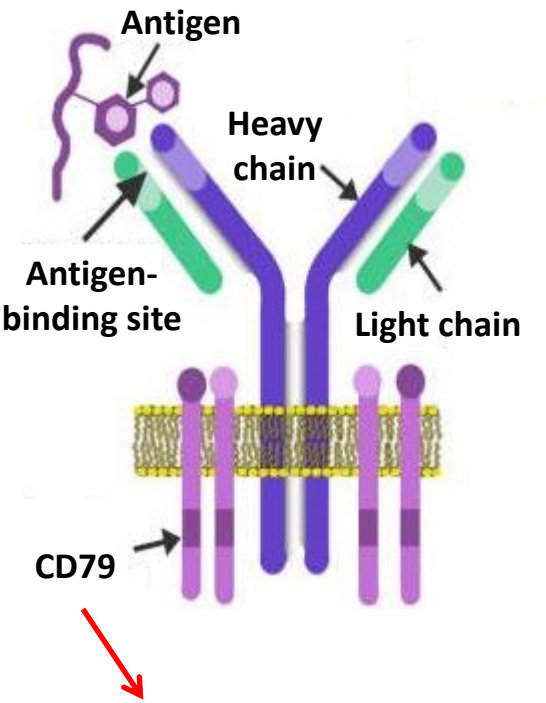
γδ T cells

- 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-recognition is **MHC-independent**.
- They mainly recognize **lipid antigens**.



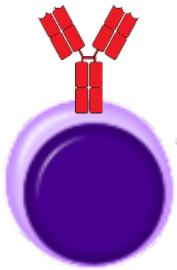
B cells

B cell receptor (BCR)



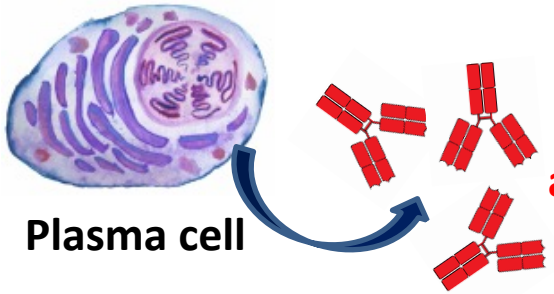
Signal transduction in the case of antigen binding

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

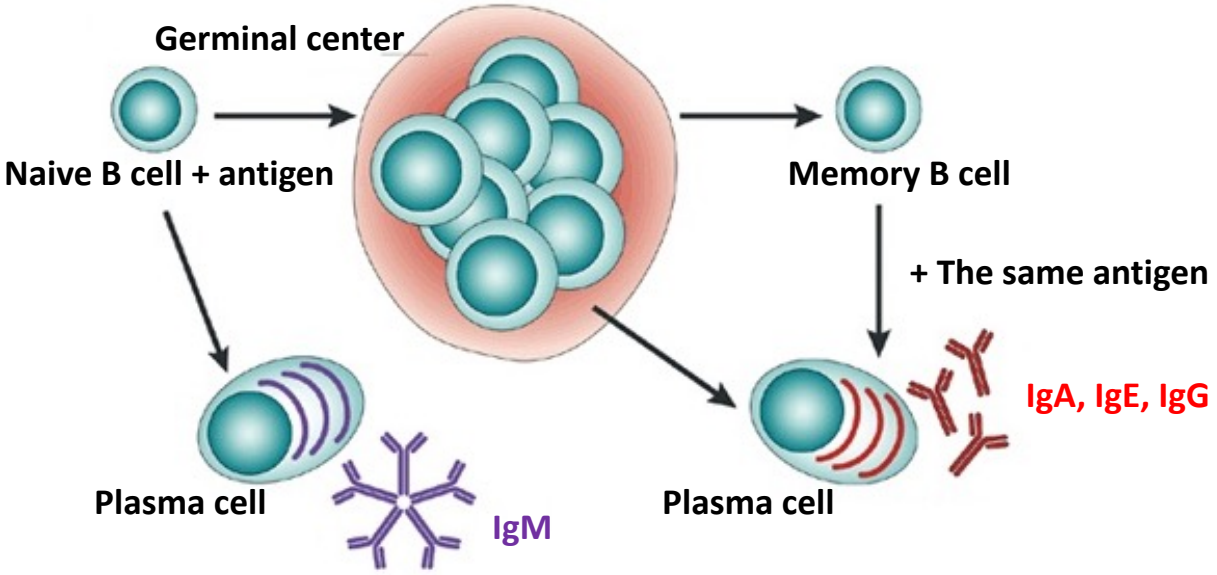


Plasma cell

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

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