What is the immune system?

- **The immune system is a complex structural and functional NETWORK composed by molecular and cellular elements.**
- **The main function of the immune system is managing of the individual integrity with defence against outside parasites and against modifications of self structures (by viral infections, tumorous transformations or other mutations).**
- **The immune network is formed by balance of attacking and tolerating type immune responses.**
- **The immune system has links to the other (endocrine, neural, metabolic) regulatory systems of the body in multiple levels influencing each other.**

Composition of the immune system

Innate

- None antigen specific
- No immunological memory
- Rapid reactivity
- Linear amplification of the reaction

Adaptive

- Antigen specific
- Immunological memory
- Activated after a latency
- Exponential amplification of the reaction

Natural

Innate-like immunity with adaptive features

Immunological recognition molecules

Innate	Natural	Adaptive
TLRs Heat shock proteins Complement	Invariant TcRs (both γδ and αβ) Natural (auto) antibodies	Immunoglobulins BcR TcR MHC I and MHC II

IMMUNOLÓGIAI ÉS BIOTECHNOLÓGIAI INTÉZET

2nd practice: Production of the cells of the immune system: hemopoesis (myeloid vs lymphoid differentiation). Types and functions of myeloid cells.

Basic Immunology

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

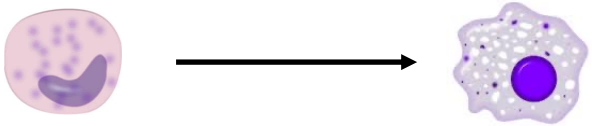
Cells of the innate and adaptive immune system

Innate:

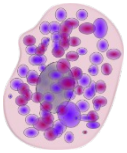
1. **Granulocytes:** 

   neutrophil, eosinophil, basophil

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

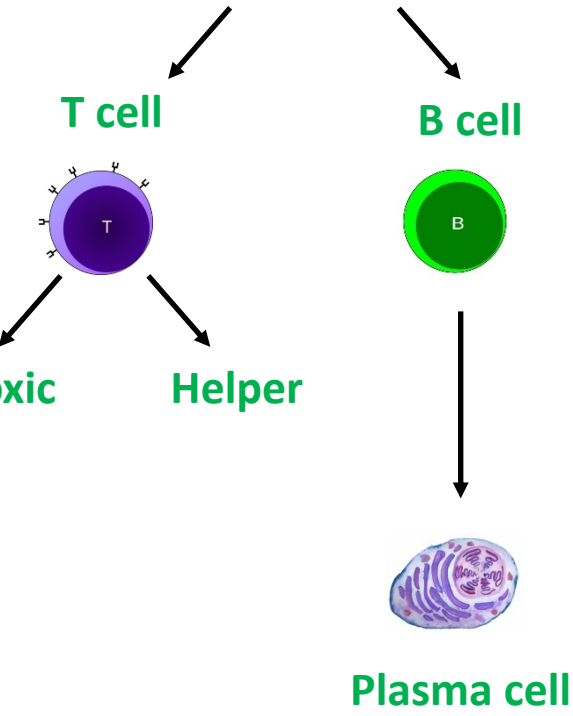


3. **Dendritic cell (DC)** 

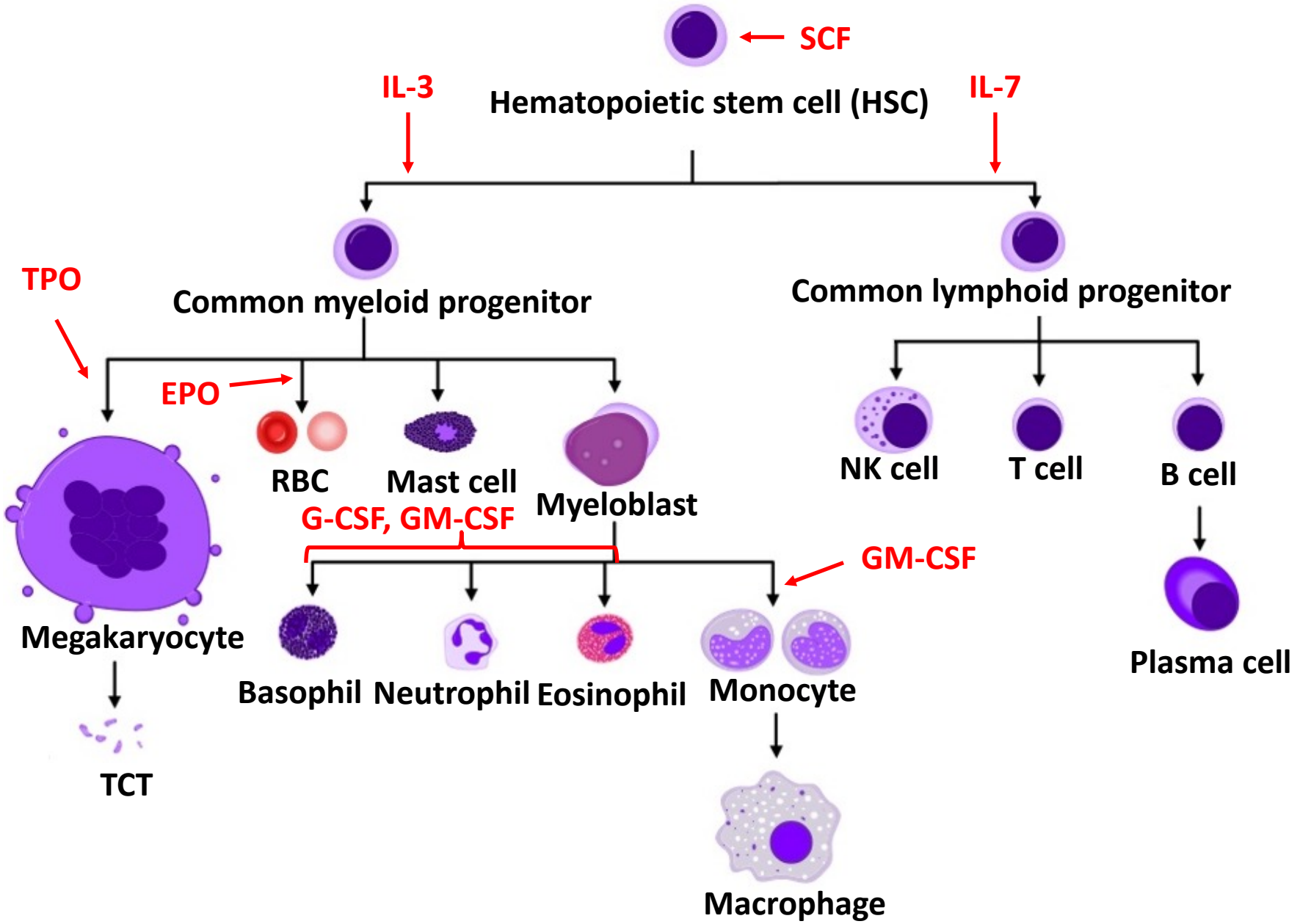
4. **Mast cell** 

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

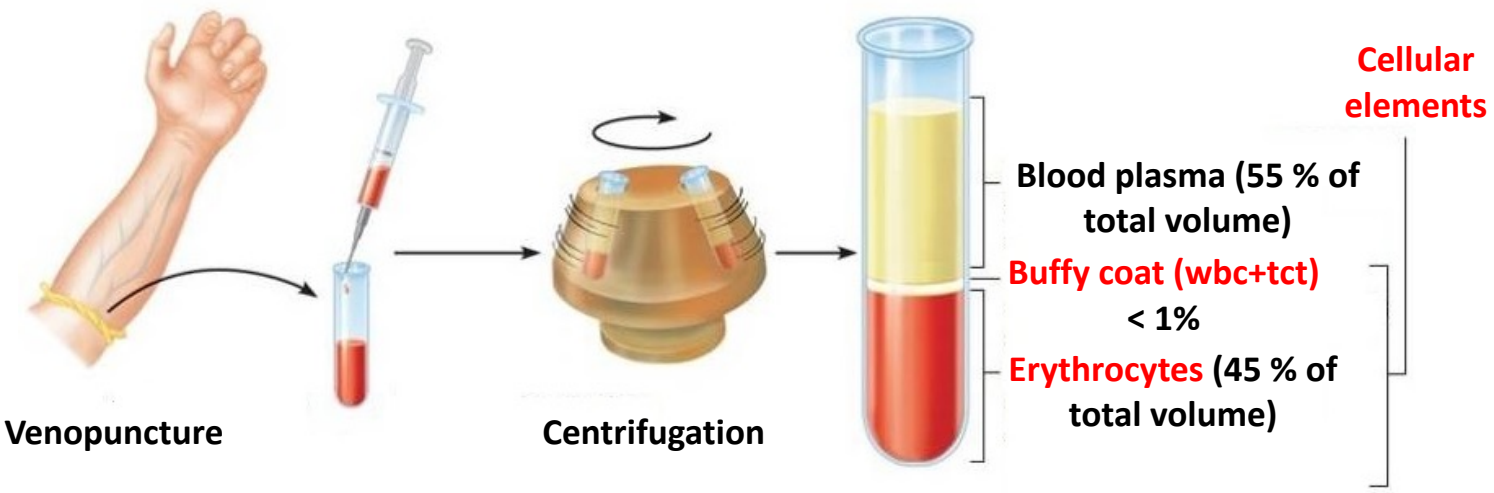
Adaptive:



Hematopoiesis

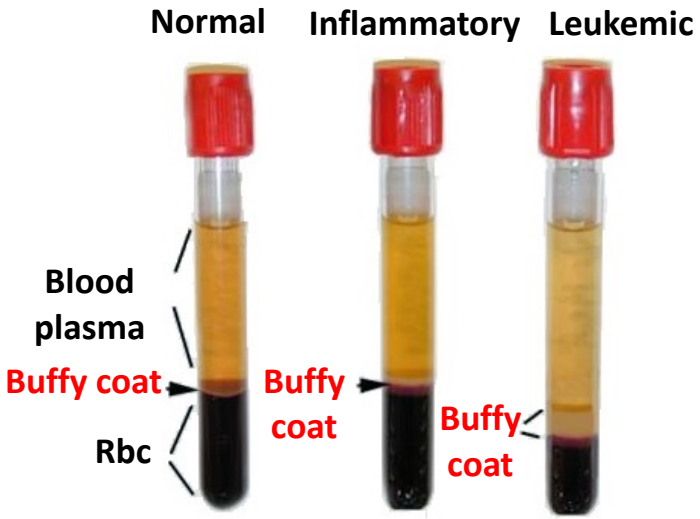


Components of the peripheral blood



Blood plasma: supernatant of anticoagulated blood
Blood serum: supernatant of coagulated blood

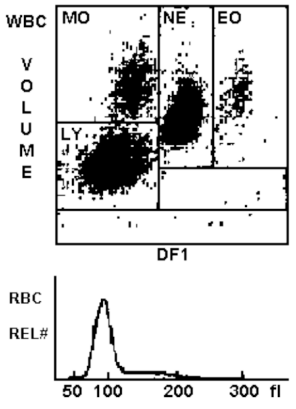
They are suitable for different laboratory tests, e.g. coagulation tests cannot be performed from blood serum.



Cellular components of blood

The laboratory blood count measurements are done by automated hematology analyzers based on the principles of **flow cytometry**. (see later)

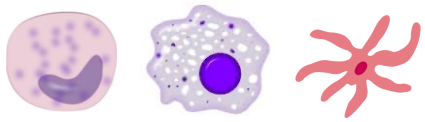
Qualitative blood count		
Cell type	Absolute number (cells/µl)	Ratio (%)
White blood cells	4500-10.000	
Neutrophil	2200-6300	55-70
Band form	120-450	3-5
Segment form	2000-6300	50-70
Eosinophil	80-360	2-4
Basophil	< 90	0-1
Monocyte	80-540	2-6
Lymphocyte	1000-3600	25-40



WBC	6.8	
	%	#
NE	52.6	3.6
LY	36.7	2.5
MO	7.8	0.5
EO	2.5	0.2
BA	0.4	0.0
RBC	5.29	
HGB	16.2	
HCT	47.0	
MCV	88.8	
MCH	30.7	
MCHC	34.5	
RDW	12.5	
PLT	179	
MPV	8.4	

Functions of the cells of the innate immune system

Neutrophil,
Monocyte,
macrophage
Dendritic cell (DC)

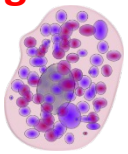


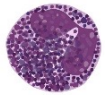
→ **Phagocytosis, Receptor-mediated endocytosis, Pinocytosis**

↓

Macrophage, DC activation → antigen presentation
Neutrophil → degranulation, NET formation

Basophil granulocyte
Mast cell



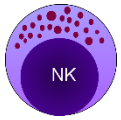


→ **Degranulation, inflammatory reaction**

Eosinophil granulocyte

→ **Defense against parasites → degranulation**

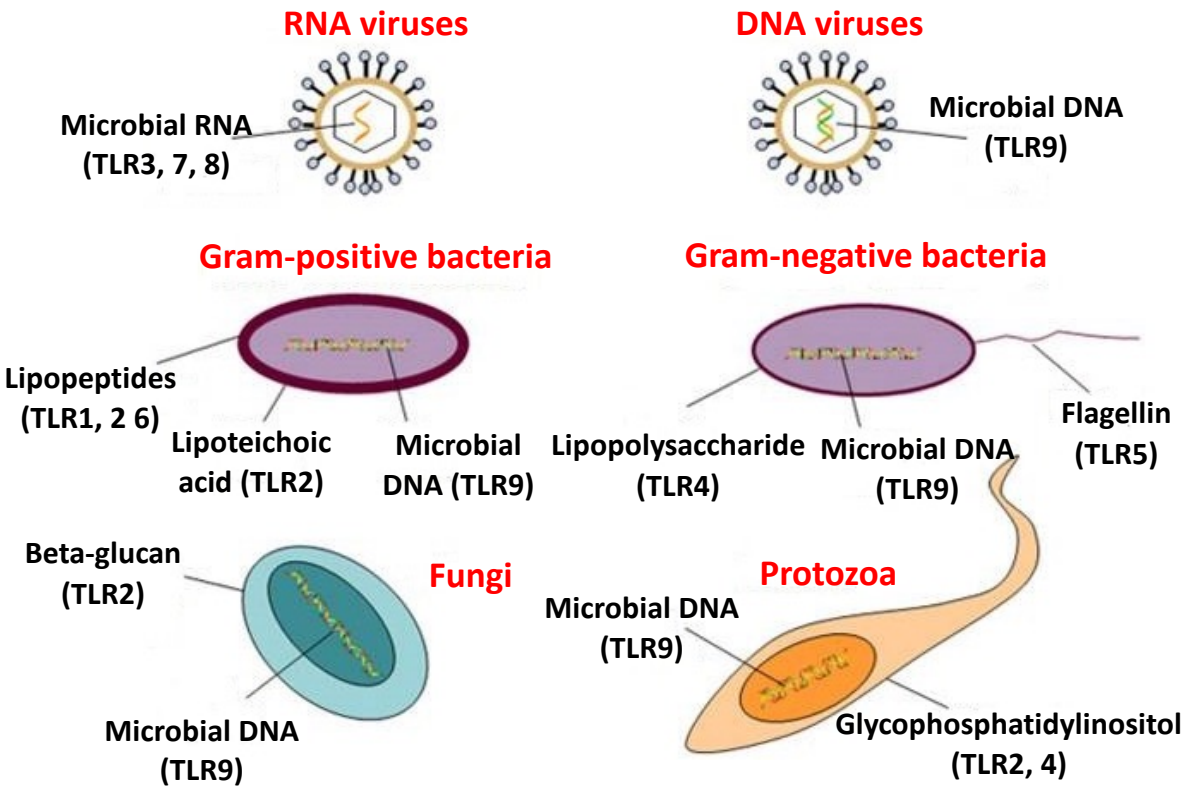
NK-cell (natural killer cell)



→ **Elimination of virus-infected and tumor cells**
Cytotoxic

Pattern-recognition

- **PAMP** (pathogen-associated molecular pattern): Molecules frequently found on pathogens which can be recognized by cells of the innate immune system.



Examples of PAMPs:
- **LPS (lipopolysaccharide)**
- Beta-glucan
- dsRNA (double stranded RNA)
- CpG-DNA (microbial DNA)
- Flagellin

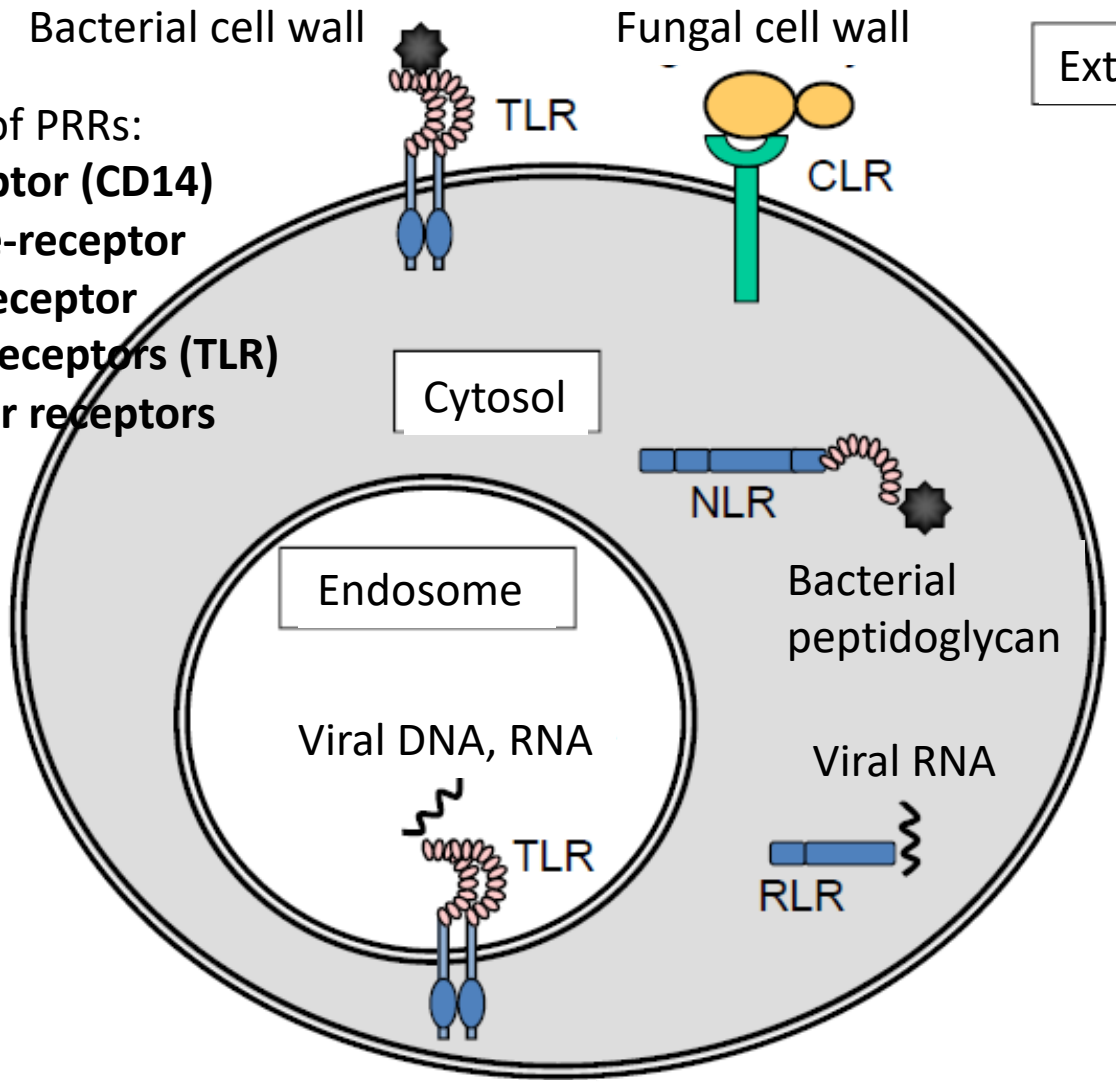
Examples of PRRs:
- **LPS-receptor (CD14)**
- **Mannose-receptor**
- **Glucan-receptor**

} C-lectin-R

- **Toll-like receptors (TLR)**
- **Scavenger receptors**

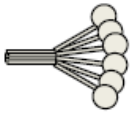
- **PRR** (Pattern-recognition receptor): Their genes do not rearrange; all our innate immune cells express the very same PRRs throughout our entire life.
- Some of the receptors are found on the **cell surface**, others are **intracellular**.

Pattern recogntion molecules



s of PRRs:
ceptor (CD14)
se-receptor
-receptor
e receptors (TLR)
ger receptors

Plasma proteins
-Complement system
-Collectins
-Pentraxins (eg. C-reactive protein)



PRR

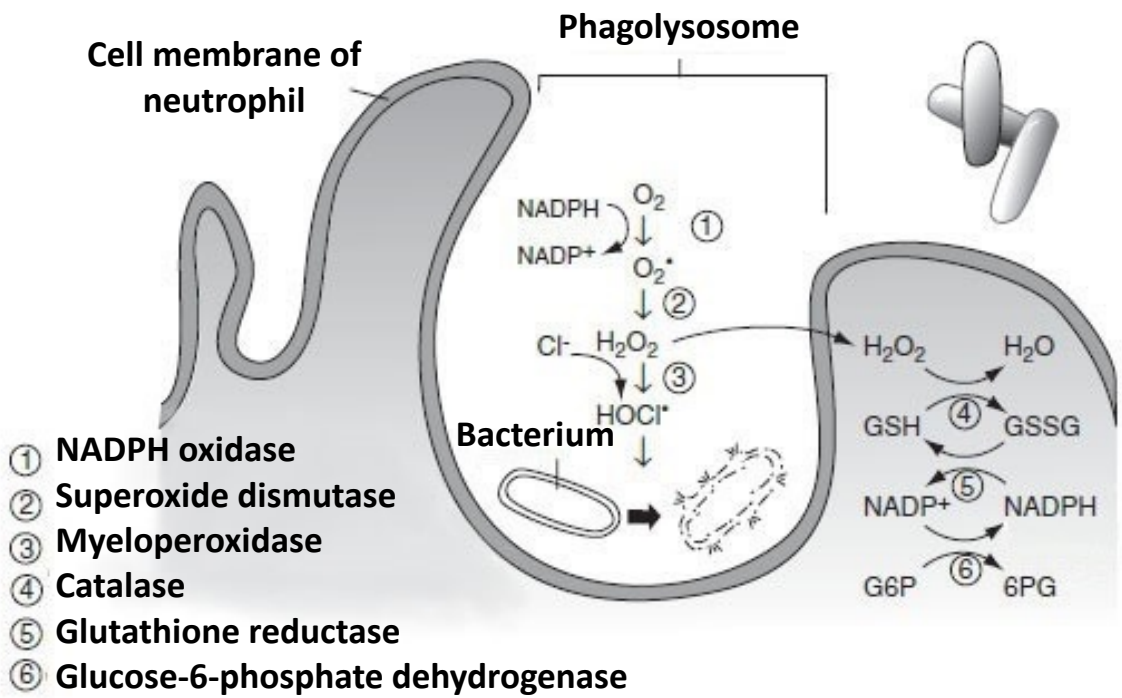
- No clonal distribution
- Less than 100 type
- Same on every celltype

TLR: Toll-like receptor
CLR: C-type lectin receptor

NLR: NOD-like receptor
RLR: RIG-like receptor

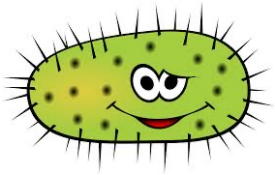
Based on A. Abbas

Respiratory burst



1. Phagocytosis (phagosome)
↓
2. Phagosome + lysosome containing enzymes and reactive oxygen species → **phagolysosome**
↓
3. The enzymes and the reactive oxygen species kill the pathogen

Neutrophil

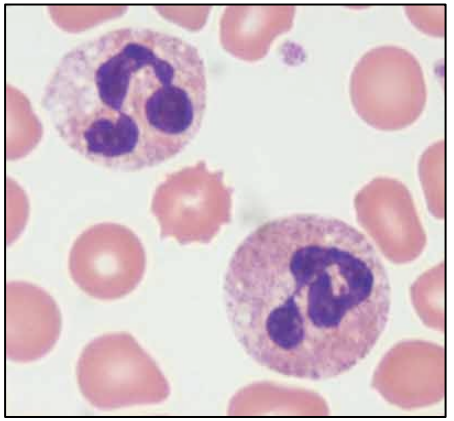


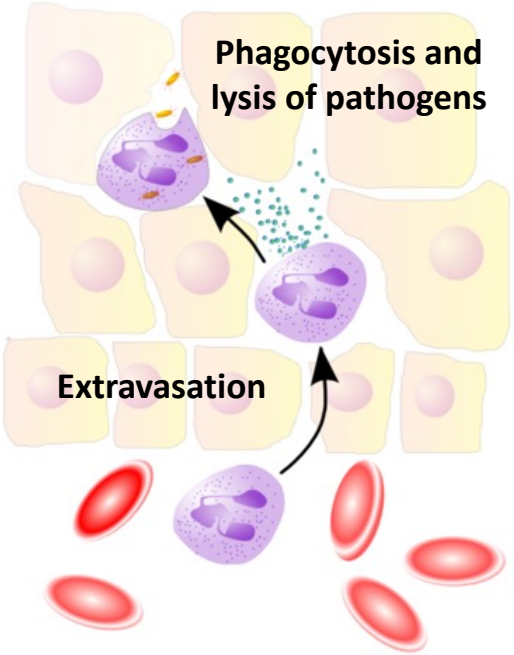
Pathogen bacterium

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





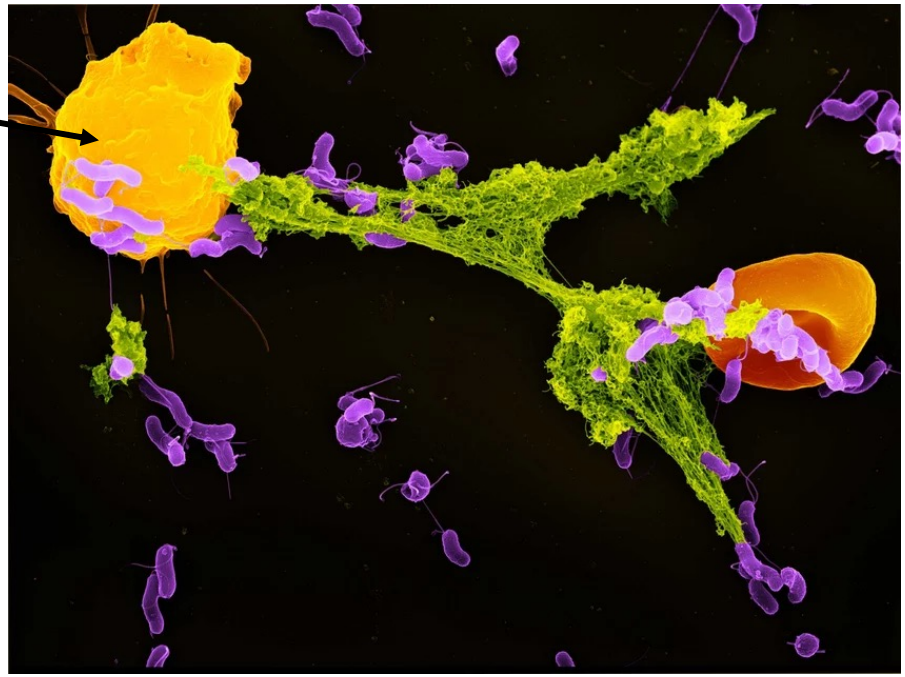
Degranulation

Neutrophil granulocytes are able to release the content of three granule types in their environment. Enzymes found in these have antimicrobial characteristics.

Granule type	Protein
asurophil (or primary)	Myeloperoxidase (MPO), baktericid/permeability increasing protein (BPI), defensins, protein degrading neutrophil elastase and catepsin G
specific (or secondary)	Alkalic phosphatase, lisozyme, NADPH-oxidase, collagenase, lactoferrin, histaminase, catelicidin
tertiary	catepsin, gelatinase, collagenase

NET: Neutrophil Extracellular Trap

Neutrophil granulocyte



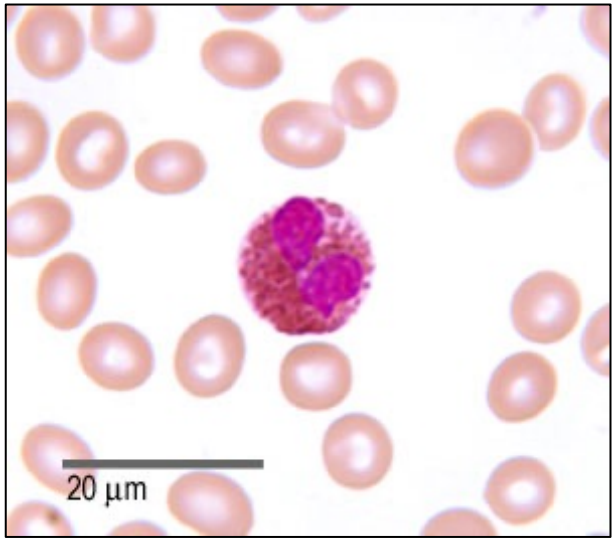
Violet: Bacterium
Green: NET
Orange: RBC

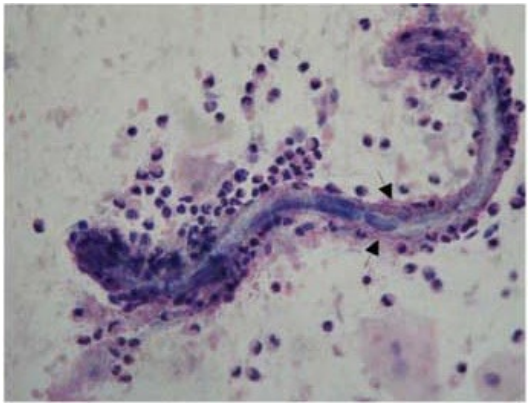
In 2004 it was discovered that the activated neutrophils release network-like DNA structures against bacteria. These so called **extracellular traps (*neutrophil extracellular trap*, NET**) are composed from materials of chromoses, chromatin and serin-proteases. They suppose that these are able to destroy bacteria themselves; moreover, they can inhibit the physical spreading of the bacteria.
In systemic sepsis NETs can be formed in the circulation, too.
It was observed that they also help blood clotting.

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

Red: Only possible after the activation of the adaptive immunity

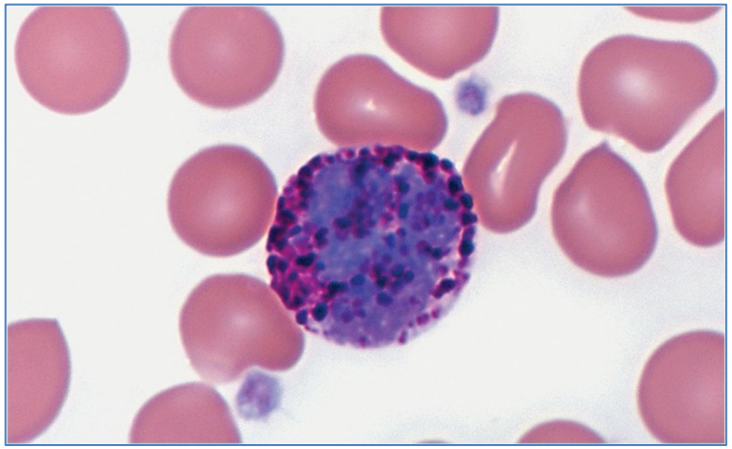


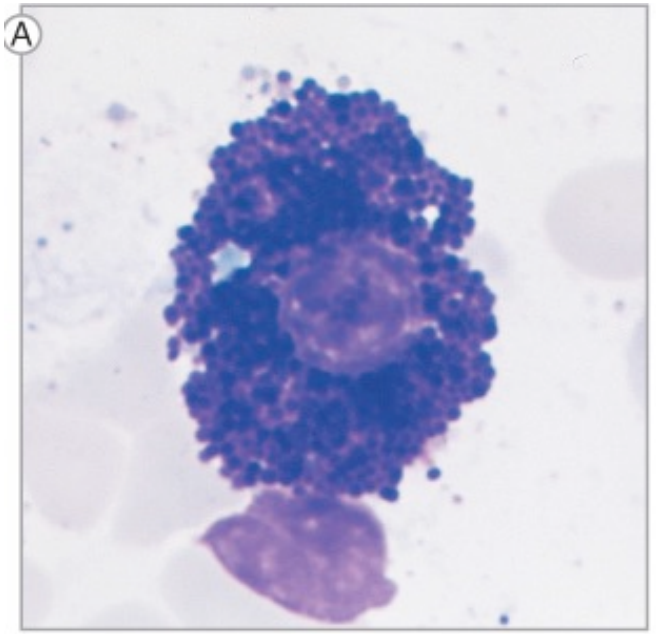


Eosinophils surrounding a *Strongyloides stercoralis* larva. (sputum from a parasitic pneumonia case)

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**



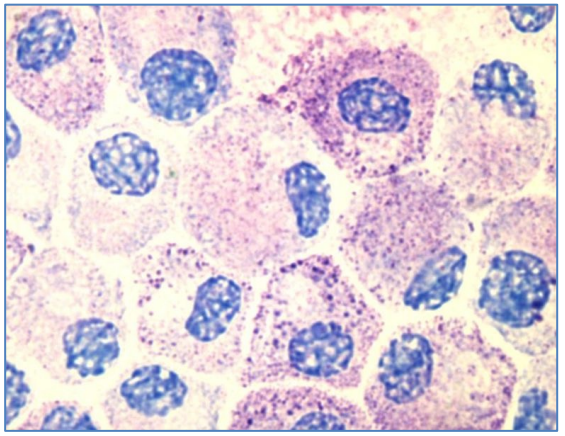


Red: Only possible after the activation of the adaptive immunity

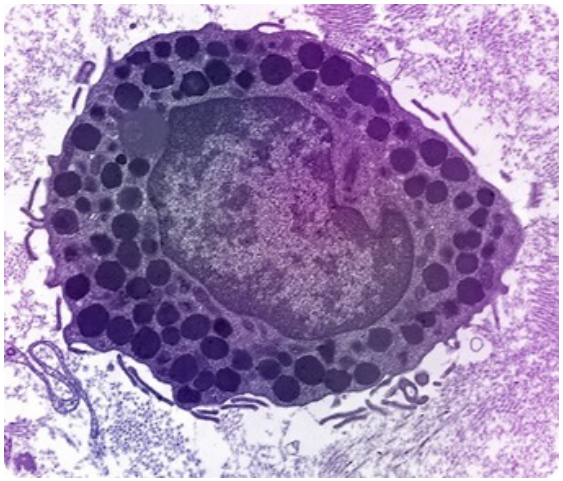
Mast cell (mastocyte)

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

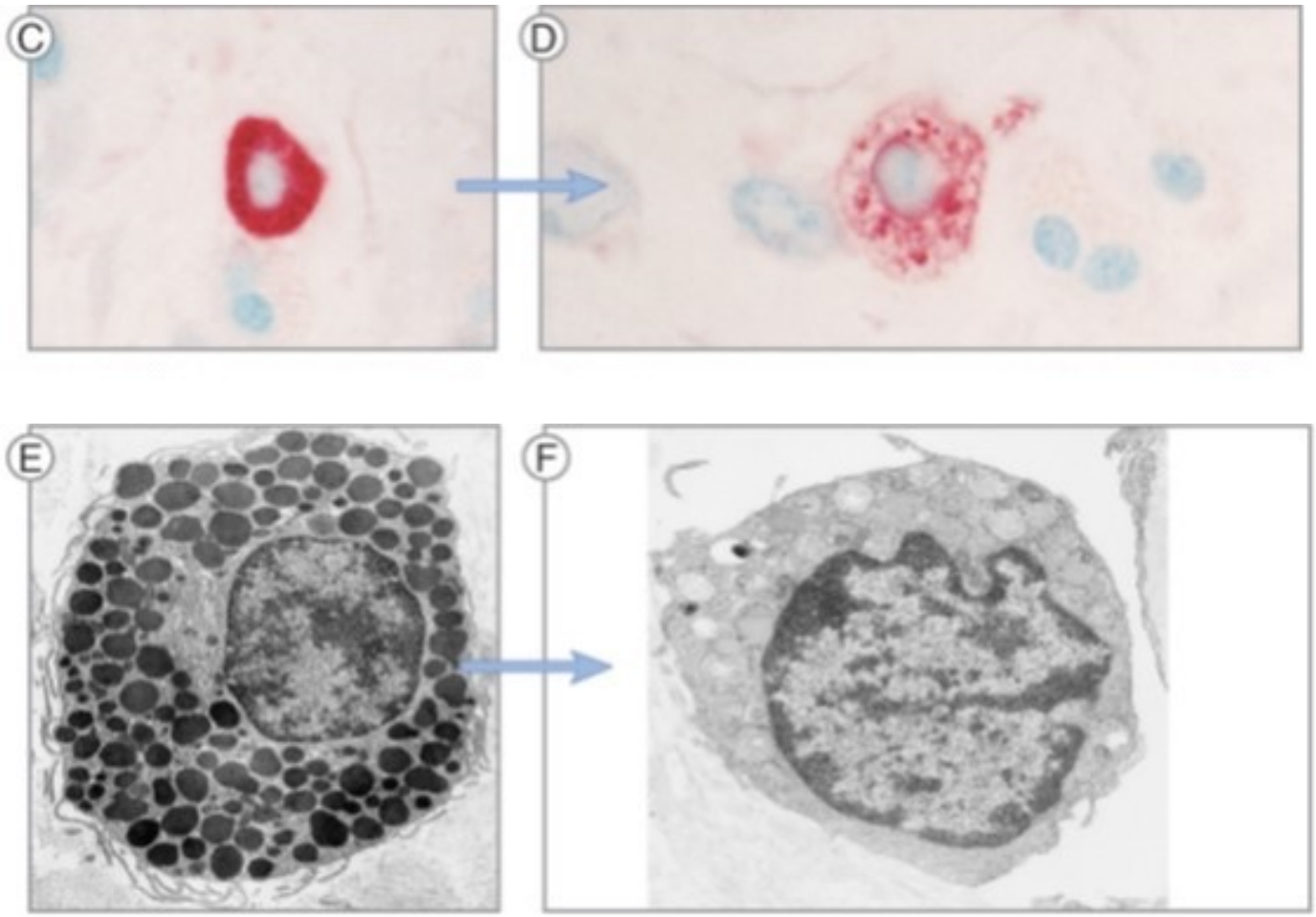


Cultured mast cells
(Toluidine blue staining)



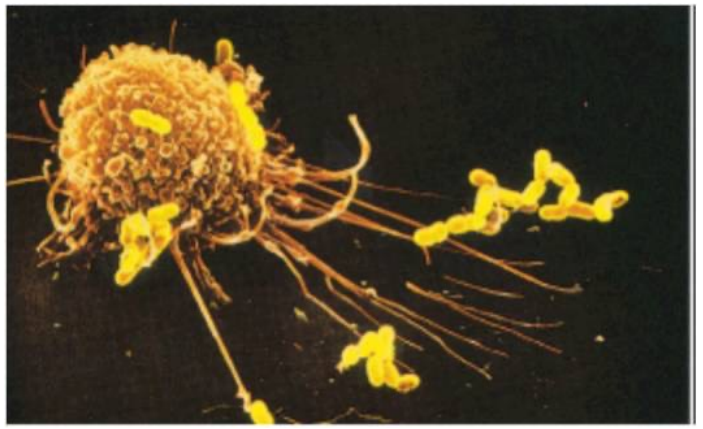
Mast cell (electron microscopy image)

Quick degranulation of a mast cell

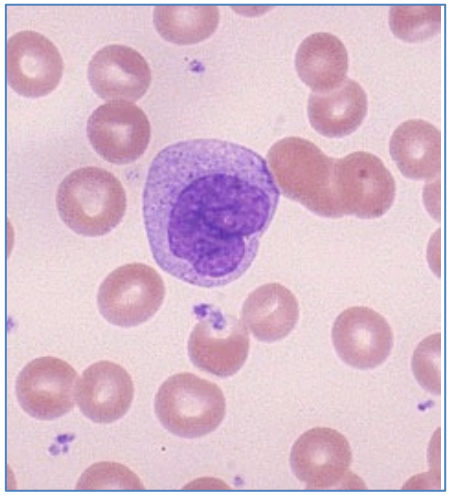


Monocyte, macrophage

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



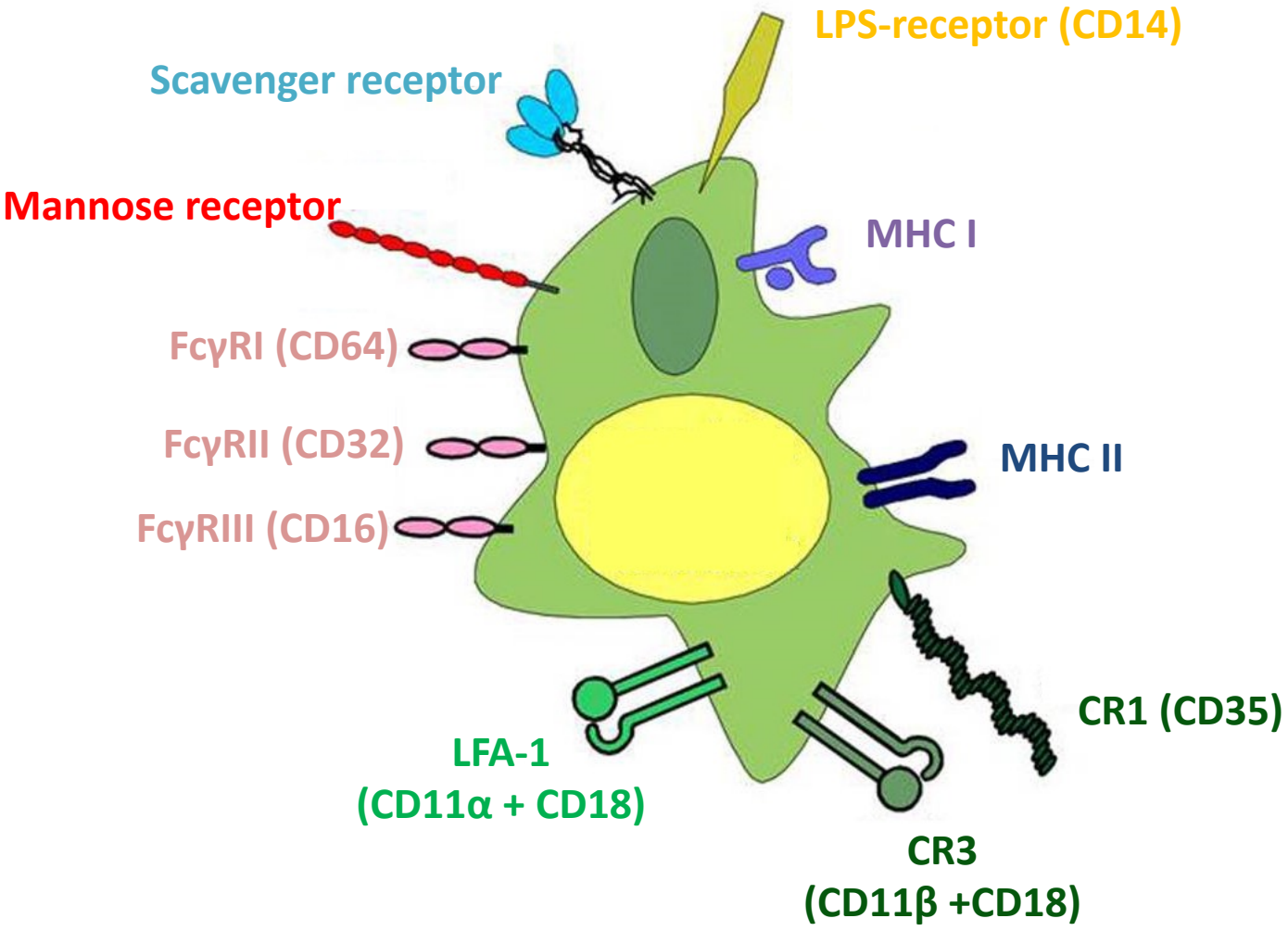
A macrophage ingesting (phagocytosing) bacteria (SEM image)



A monocyte in a blood smear

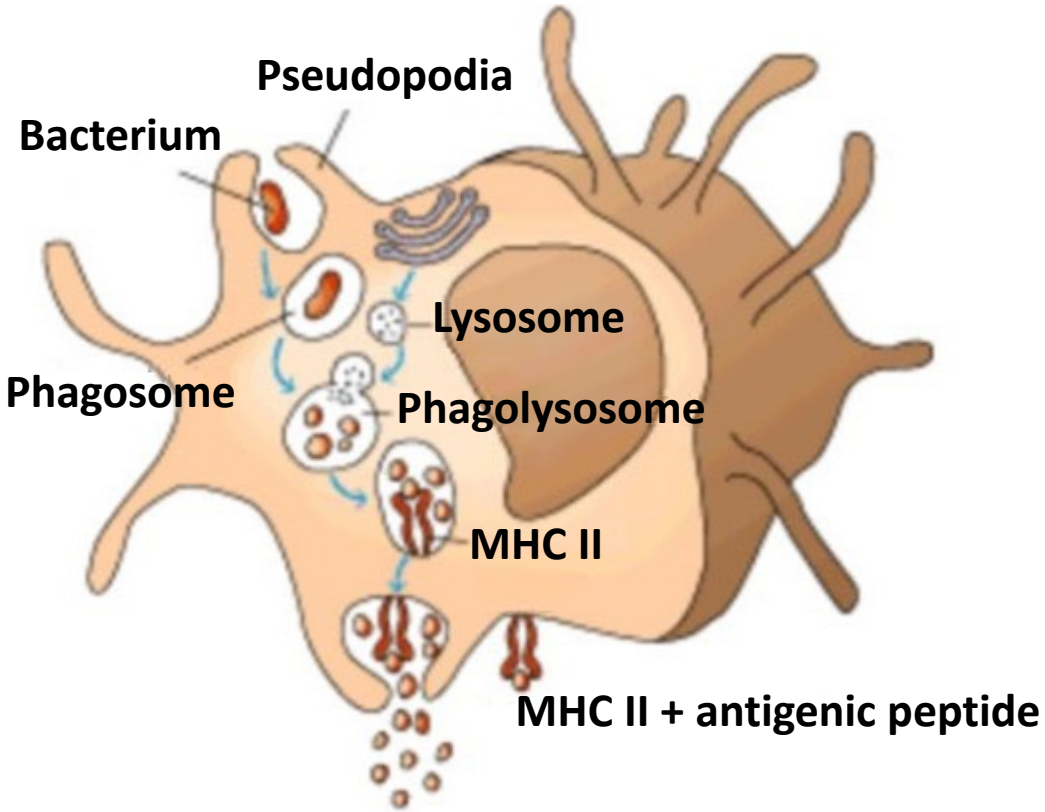
Red: Only possible after the activation of the adaptive immunity

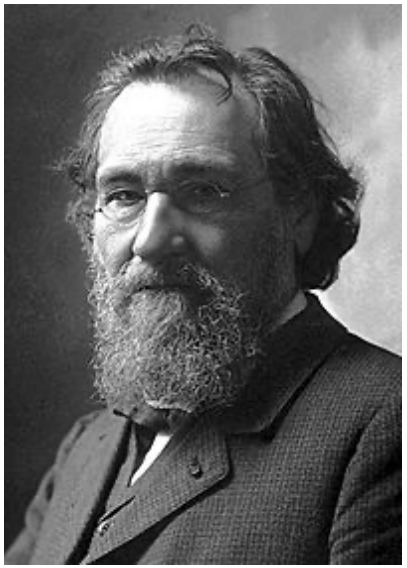
Surface molecules of macrophages



Phagocytosis

Phagocytosis and antigen presentation of macrophages:

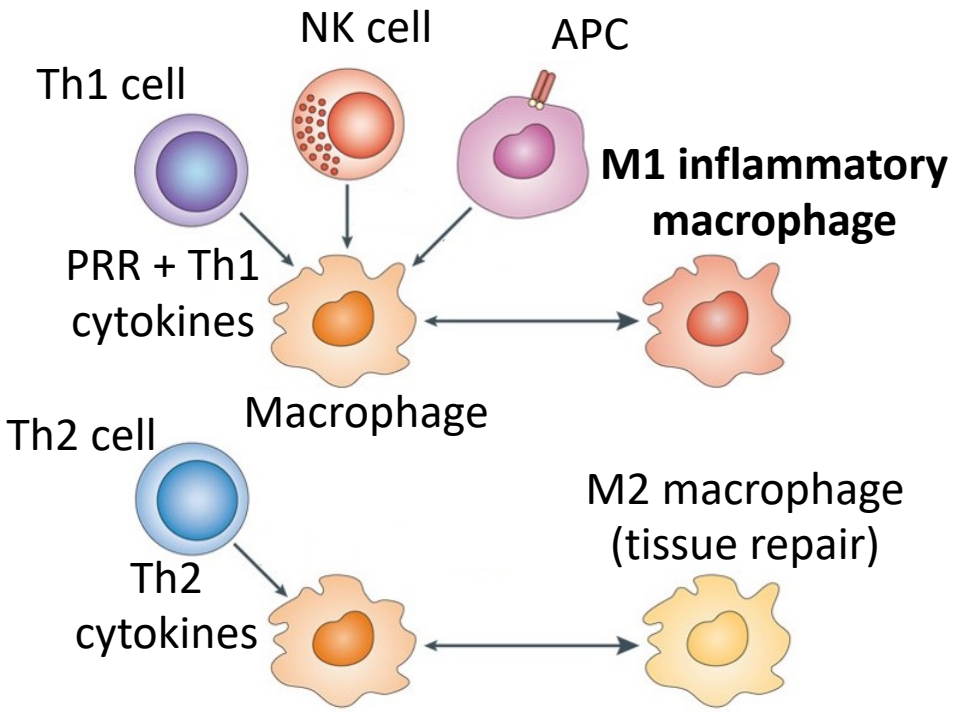




Ilya Ilyich Mechnikov who discovered macrophages and the phenomenon of phagocytosis.

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

Activation of macrophages

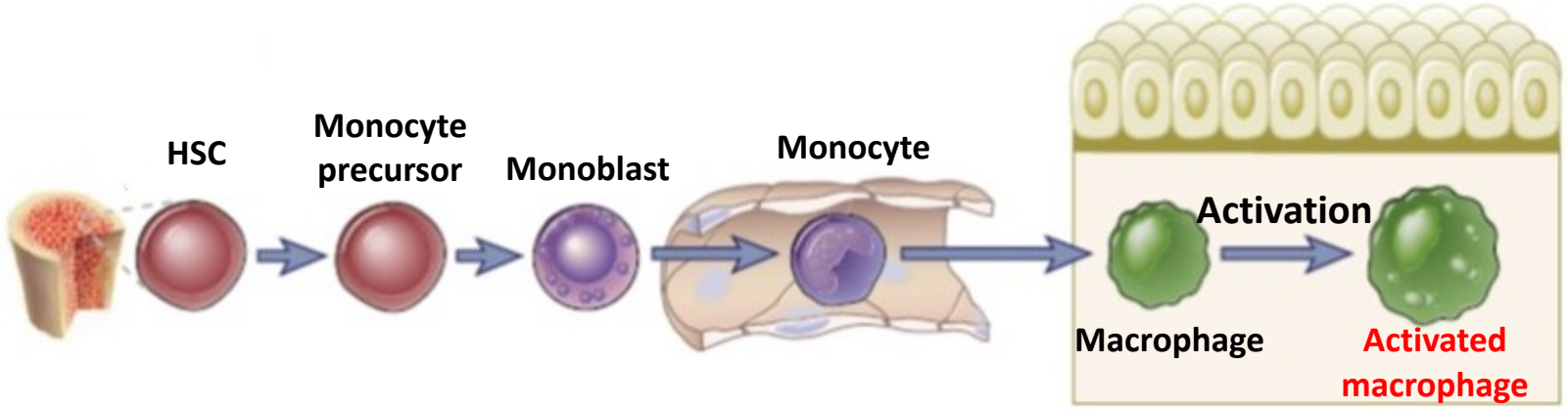


EFFECTS OF CLASSIC ACTIVATION[10.]:

- **Increased phagocytosis**
- Production of **inflammatory cytokines** (see later)
- Production of **chemokines**
- **Increased expression of MHC II**
- **They express costimulatory molecules** on their surface (e.g. CD40, CD80, CD86)

HYPERACTIVATED M1 MACROPHAGE:

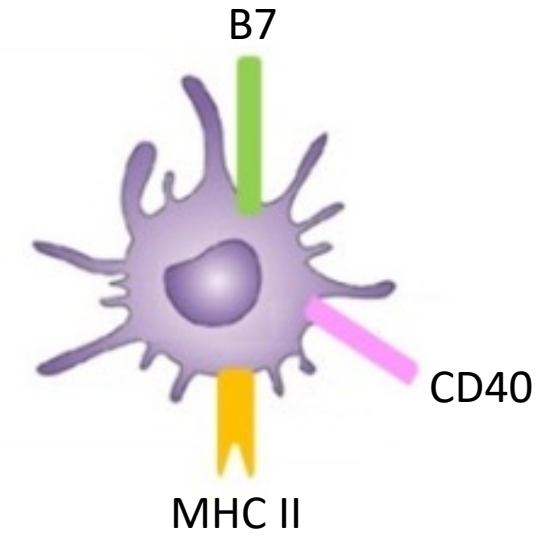
- **Has anti-tumor activity**

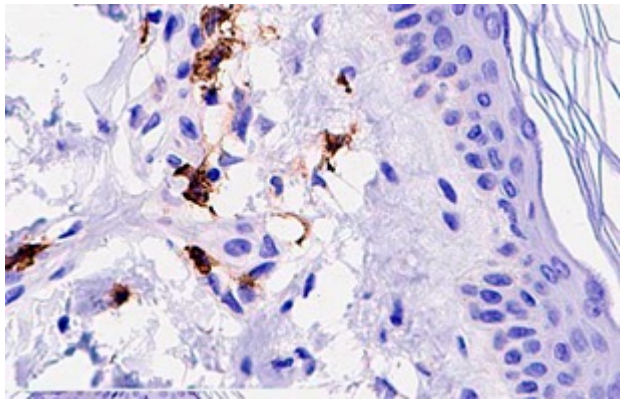


Dendritic cell (DC)

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

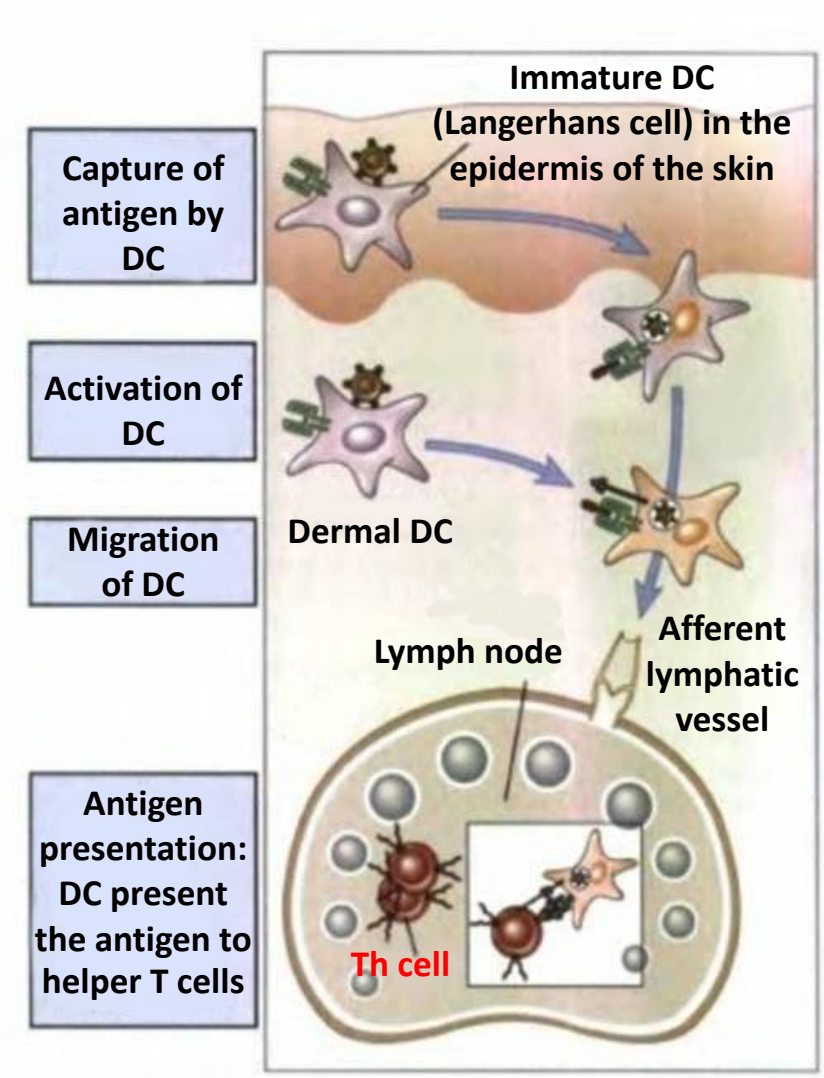
Red: Only possible after the activation of the adaptive immunity





Dendritic cells in the skin (DC-SIGN immunoperoxidase staining, abcam)

Function of dendritic cells



1. They **capture antigens** in the tissues with **PRR**s
2. They transport the captured antigen to the draining **lymph node**
3. They present the antigen on **MHC II** molecules to **helper T cells**

Antigen presentation of resting, „immature" DCs:
MHC II^{low}/CD80 ^{low} /CD86 ^{low} (no costimulation)

↓

TOLERANCE

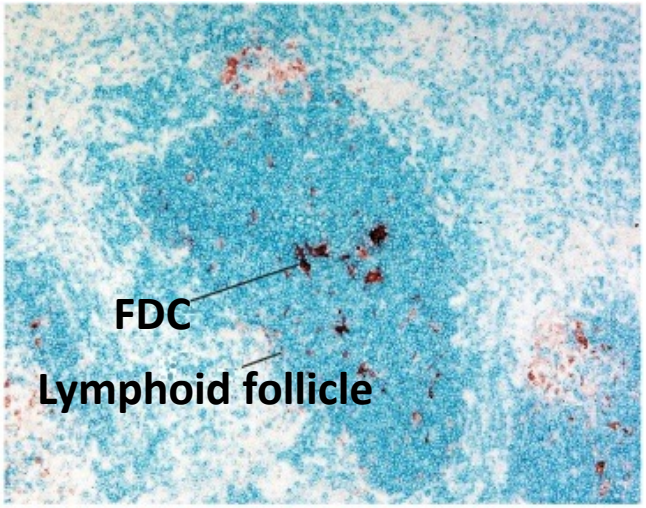
Antigen presentation of DCs activated by PRRs:
MHC II^{high}/CD80 ^{high} /CD86 ^{high}/CD40+

↓

IMMUNE RESPONSE

Follicular dendritic cell (FDC)

Found in:	Lymphoid follicles
Origin:	Non-hemopoetic (connective tissue stroma)
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