II. Innate Immunity

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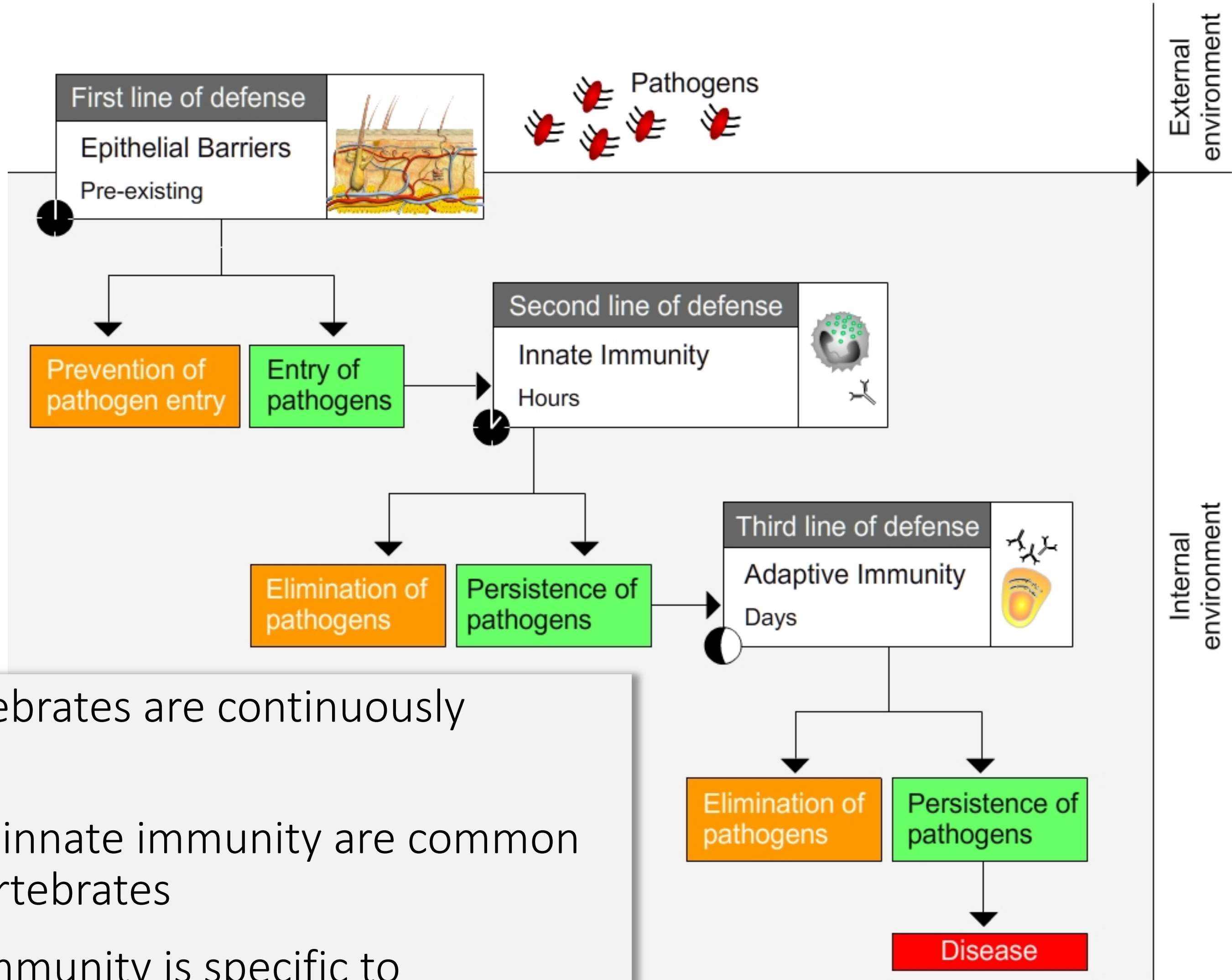
Three lines of defence against infection

1. Epithelial barriers
2. Innate Immunity
3. Adaptive Immunity

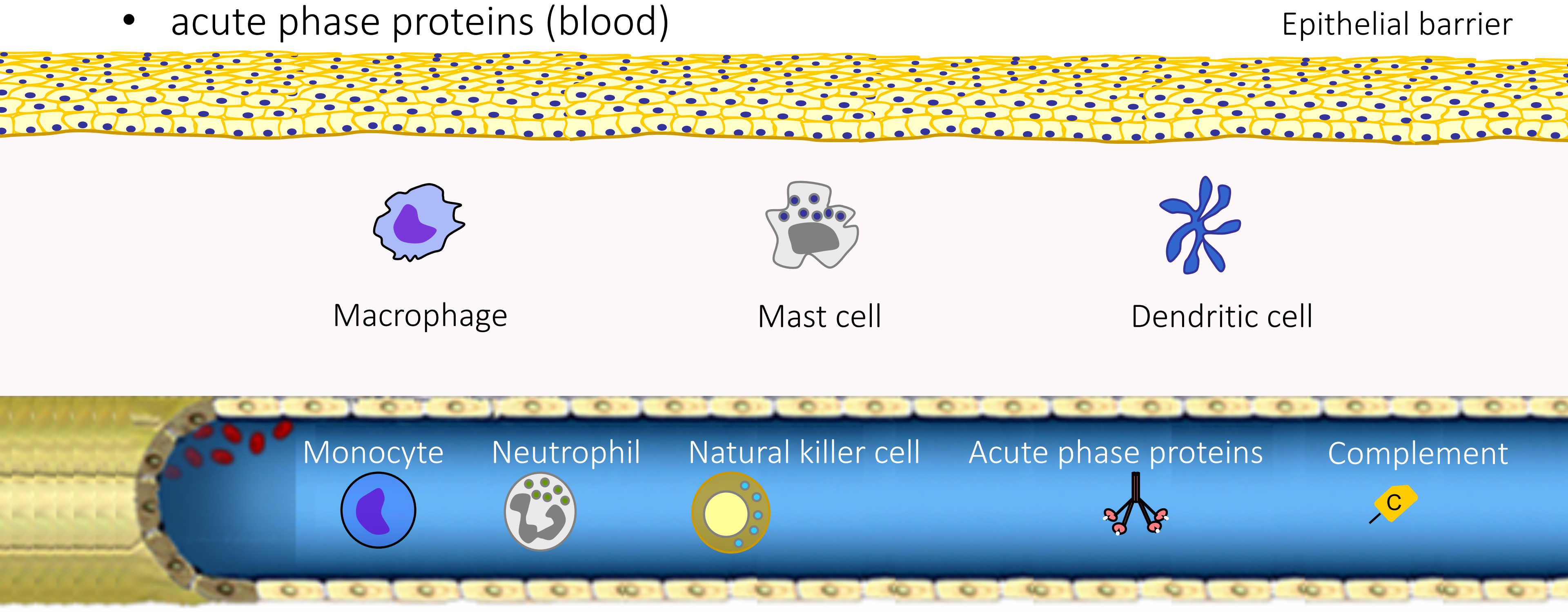


- Invertebrates and vertebrates are continuously exposed to microbes
- Epithelial barriers and innate immunity are common to invertebrates and vertebrates
- B and T cell adaptive immunity is specific to vertebrates

The Innate Immune system

The innate immune response is mediated by the coordinated action of several types of :

- **effector cells**
  - stationed in tissues (macrophages, mast cells, dendritic cells)
  - circulating in blood (monocytes, natural killer cells, neutrophils)
- **effector molecules**
  - complement system (blood)
  - acute phase proteins (blood)



Outline

I. The innate immune system: Effector cells

II. The innate immune system: Effector molecules

III. The innate immune system: The inflammatory response

IV. The innate immune system: Recognition and Role

II-A-B. Effector cells

The innate immune system

First line of defence: epithelial barriers

Physical barriers

- **Stratified epithelia**

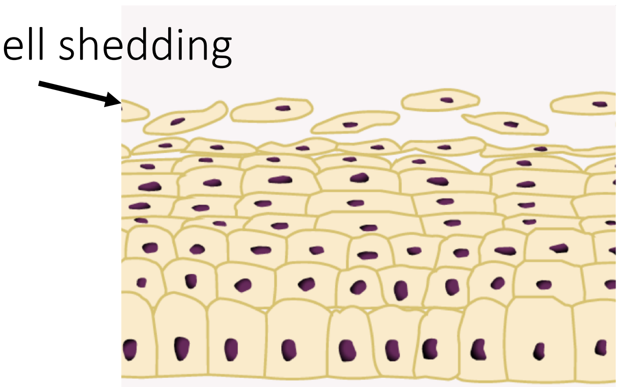
(skin, oral cavity, esophagus and vagina)

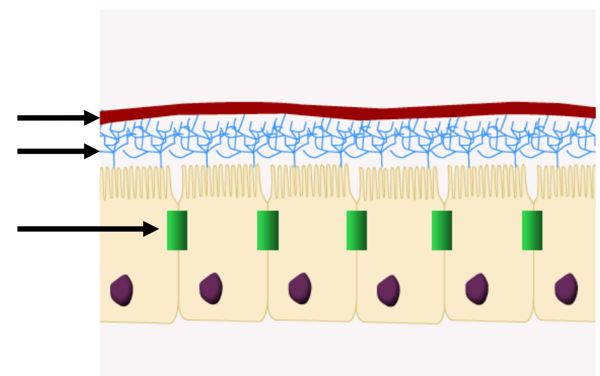
  - multiple cell layers
  - rapid cell turn over

- **Simple epithelia**

(intestine, uterus and respiratory tract)

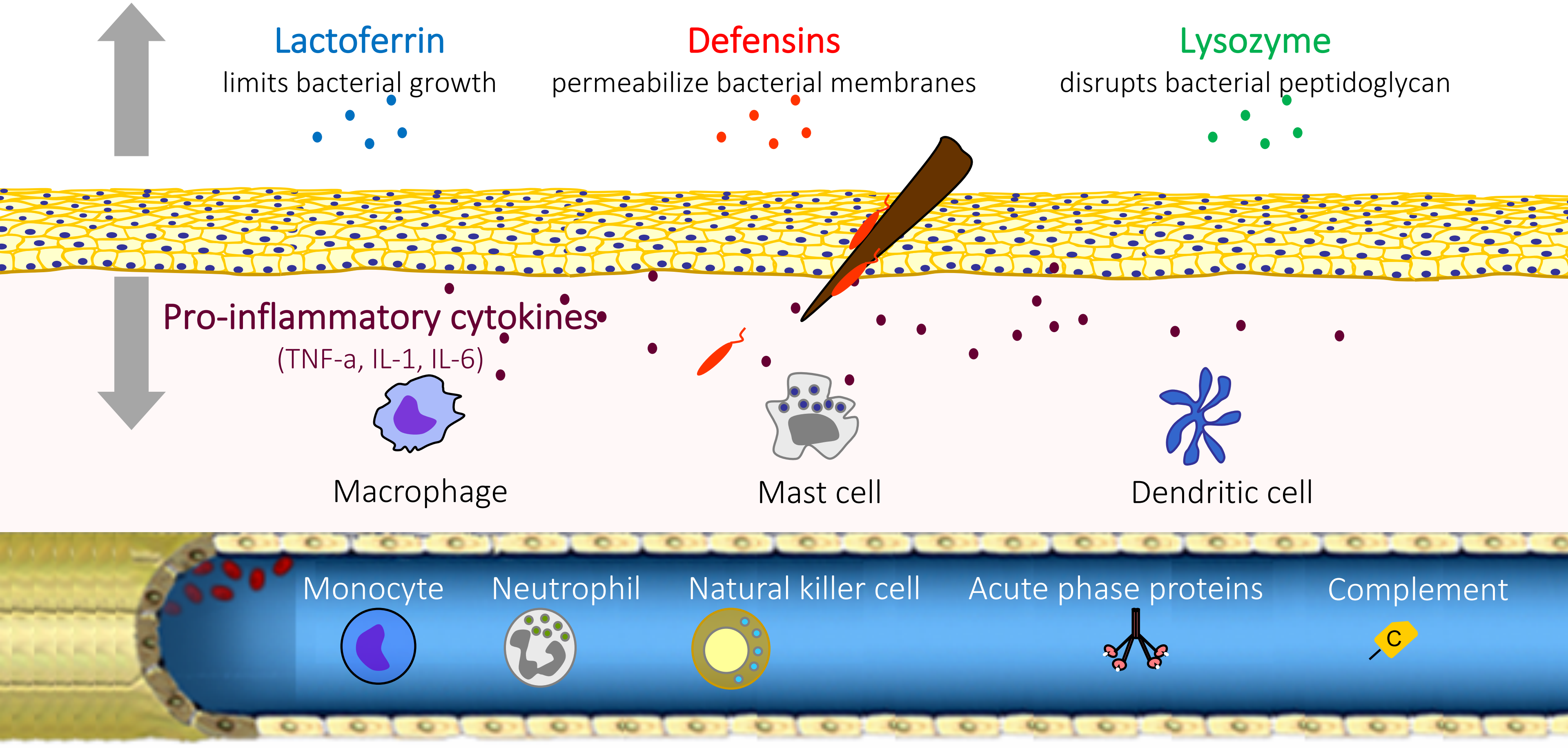
  - membrane specialization (tight junction)
  - Glycocalyx
  - mucus secretion
  - rapid cell turn over





Epithelial cells: Effector and Signaling function

- First cells to encounter pathogens
- Secrete a battery of **antimicrobial factors** at their apical surface
- Send out **pro-inflammatory molecules** at their basolateral surface to alert underlying immune cells



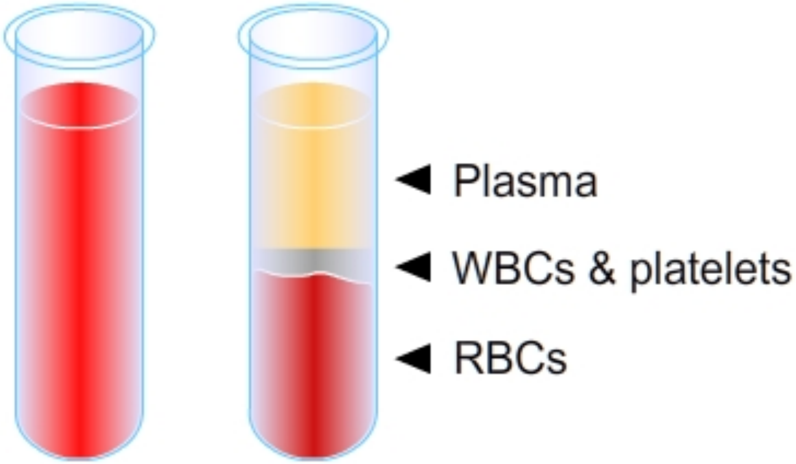
Leukocytes: white blood cells

Blood is composed of serum, red blood cells and white blood cells (**leukocytes**).

Specific blood cell populations are identified by markers (CD= cluster of differentiation).

Leukocytes are divided into **myeloid** and **lymphoid cells**.

Leukocytes are produced from **stem cells in the bone marrow** or from **peripheral cells** (e.g. resident macrophages).



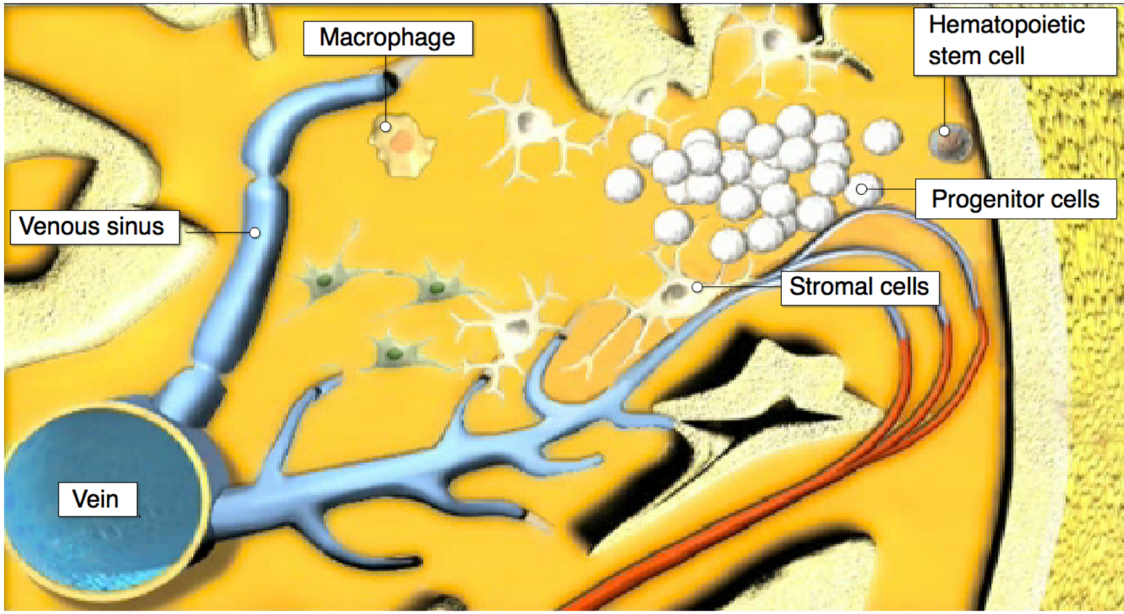
55%

<1%

45%

Generation of the leukocyte lineages

- All leukocytes circulating in blood originate from **stem cells in the bone marrow**
- The process that allows **differentiation and maturation** of leukocytes from stem cells is called **hematopoiesis**.
- Hematopoiesis is divided in two main arms:
  - **Lymphopoiesis** generates
    - B and T lymphocytes
    - Natural killer cells
  - **Myelopoiesis** generates
    - granulocytes
    - monocytes
    - dendritic cells
    - platelets
    - erythrocytes



Myelogenesis

Generation of the leukocyte lineages

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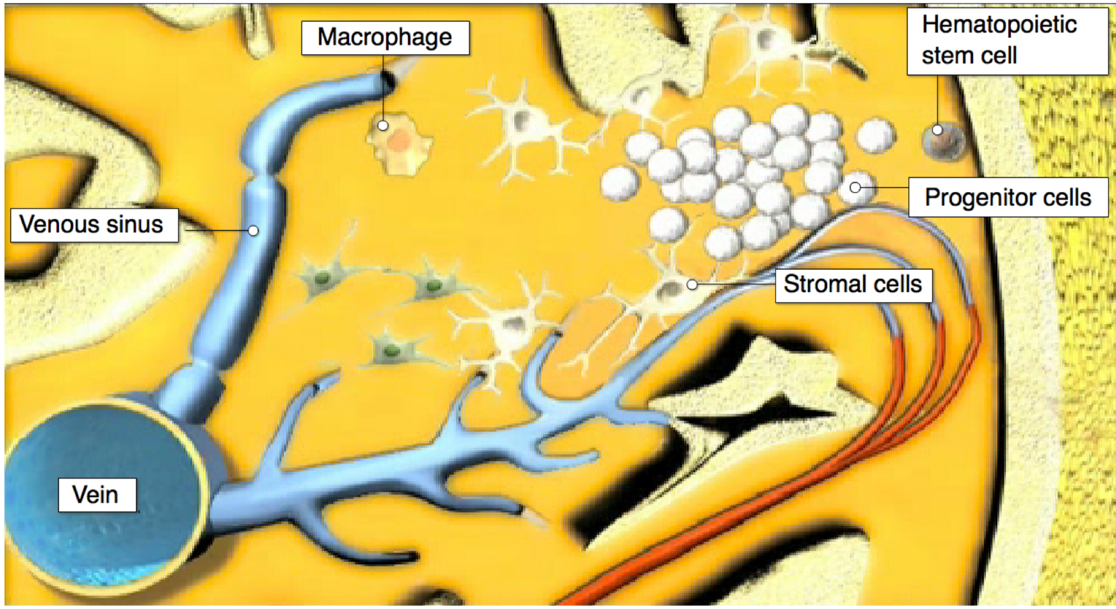
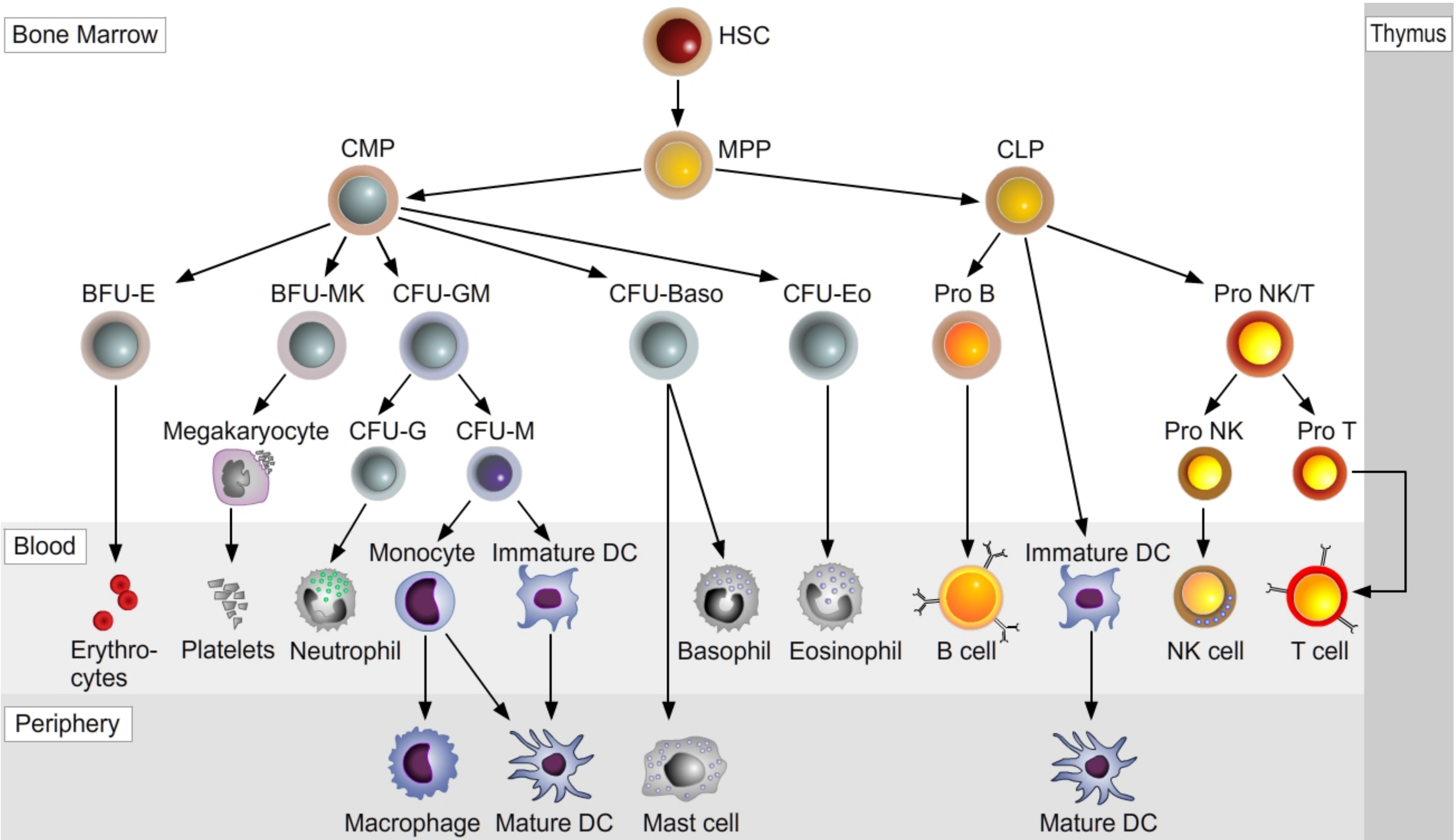


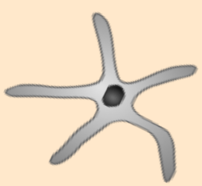
Red blood cell generation

Hematopoiesis is a complex differentiation process*



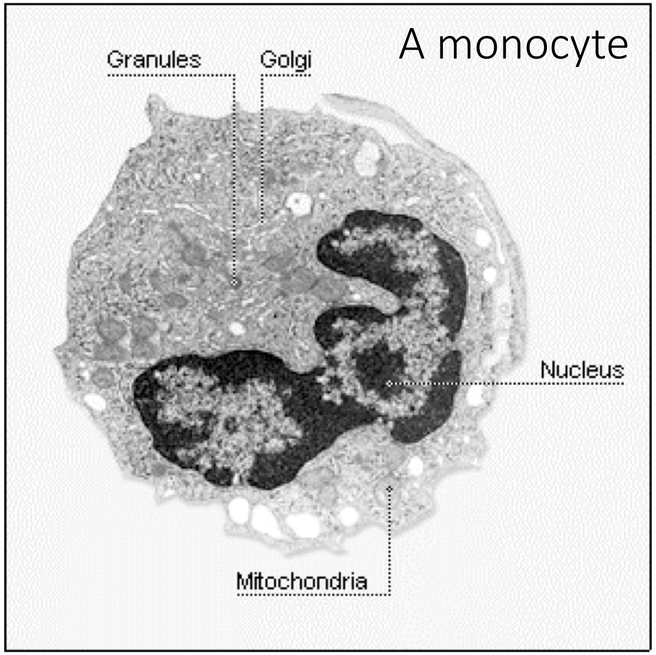
Phagocytes

2 classes:
- Non professional: endothelial cells
- Professional: neutrophils, macrophages, dendritic cells (DCs)

	Cell	Localization
	Monocytes	Blood
	**Macrophages:** • Histiocytes • Alveolar macrophages • Mesangial cells • Astrocytes, microglial cells • Kupffer cells • Osteoclasts	**Tissues** Loose connective tissues Lungs Kidneys Brain Liver Bone
	**Dendritic cells (DCs):** • Langerhans cells • Interstitial DCs • Plasmacytoid DCs	**Tissues/secondary lymphoid organs** Skin Connective tissues Secondary lymphoid organs
	**Granulocytes:** • Neutrophils • Eosinophils/ basophils	 Blood/tissues Blood/tissues
	Mast cells	Tissues

Professional Phagocytes: **Monocytes**

- **Monocytes** (mononuclear phagocytes) represent 3-10% of leukocytes. They can **differentiate into macrophages and dendritic cells** in peripheral tissues.



- Various types of macrophages:
  - Intestinal macrophages in the gut
  - Alveolar macrophages in the lung
  - Histiocytes in connective tissues
  - Kupffer cells in the liver
  - Mesangial cells in the kidney
  - Microglial cells in the brain
  - Osteoclasts in the bone

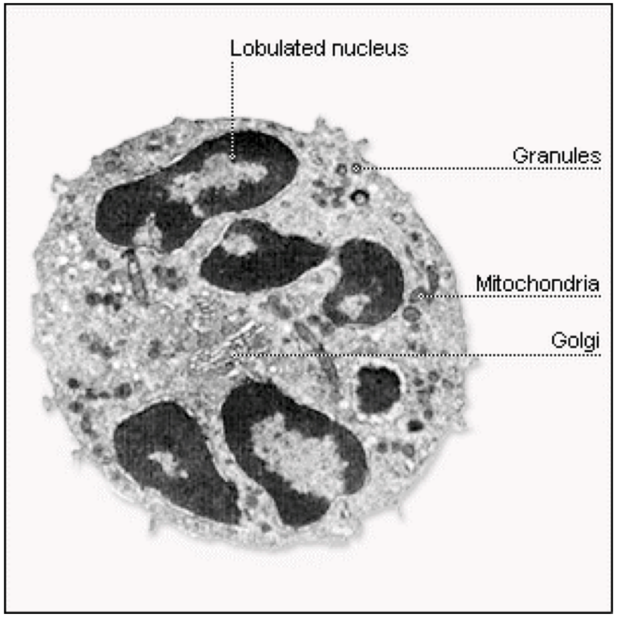
- Macrophages are **activated** upon binding of **microbial molecules to specialized receptors (PRRs).**

- Macrophages can be **activated by T Helper cells** and exhibit increased **bactericidal activity** (increased phagocytic activity, higher levels of hydrolases, secreted soluble factors).

Professional Phagocytes: **Granulocytes**

Neutrophils represent 50-70% of leukocytes

- high turn-over ($>10^{11}$ cells per day), short lived (few days)
- found in the blood but migrate into tissues during inflammation
- Phagocytic, store lytic enzymes and bactericidal substances in granules which fuse with phagosome



A neutrophil

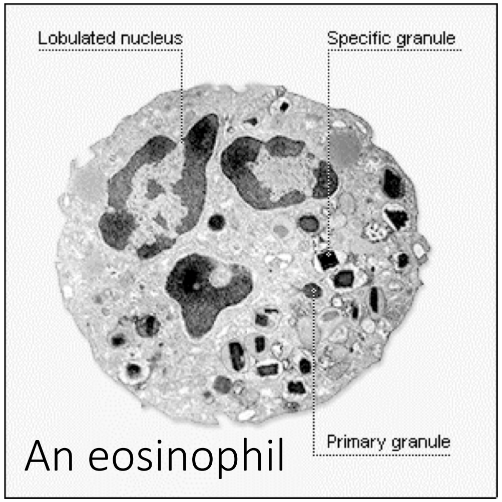
Professional Phagocytes: **Granulocytes**

Eosinophils

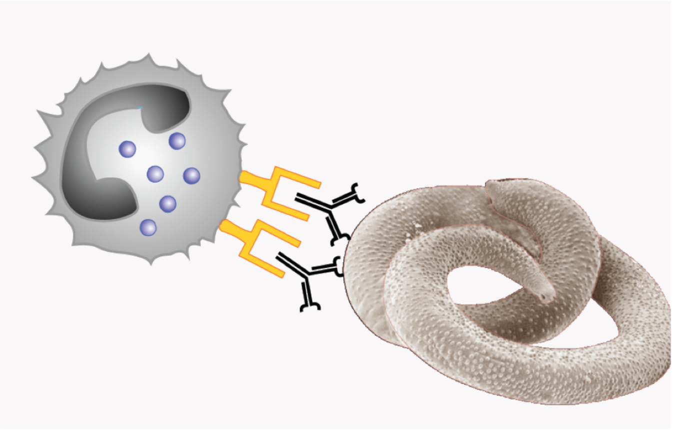
- Motile phagocytic cells (less than neutrophils)
- Play a role in defense against parasitic organisms by secreting contents of eosinophilic granules which may damage parasite membrane.

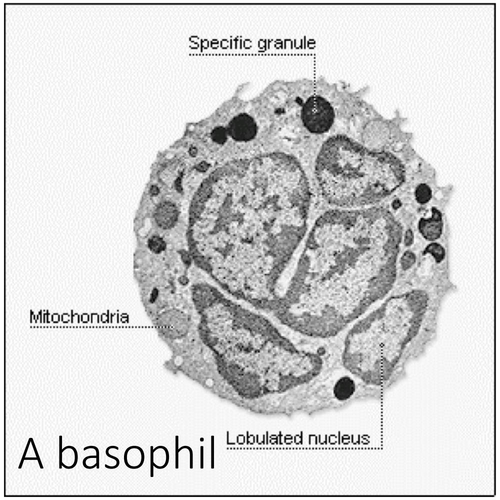
Basophils

- Non-phagocytic, release pharmacologically active substances (e.g. histamine)
- Play a role in allergic responses



An eosinophil

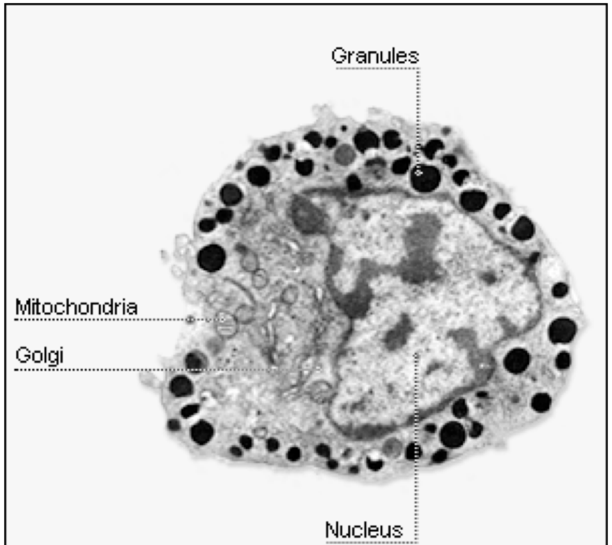




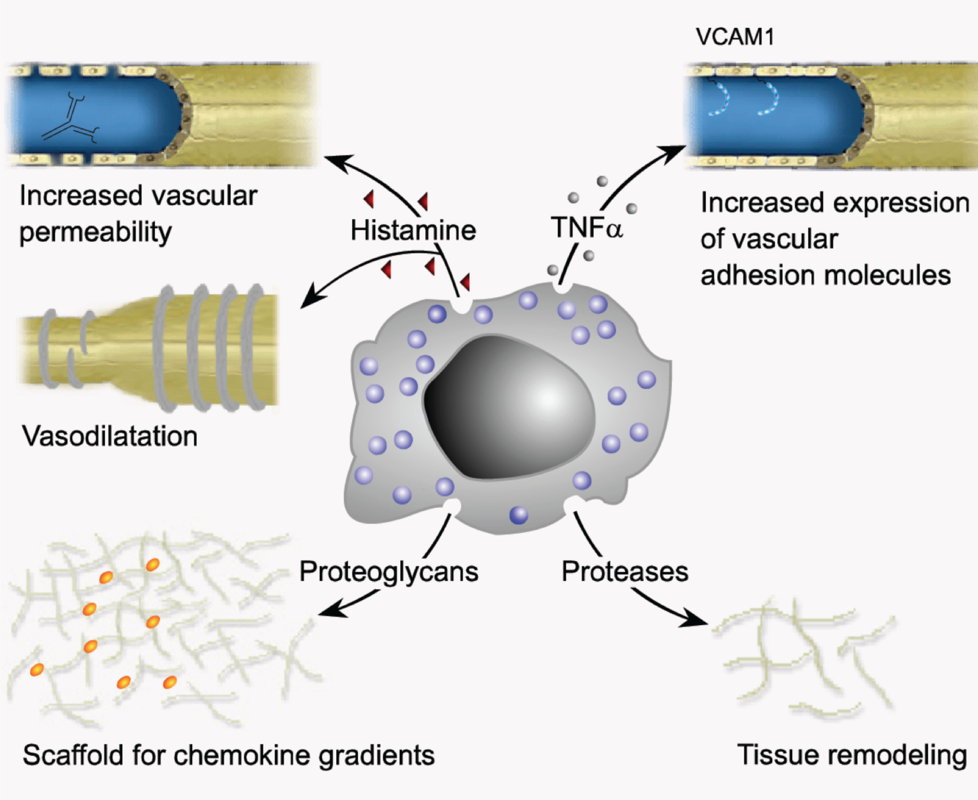
A basophil

Mast cells

- Resident cells of the myeloid lineage
- Contain many granules (Histamines, proteases)
- Contribute to inflammatory and allergic responses
- Express Fc receptor for IgE

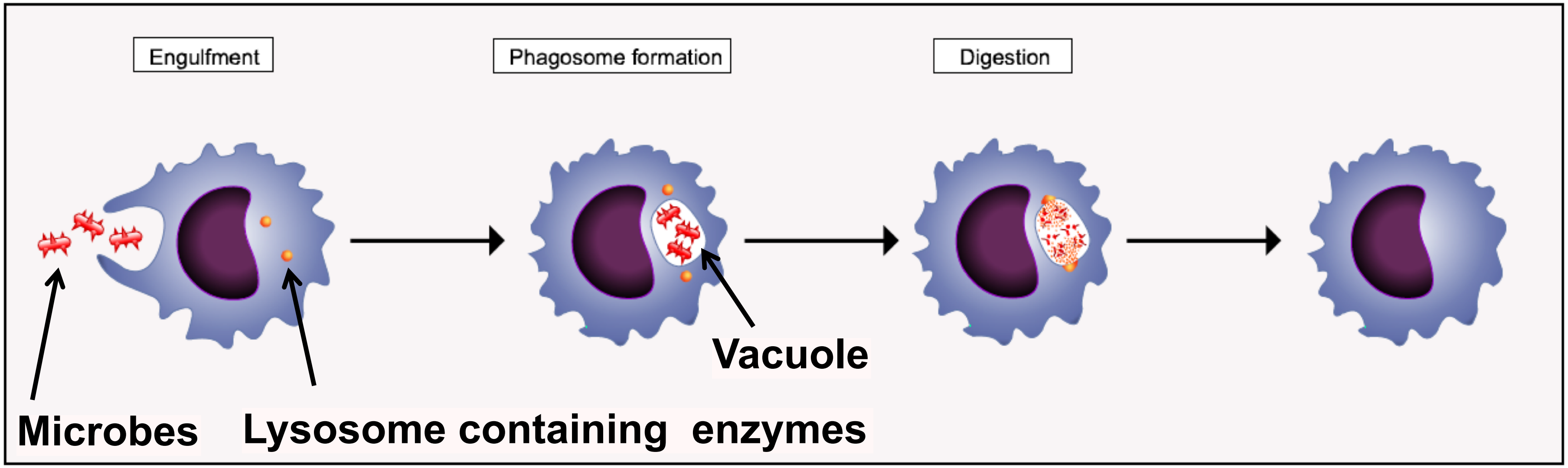


A mast cell



Phagocytosis (1)

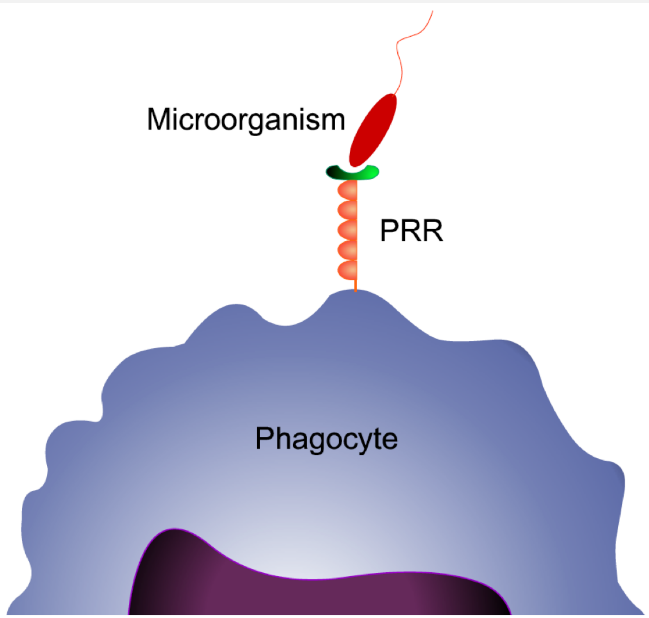
- Internalization of large particles (>0,5μM)
- Clathrin independent, actin dependent
- Multistep process: recognition, engulfment, phagosome maturation and digestion after fusion with lysosomes



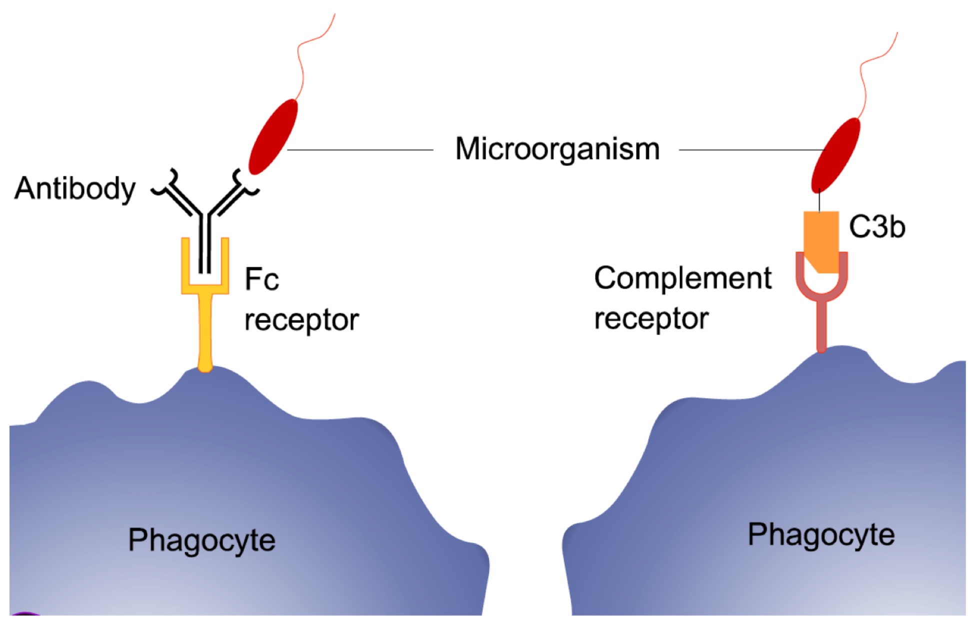
Phagocytosis (2): **Recognition**

- **Direct or indirect** internalization of large particles (>0,5μM)
- **Phagocytic receptors** are cell surface receptors found on macrophages, neutrophils and dendritic cells.
- **Opsonization** is the binding of a molecule (e.g. antibody, complement) to a microbe to facilitate its phagocytosis

Direct recognition



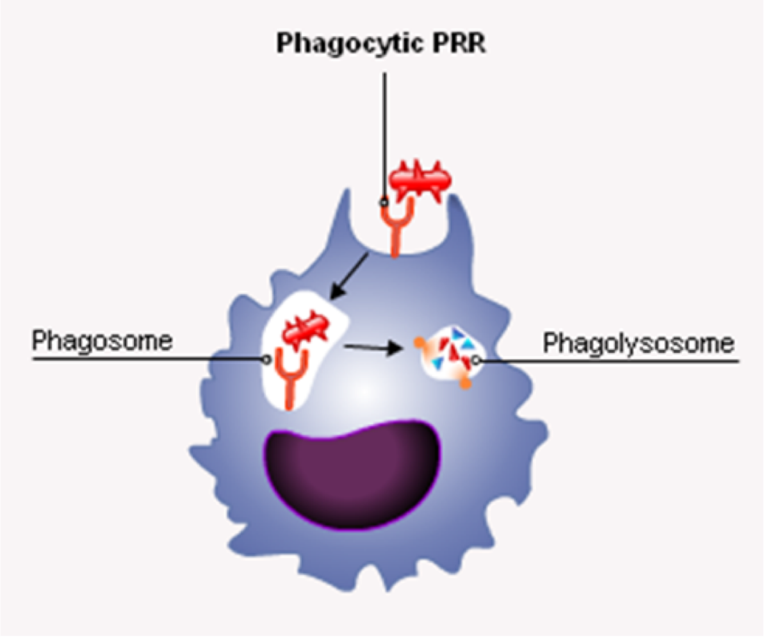
Indirect recognition (opsonization)

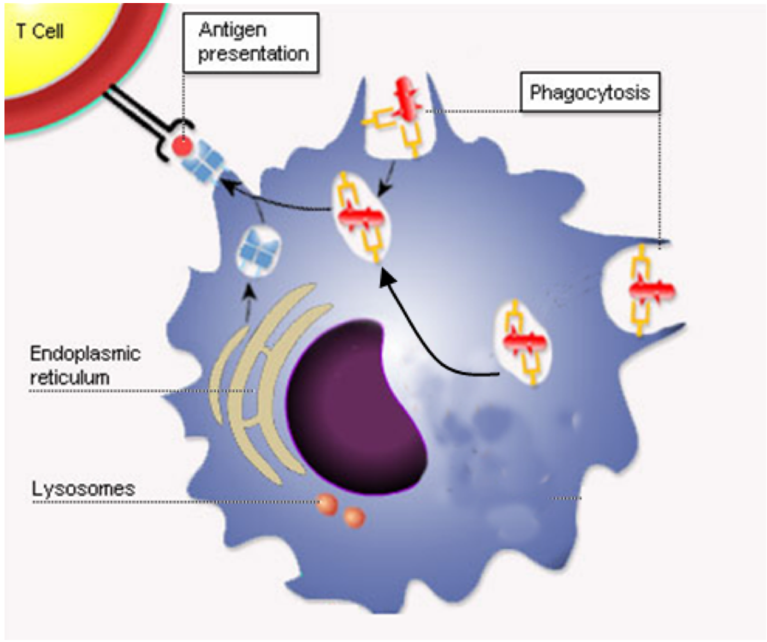


Phagocytosis (3): **Functions**

Phagocytic receptors couple **microbe recognition and pathogen internalization** to :

- **intracellular killing** (macrophages, neutrophils)
- **presentation** of pathogen fragments to T cells (dendritic cells)





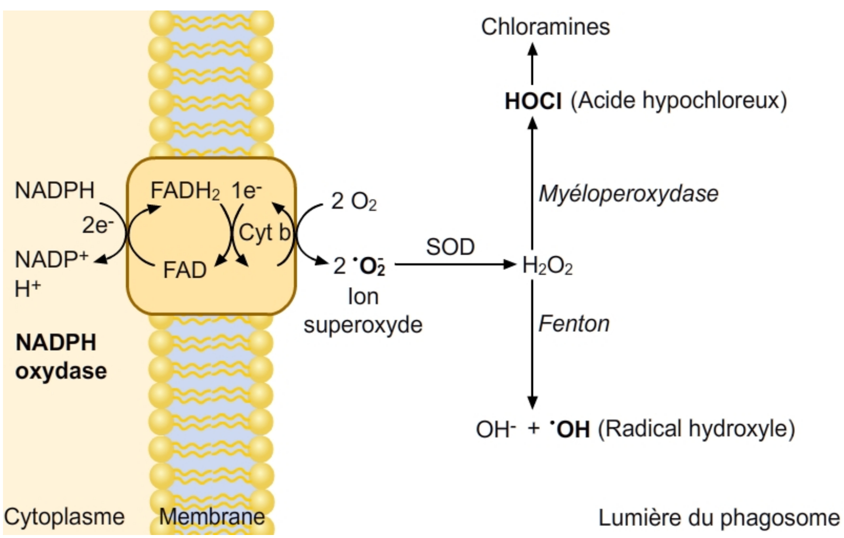
Phagocytosis (4): **Killing**

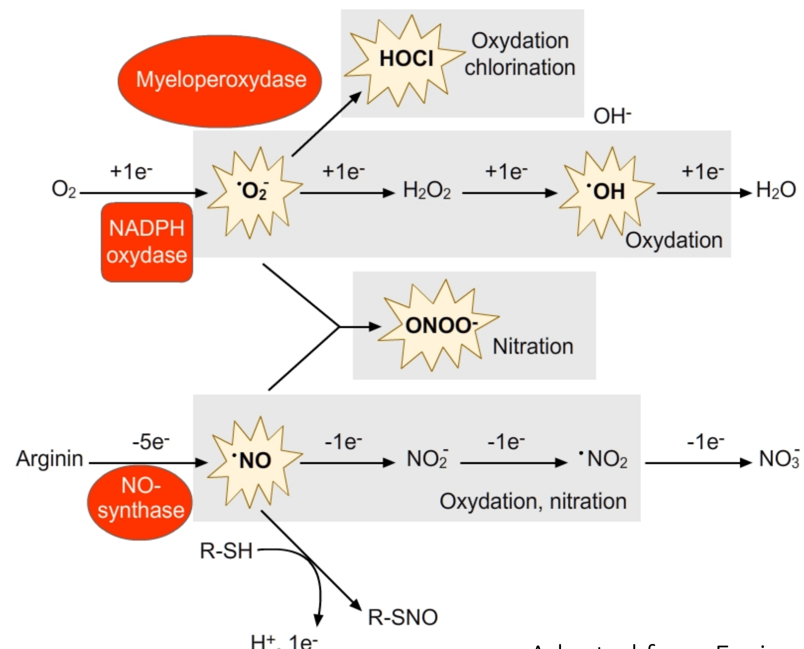
Killing is mediated exclusively by professional phagocytes and involves 2 types of killing agents: antimicrobial compounds and free radicals.

Antimicrobial compounds

- Proteases (cathepsins, elastase), lysosymes and acidity participate in the digestion of ingested micro-organisms
- Antimicrobial peptides
- Lactoferrin (iron sequestration)

ROS (Reactive oxygen species)*





Adapted from Espinosa

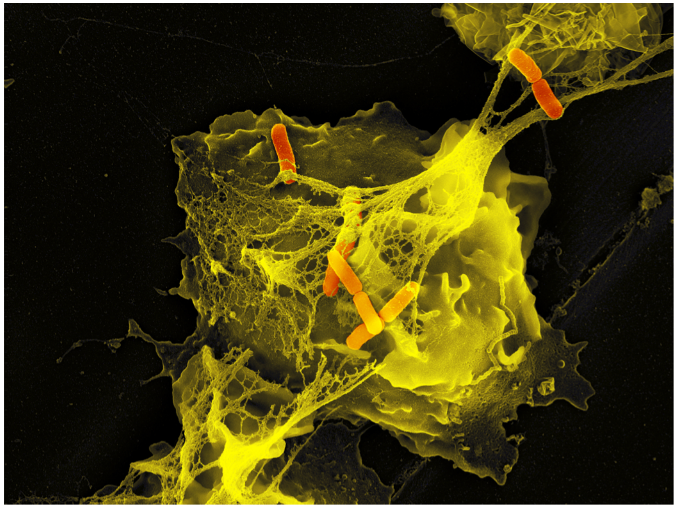
Note: ROS are produced by the NADPH oxidase. NO· is generated by the NO-synthase. This oxidative burst is crucial as patients deficient in NADPH have recurrent bacterial and fungal infections.

Degranulation (e.g. neutrophils)

Neutrophils release many molecules when they are in contact with pathogens. These include **Lactoferrin, BPI** (neutralisation of LPS), **lysozyme**, **proteases**…

Neutrophils release products (DNA, Histones) forming **extracellular traps** or NETs.

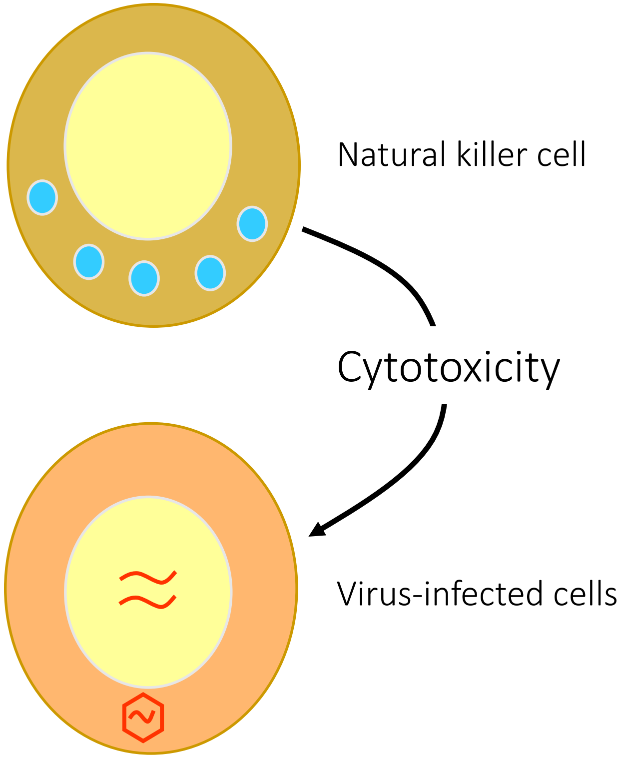
Large parasites cannot be phagocytosed. Anti-parasitic defenses involve the release of toxic compounds (**Eosinophil Cationic Peptides** (EDP), **Eosinophil Derived Neurotoxin (**EDN), **peroxidases**) by other **granulocytes (eosinophils, basophils, mast cells)**



Colored scanning electron micrograph showing stimulated neutrophil with NETs and trapped Shigella bacteria. © Max Planck Institute for Infection Biology

Natural killer cells: professional killers of infected cells and tumor cells

- NK cells are large granular lymphocytes circulating in the blood and represent 5-10% of blood lymphocytes.
- **Cytotoxic**, involved in the elimination of tumor cells and virus infected cells
- **Innate immune cells**, do not have an antigen-binding receptor, recognize „altered“ host cells



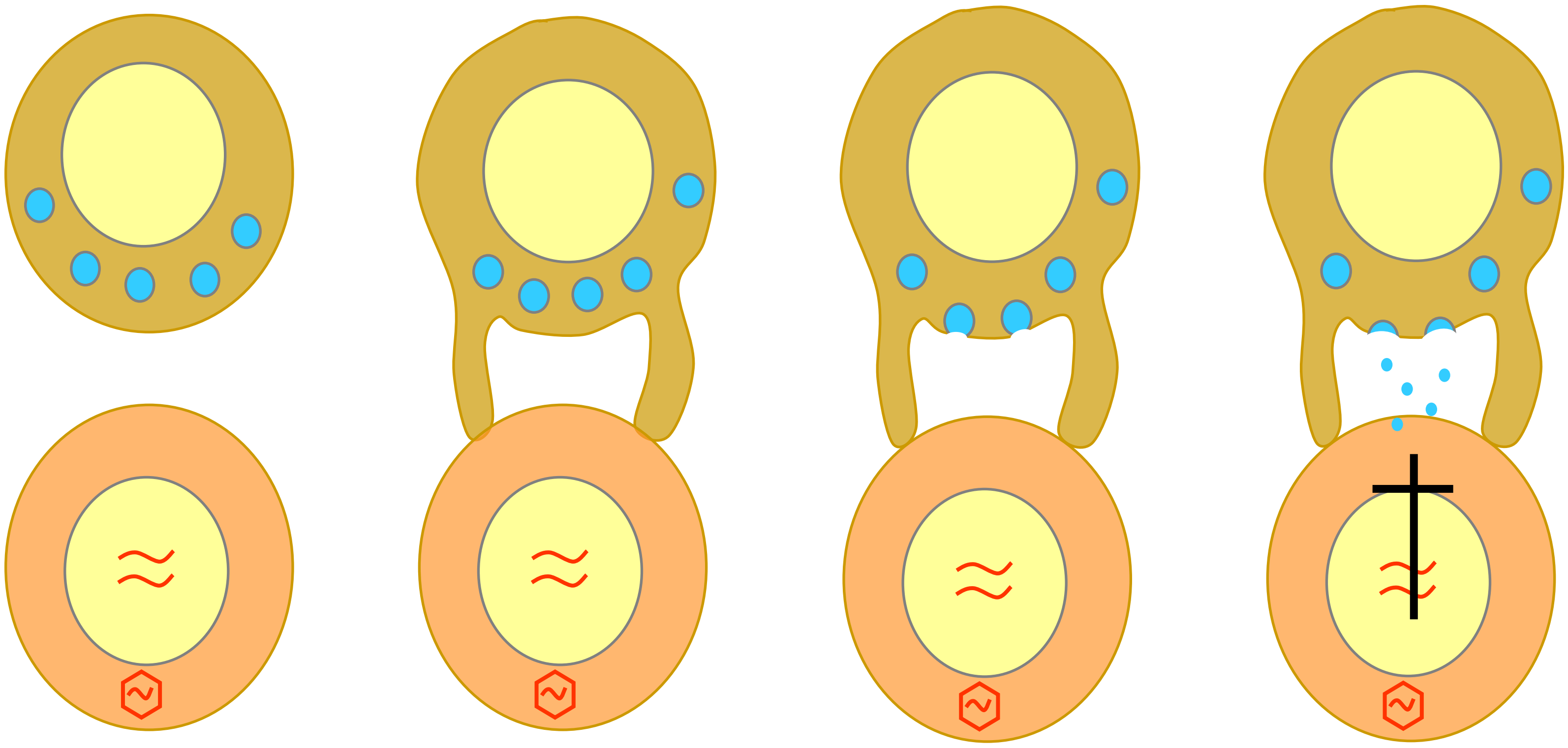
- Intracellular Parasites:
  - Bacteria : *Listeria monocytogenes*
- Viral infections:
  - Mouse Cytomegalovirus (MCMV)
  - Influenza Virus
  - Herpes Simplex Virus (HSV)

Note: NKT cells have characteristics of both NK and T cells (express TCR and NK markers); NKT cells recognize lipid-antigens in association with CD1 (not MHC).

Natural killer cells: Effector Mechanisms (1)

1) Cell-mediated cytotoxicity

NK cells are constitutively cytotoxic. Their activity does not increase after a second challenge.

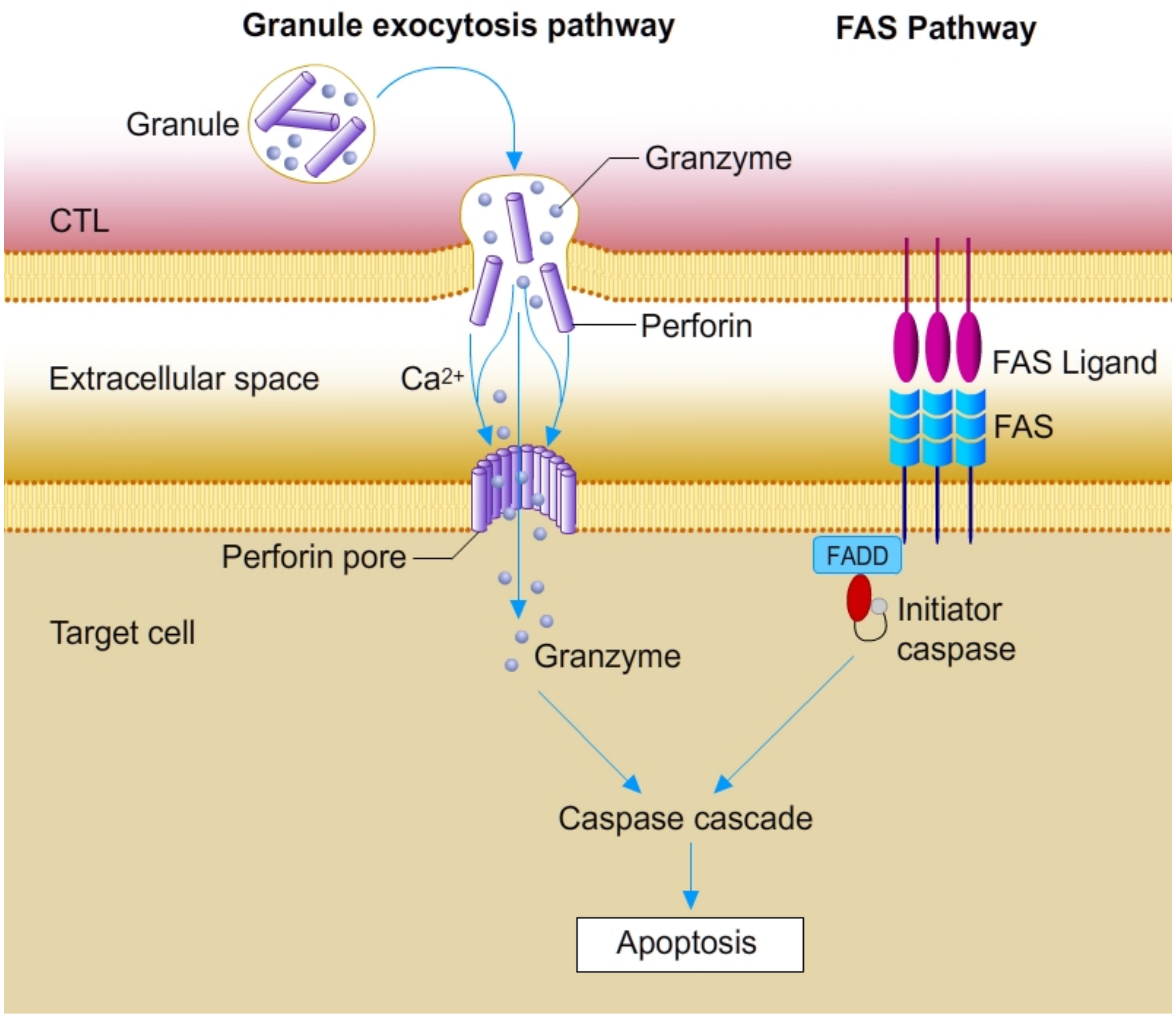


NK cells: Two ways of killing

NK cells kill by

- making contact with their target cells and **releasing** substances from their granules (**granzymes, perforin**) that **make pores in the target cells**, causing them to die.

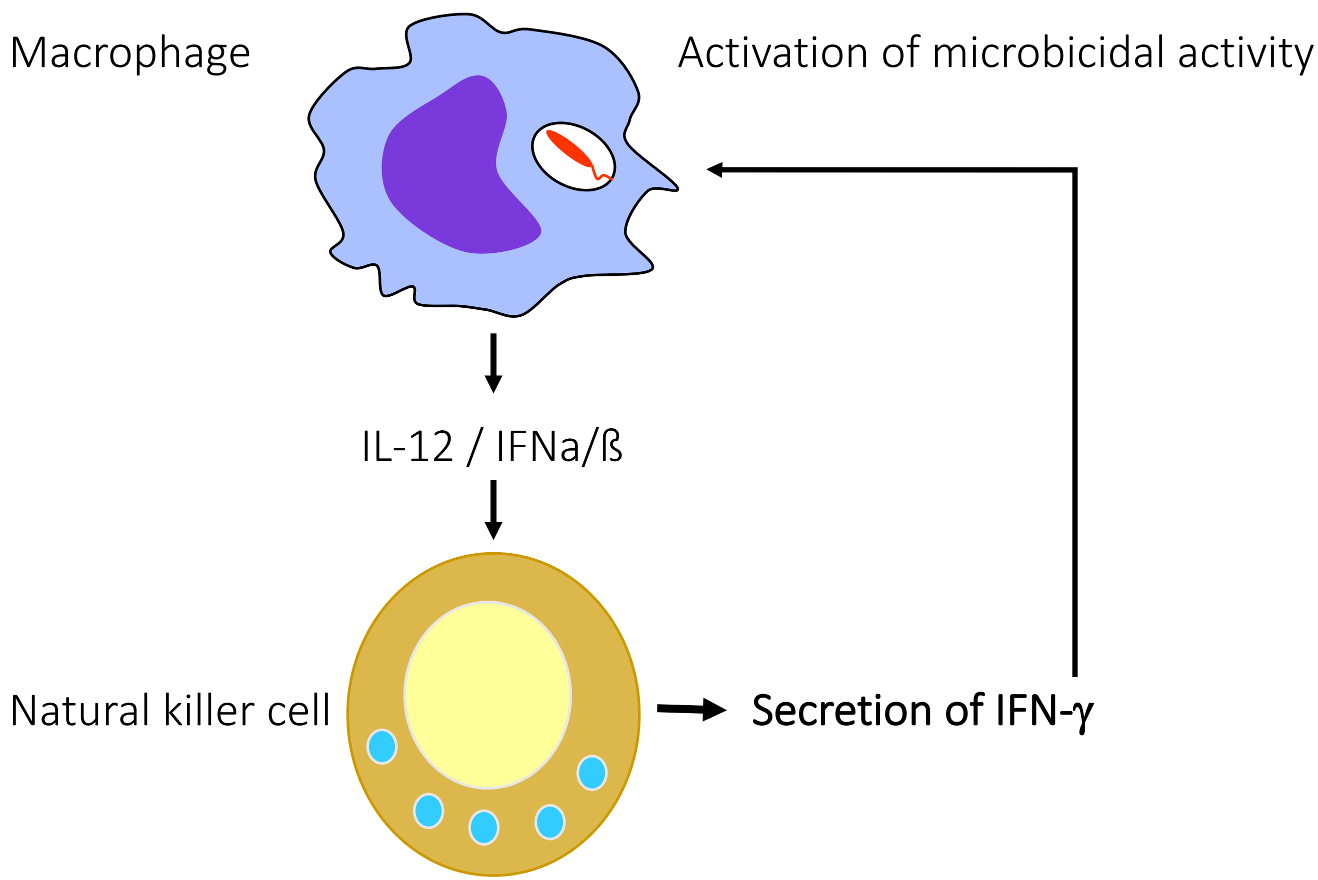
- expressing ligands that **induce apoptosis by Death receptors (Fas/FasL).**



Natural killer cells: Effector Mechanisms(2)

2) Secretion of cytokines

NK cells produce IFN-γ that stimulates macrophages and TNF-α (=LTα) that induces DC maturation. After a phase of amplification, NKs die by apoptosis. NK cells are an early component of the host response to viral infection.



Natural killer cells: recognition mechanisms

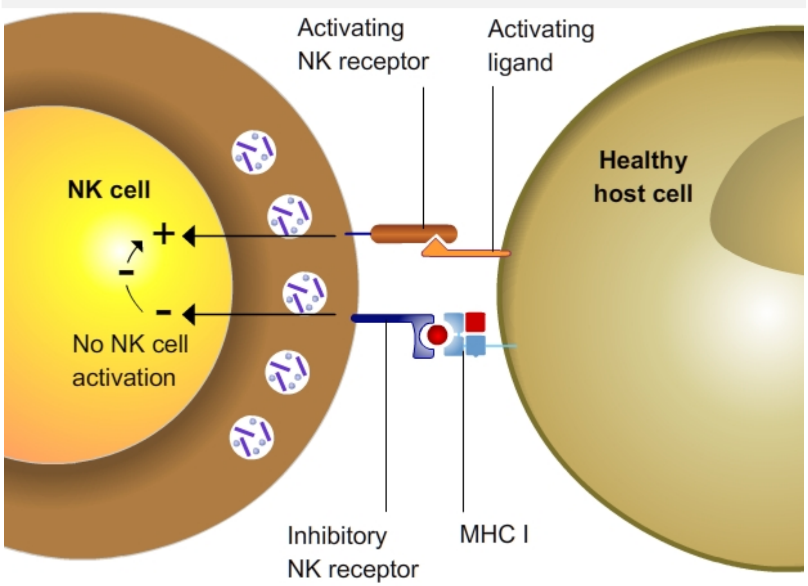
How is NK cell-mediated lysis of target cells regulated if they are constitutively cytotoxic?

- Two modes of recognition involving either **NK Receptors (NKR)** or **low affinity FcR receptor to IgG**
- Recognize either 'missing self' or 'altered self' through distinct NKRs.
- Dynamic balance between
  - **Activating receptors** (sensing viral proteins, or host stress proteins (MICA, MICB)
  - **Inhibitory receptors** (sensing MHC class 1, host molecular signature of 'self')

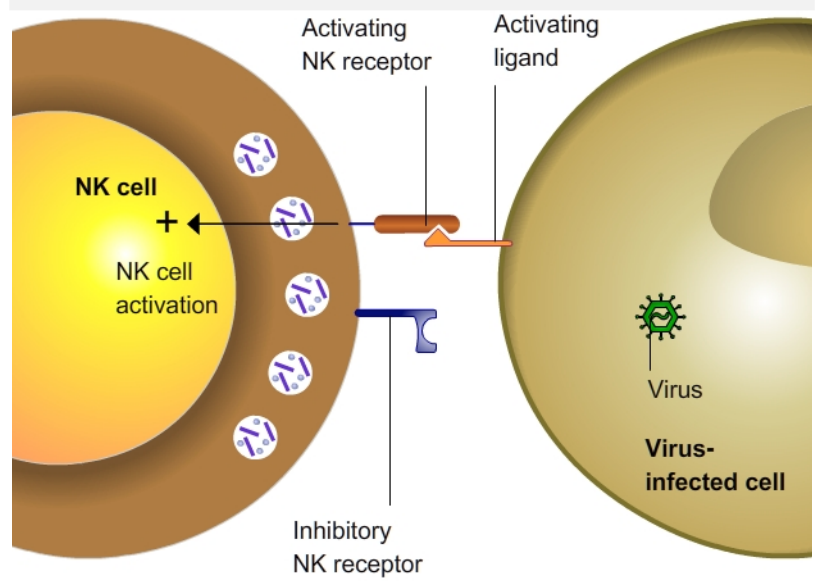
Natural killer cells: Recognition by ‘missing self’

- The **missing self recognition** is based on the detection of self molecules that are:
  - normally expressed by healthy host cells.
  - down-regulated or lost in host cells upon infection or malignant transformation.
- NK cells express **two types of receptors**:
  - **Activating receptors** recognize yet undefined activating ligands on host cells and promote NK cell activation.
  - **Inhibitory receptors** are specific for MHC I molecules and prevent NK cell activation.

No NK cell activation



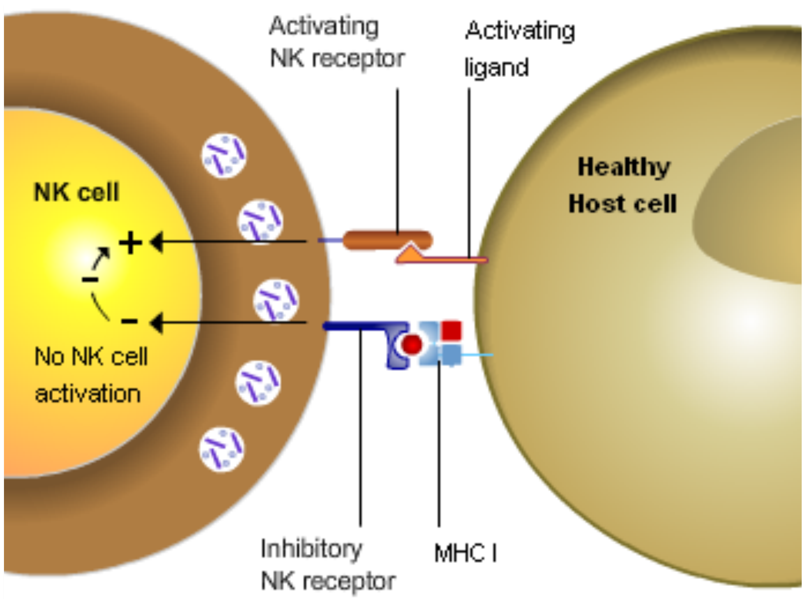
NK cell degranulation



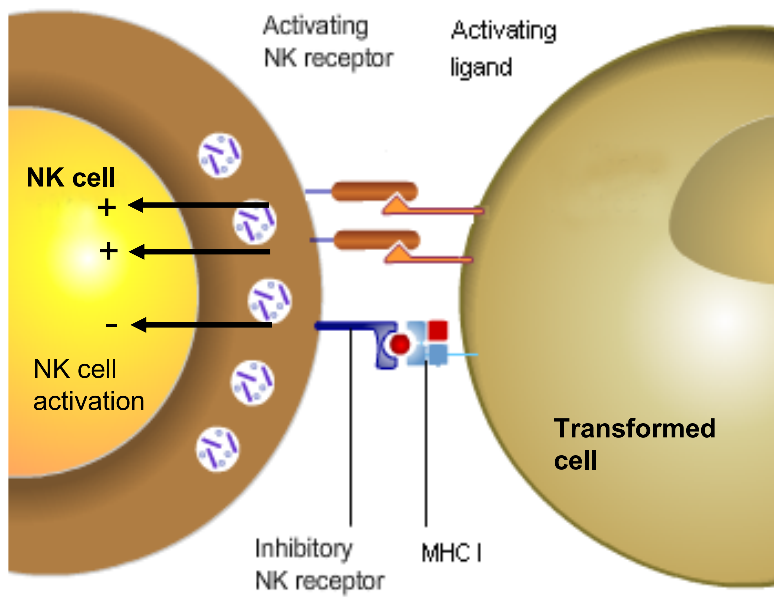
Natural killer cells: Recognition by ‘altered self’

- The **altered self recognition** is based on the detection of markers that are:
  - normally absent or expressed at low level on healthy host cells.
  - up-regulated in host cells upon infection or malignant transformation.
- Typical example: **inducible self proteins** such as MICA and MICB
  - "non-classical" MHC class I molecules that are normally present a low levels but up-regulated in response to cellular stress (epithelial tumors, Mycobacterium tuberculosis infection).
  - ligands for by NKG2D (activating receptor on NK cells)

No NK cell activation

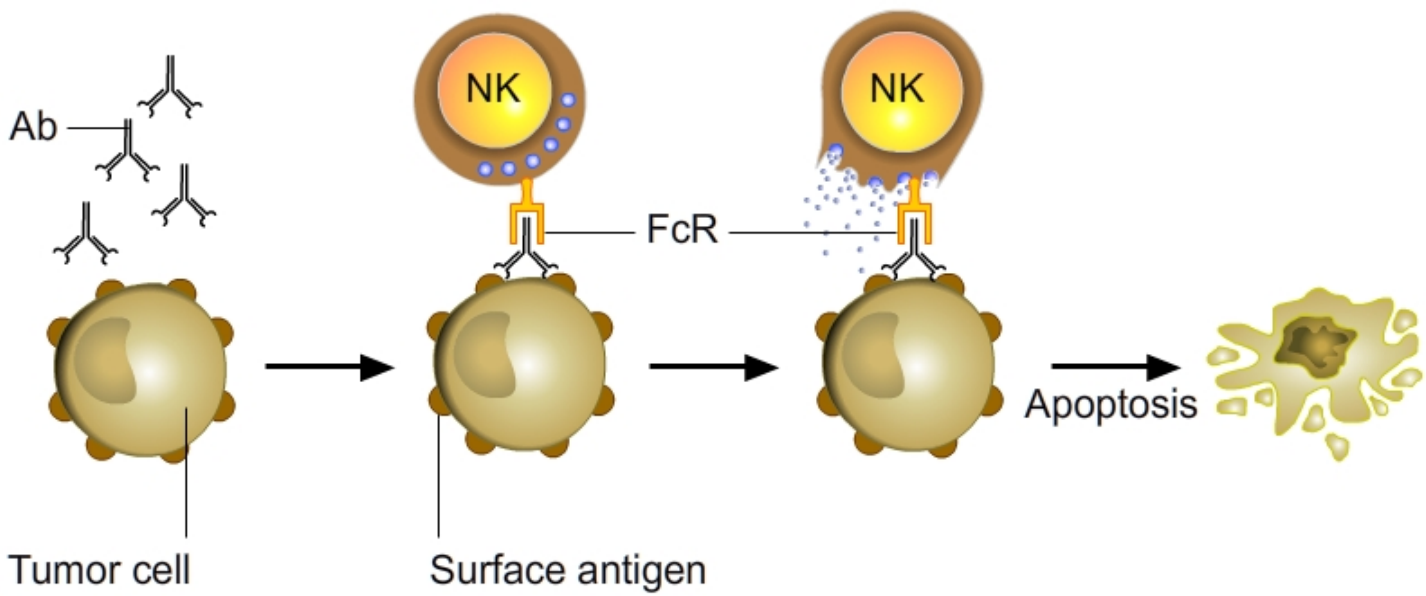


NK cell degranulation



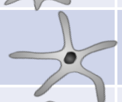
Natural killer cells: Recognition by FcR

- Typical example: **host cells express foreign molecules**
  - **DNA viruses** are implicated in the development of a variety of **tumors** (e.g. EBV causes B cell lymphomas)
  - In such tumors, **virus-encoded protein antigens** may be found on the surface of the tumor cells.
  - NK cells are directed to IgG-coated target cells by way of their FcR receptors



Conclusion 2AB: Innate immune cells

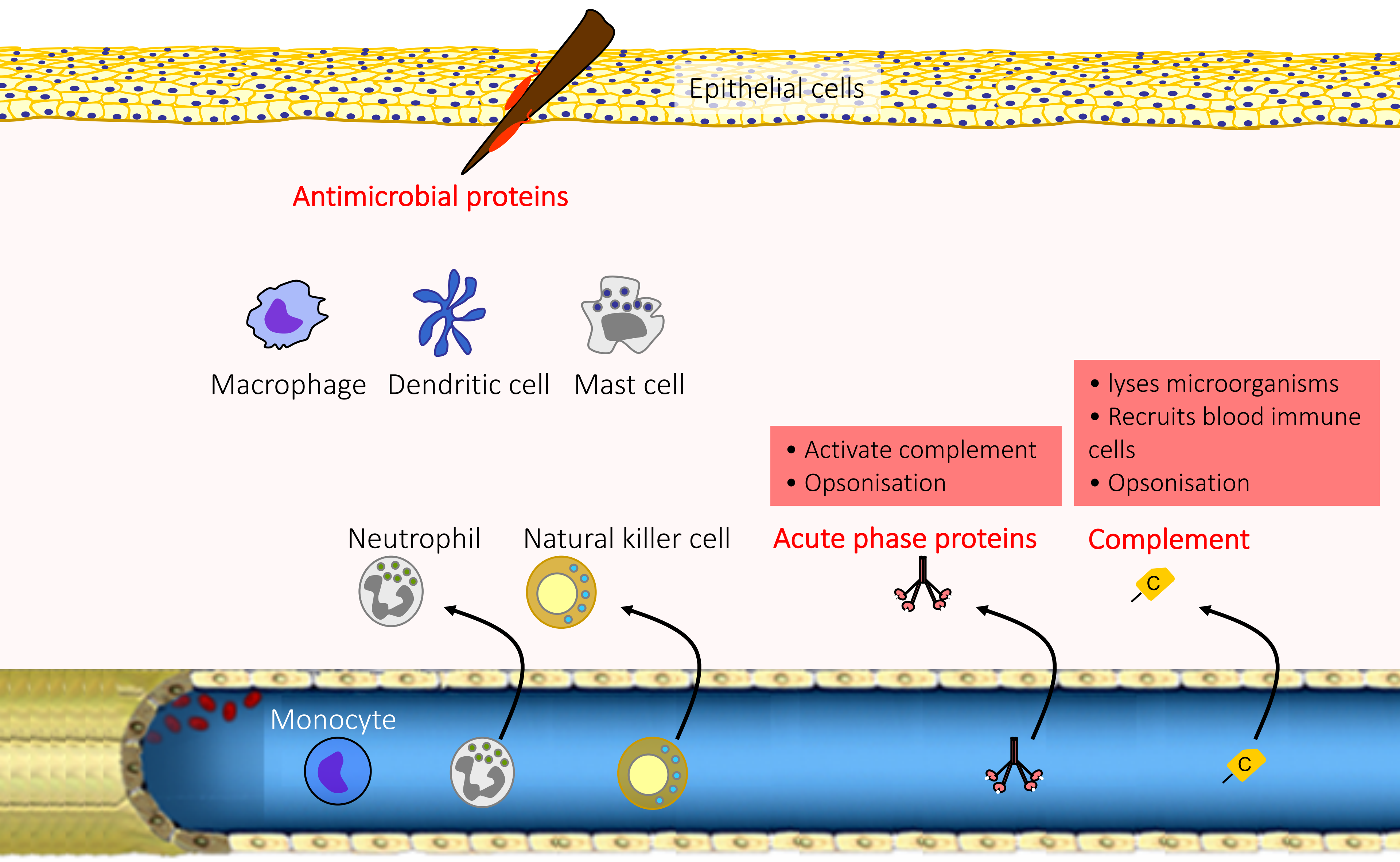
- All cells of the body are capable of immune responses
- Epithelial cells form the first barrier. They secrete antimicrobial factors and cytokines and have regenerative capacity.
- Different types of circulating and resident innate cells specifically evolved to combat infection:

<table>
<tr><th></th><th colspan="2">Cell type</th><th>Origin</th><th>Localization</th><th>Role</th></tr>
<tr><td></td><td colspan="2">Monocytes</td><td rowspan="2">Myeloid</td><td>Blood</td><td rowspan="3">Phagocytosis, antigen presentation</td></tr>
<tr><td></td><td colspan="2">Macrophages</td><td rowspan="2">Tissues</td></tr>
<tr><td></td><td colspan="2">Dendritic Cells</td><td>Myeloid / lymphoid</td></tr>
<tr><td></td><td rowspan="3">Granulocytes</td><td>Neutrophils</td><td rowspan="3">Myeloid</td><td>Blood</td><td>Phagocytosis, degranulation</td></tr>
<tr><td></td><td>Basophils</td><td>Blood</td><td rowspan="2">Inflammation, allergy</td></tr>
<tr><td></td><td>Eosinophils</td><td>Blood & tissues</td></tr>
<tr><td></td><td colspan="2">Mast cells</td><td>Myeloid</td><td>Tissues</td><td>Inflammation</td></tr>
<tr><td></td><td colspan="2">Natural Killer cells</td><td>Lymphoid</td><td>Blood</td><td>Cytotoxicity</td></tr>
</table>

II.C. Effector molecules

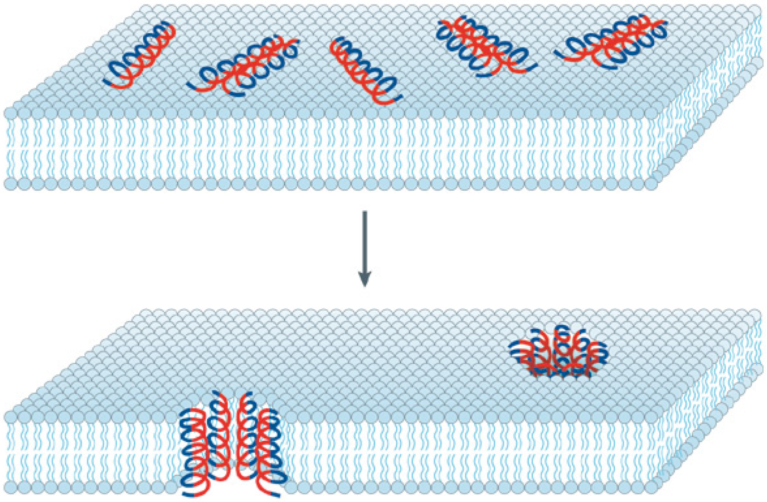
The innate immune system

Effector molecules



Antimicrobial peptides

- **Small** (3-5kDa), **cationic** peptides with disulphide bonds (e.g. α or β **defensins, cathelicidins**…)
- **Large spectrum** of activity (natural antibiotics), require high concentration
- Released by **neutrophils** or produced by **epithelia** (constitutive or inducible)
- Permeabilize the envelope of microbes
- Produced by animals and plants



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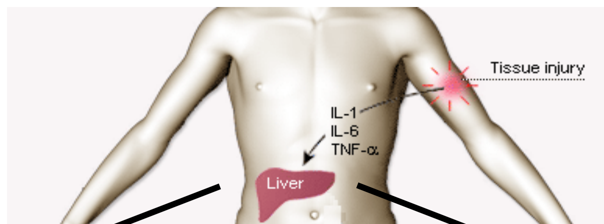
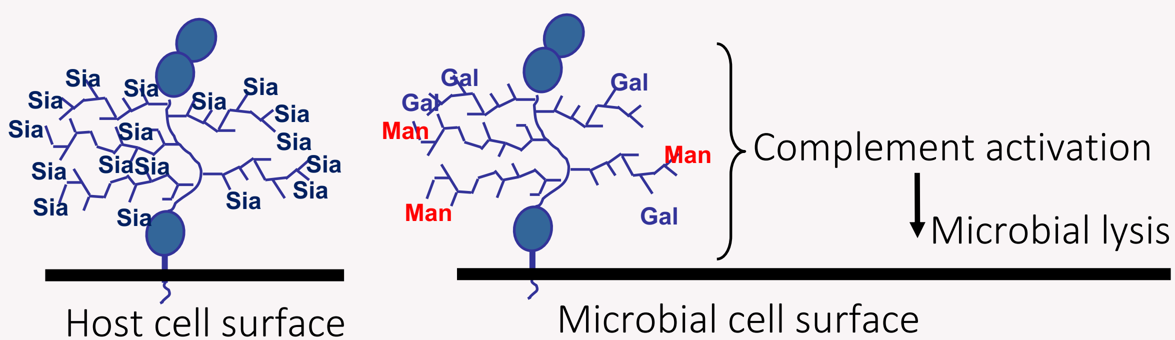
Acute phase proteins

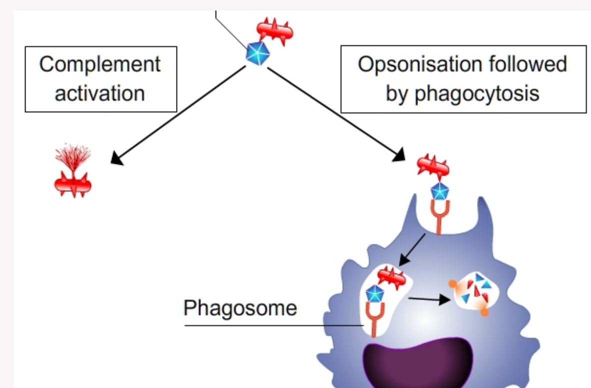
- **Plasma proteins** that are always present in the blood, whose concentration changes during infection.
- **Secreted** into the circulation **by the liver**
- Include **MBP, CRP, Complement factors, LBP binding proteins, ROS inhibitors**
- 10% of plasmatic proteins are **protease inhibitors** (α2-macroglobulin, serpins) which block microbial proteases.



MBP/MBL (Mannose binding protein/lectin)



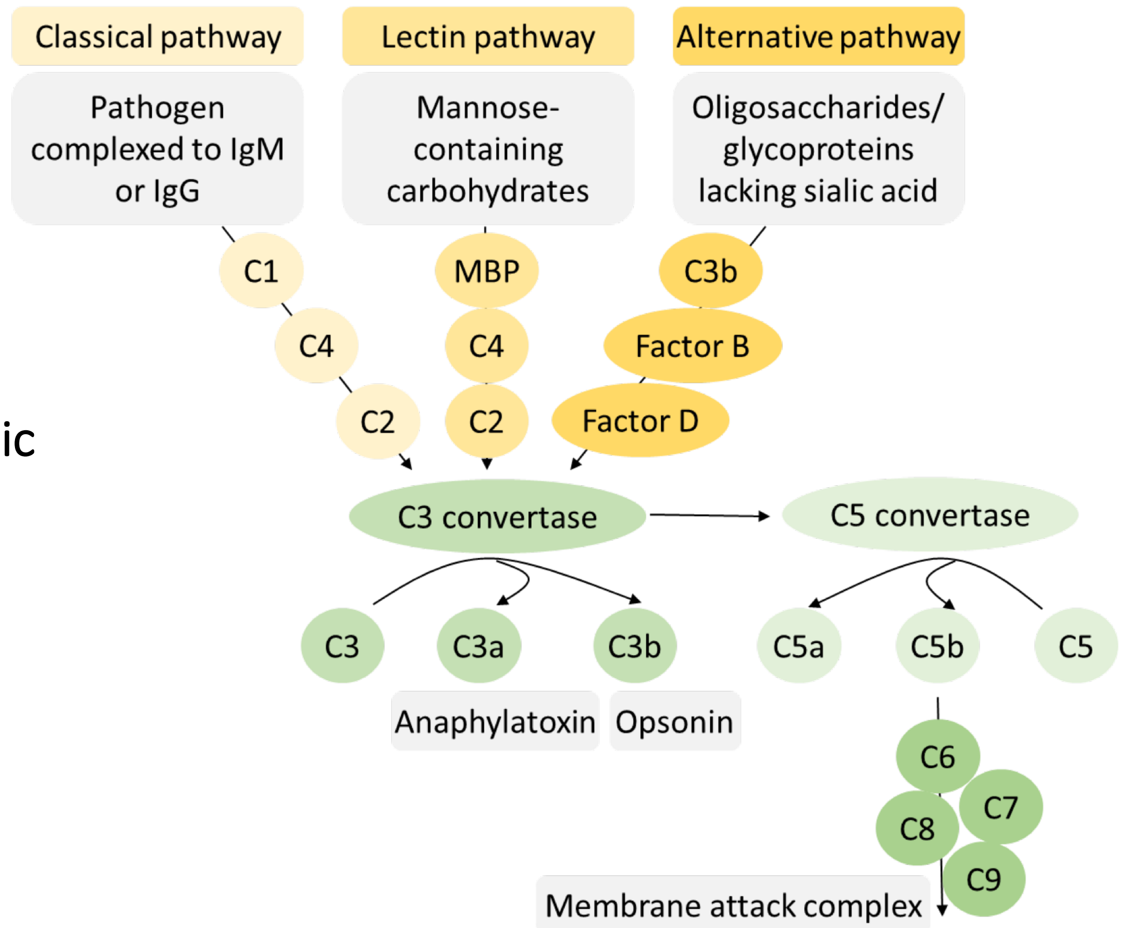
CRP (C reactive protein)



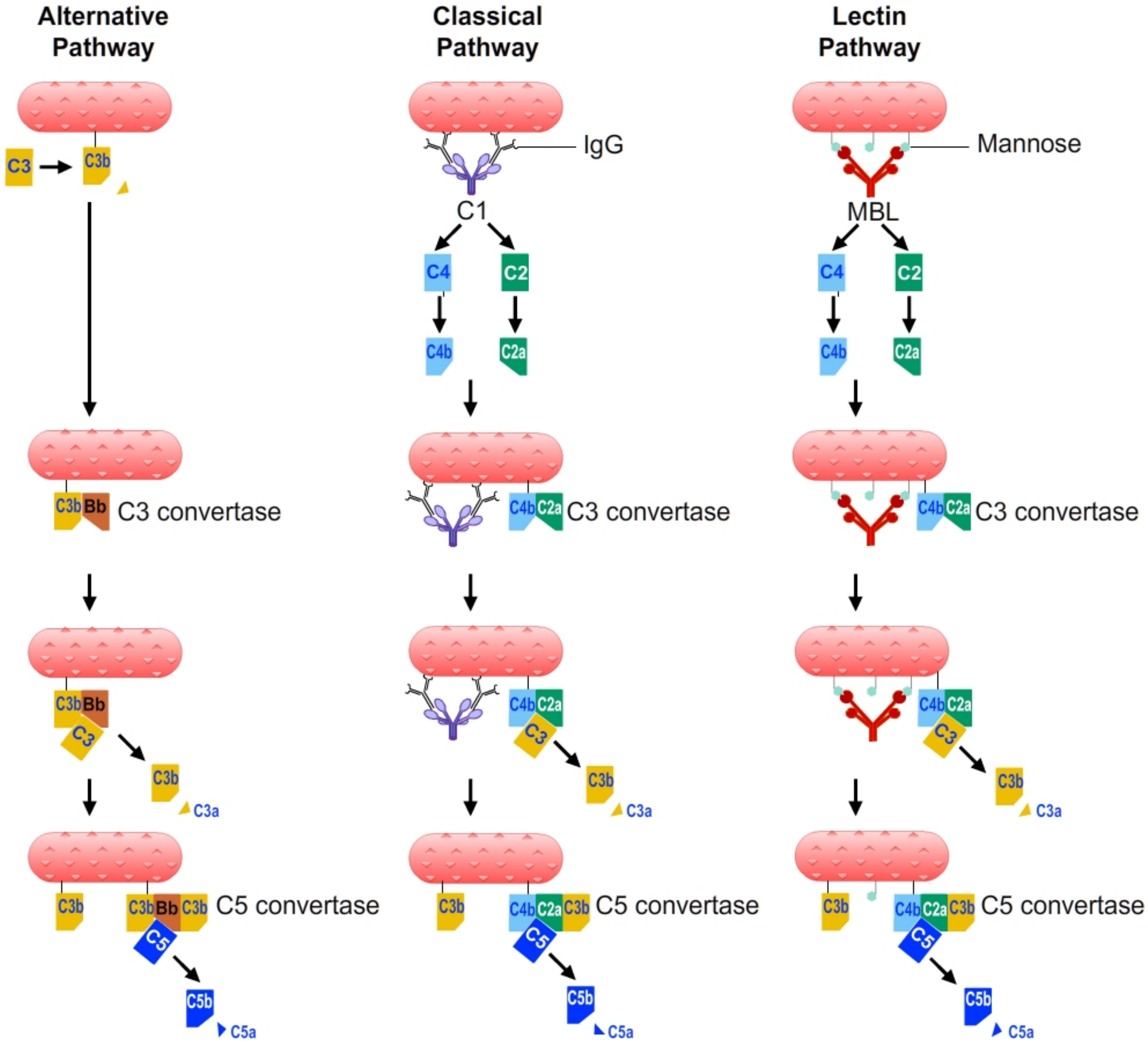
The complement cascade

- Discovered by Jules Bordet as a heat-labile component of normal plasma that **promotes opsonization and killing of bacteria by antibodies**, i.e. ‘complements’ the antibacterial activity of antibodies.

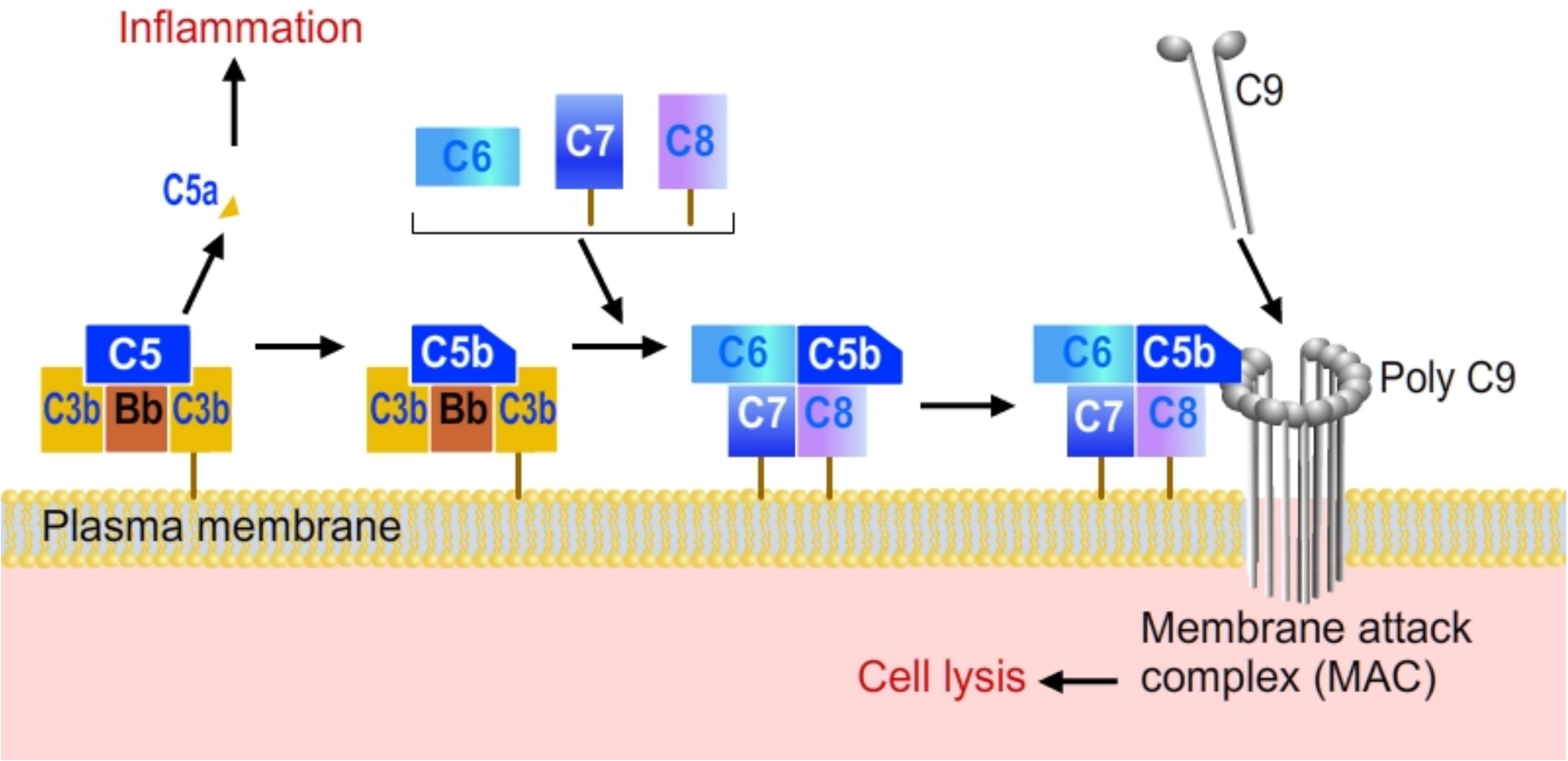
- Originally **evolved as part of innate immune system**
- Set of **~30 proteins** present in blood in active form (C1 - C9, factor B, factor D…)
- **Activated** upon pathogen recognition **through a proteolytic cascade**



The early steps of complement activation



The late steps of complement activation



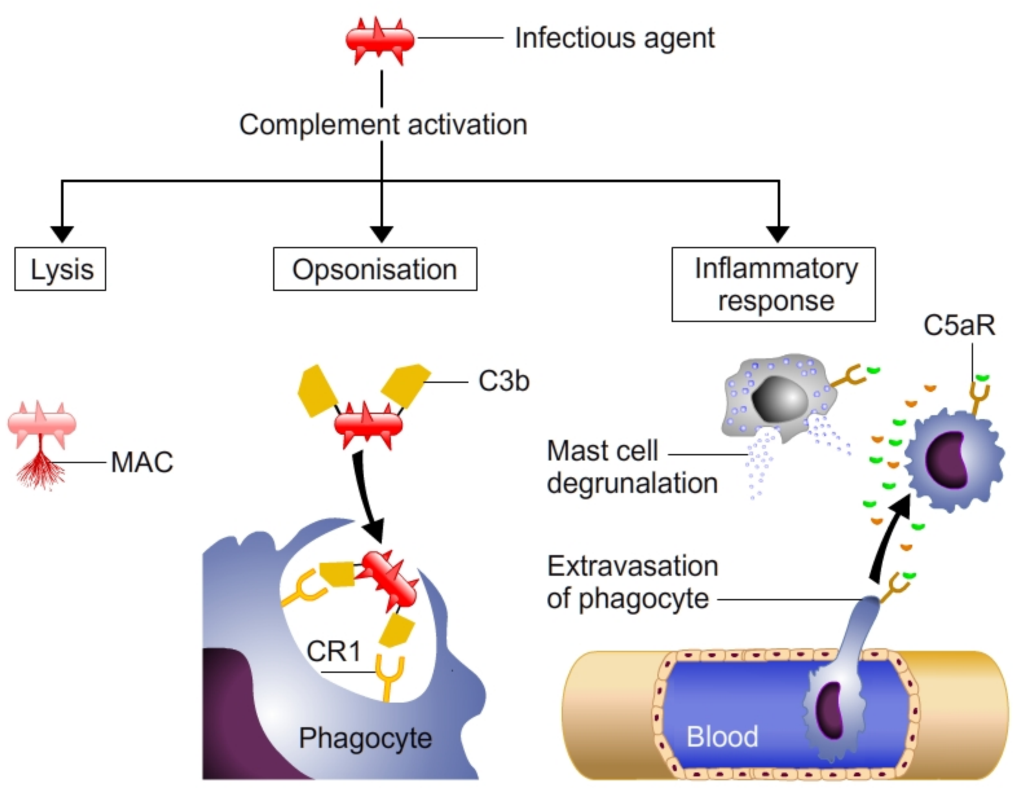
The late steps of complement activation start **after the C5 convertase forms** and are **identical in the alternative and classical pathways**.

Products generated in the late steps **induce inflammation** (C5a) and **cell lysis** (the membrane attack complex [MAC]).

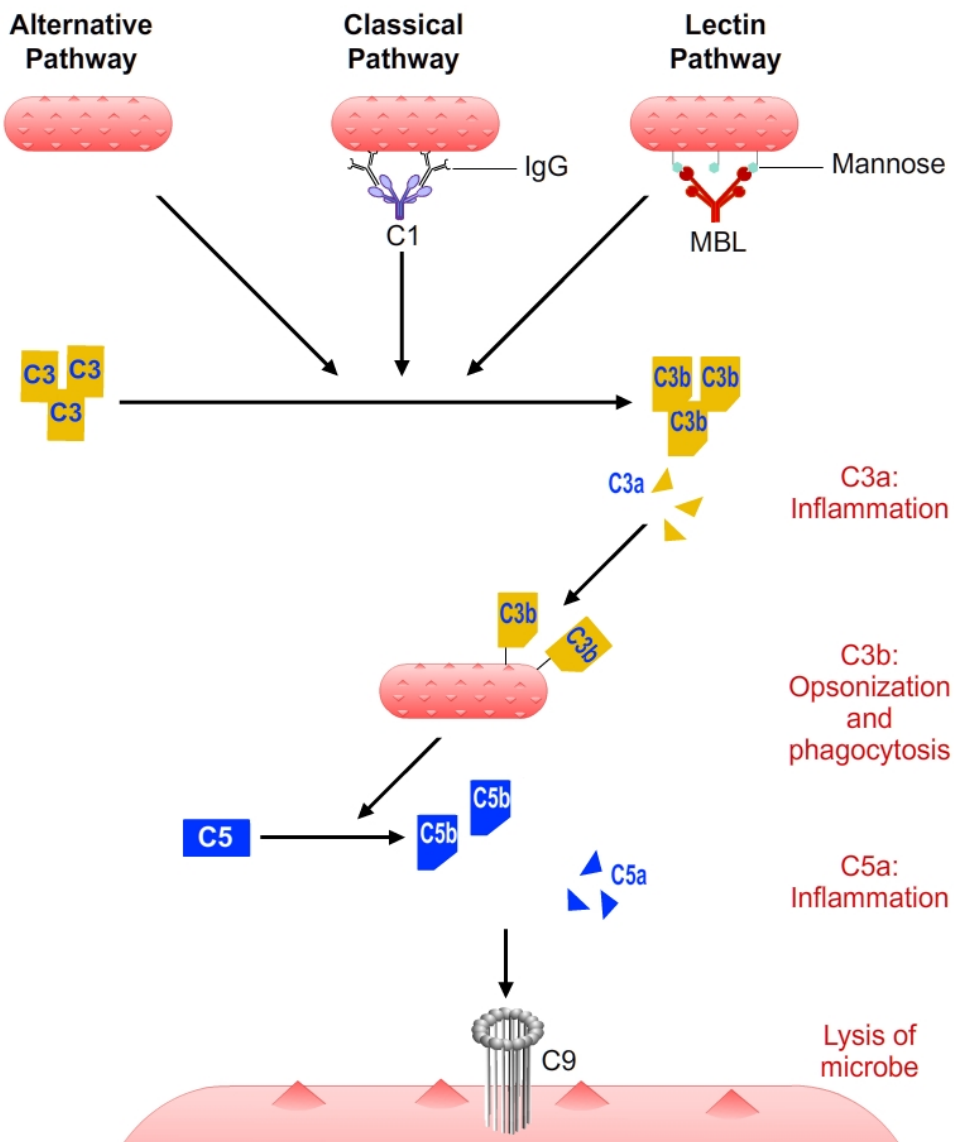
The complement cascade

Complement serves three main functions in innate immunity :

- **pathogen lysis** through the formation of a membrane attack complex (MAC)
- **opsonisation**: C3b binds to microbes making them susceptible to engulfment by phagocytes expressin receptors for C3b.
- **inflammation**: recruitment of more defense cells through C5a and C3a



Summary: Pathways of complement activation

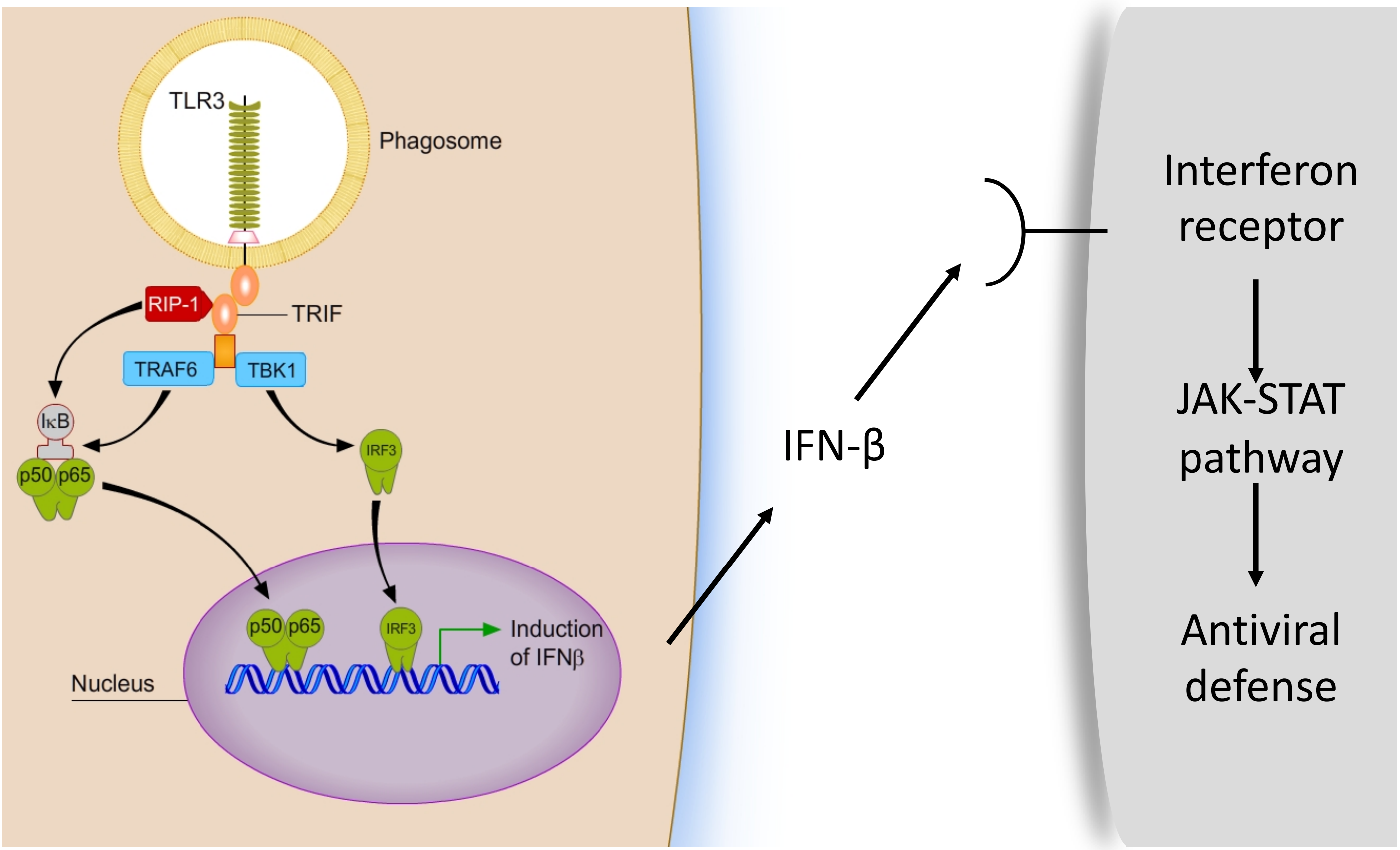


The complement system can be **activated by three distinct pathways**, all of which lead to the **production of C3b** (**early steps**). C3b initiates the **late steps** of complement activation, culminating in the production of numerous peptides and **polymerized C9** (which forms the **membrane attack complex**, so called because it creates holes in plasma membranes).

See image for principal functions of proteins produced at different steps.

Defense mechanisms by Type I Interferons

- **Virus-infected cells** produce **type I Interferons (IFN-α and IFN-β)**
- IFN genes are **induced by NF-κB upon binding of dsRNA to TLR3**
- IFN binds to **IFN receptors** in nearby cells and induces the **JAK-STAT pathway** (antiviral defence)



Defense mechanisms by Type I Interferons

- Viral dsRNA in infected cells induces **IFN α/β expression**
- IFN α/β generates an "**antiviral state**" in infected and surrounding cells (inhibition of translation, expression of antiviral genes, …)

Virus-infected host cell

- **IFN α**
- **IFN β**

- **Resistance** to viral replication (all cells)
- Increased **MHC class I** expression (all cells)
- More **antigen presentation** (all cells)
- **NK cell activation** to kill virus-infected cells

Conclusion 2C: Effector Molecules

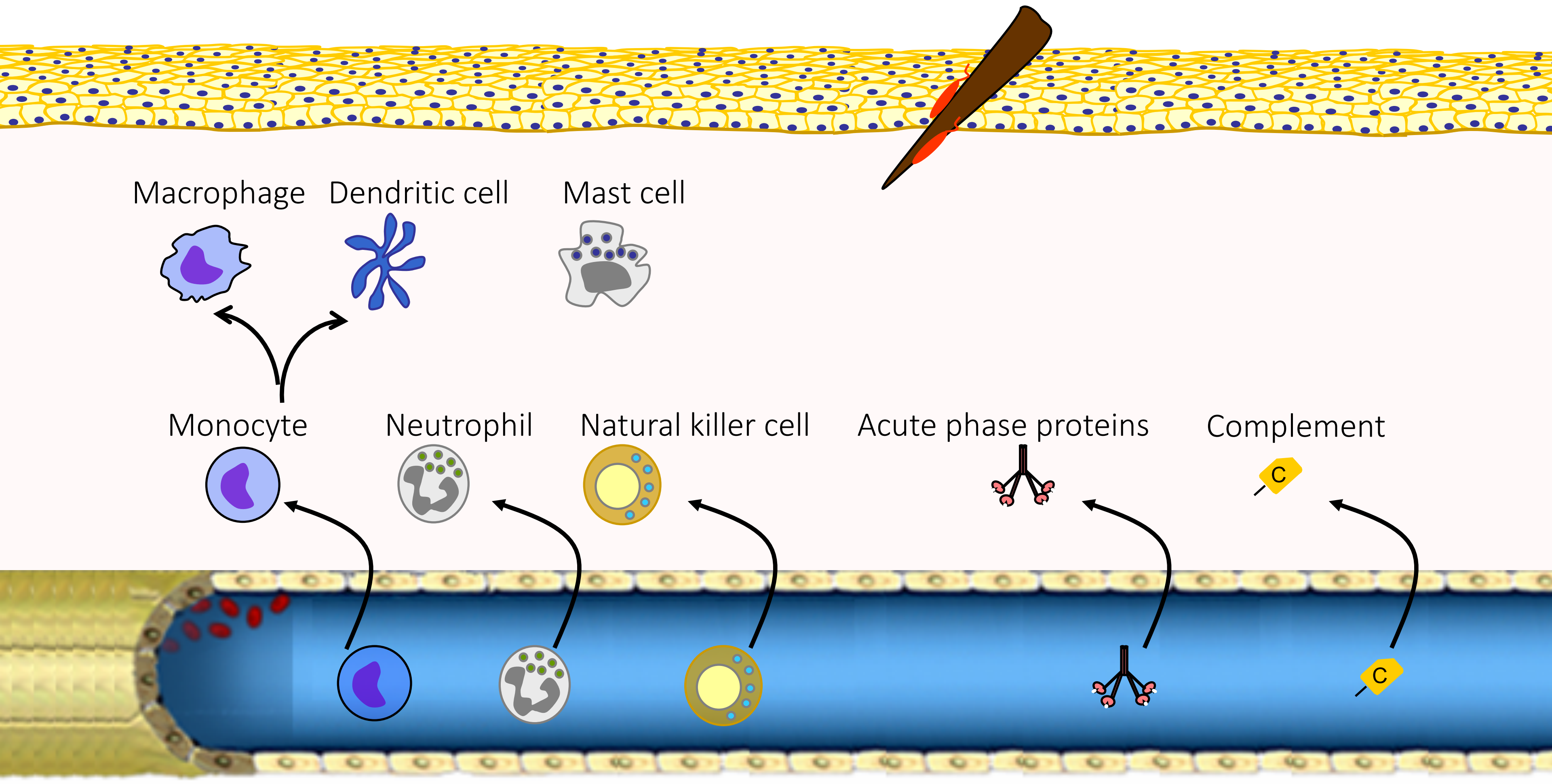
- **Antimicrobial peptides** : constitutive or inducible defense found in all organisms
- Plasma proteins including **acute phase proteins** are produced by the **liver** and promote complement activation, opsonisation, protease inhibition…
- The **complement cascade** is a sophisticated immune defense
    - **Three modes of activation**: MBL or C3 hydrolysis (innate) or C1-Ig (adaptive)
    - **Three functions**: Inflammation, Opsonisation and Destruction (MAC)
- **Type I Interferons** activate **antiviral defense** in nearby infected cells.

II.D. The inflammatory response

*Celsus (Roman encyclopaedist, 25 BC) is credited with recording the **cardinal signs of inflammation**: **calor** (warmth), **dolor** (pain), **tumor** (swelling) and **rubor** (redness and hyperaemia).*

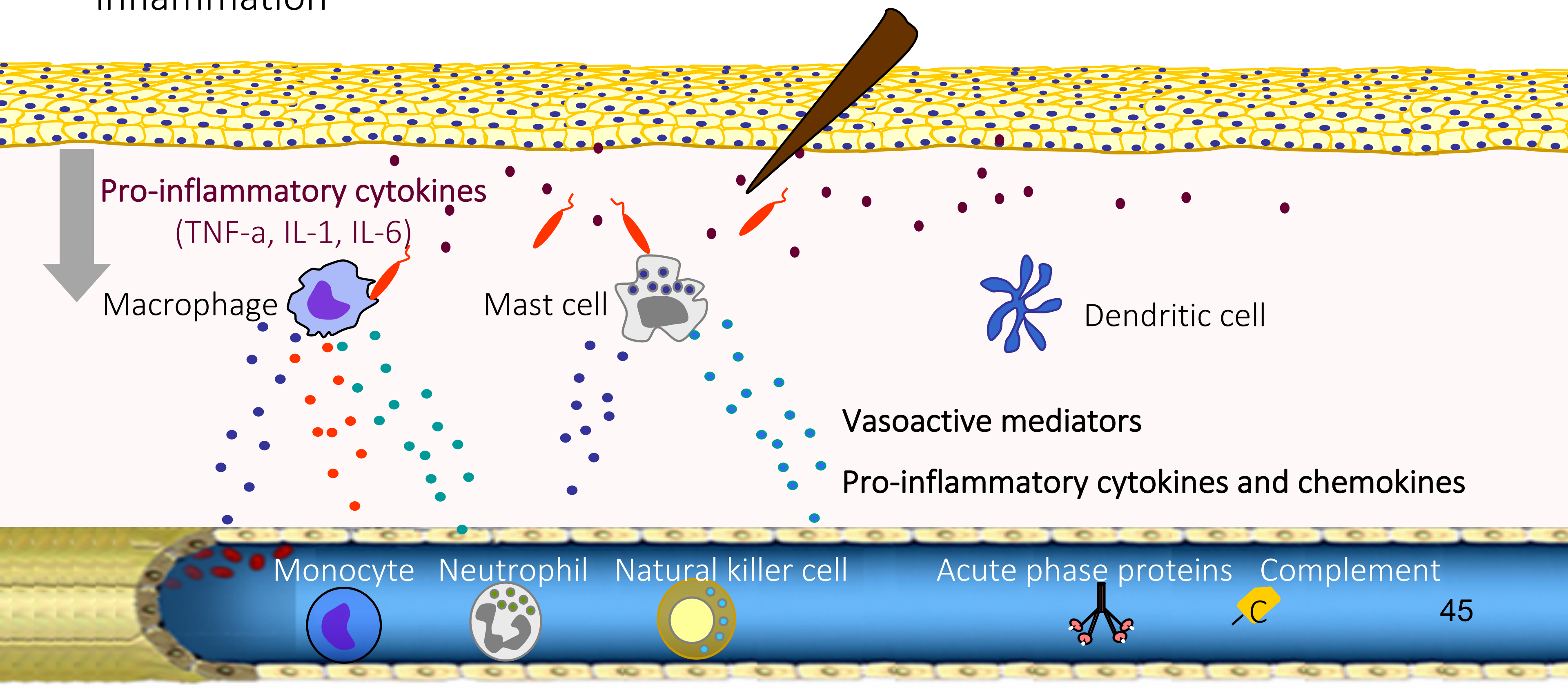
Local inflammation

- Inflammation is initiated by macrophages and mast cells responding to pathogens and epithelial mediators.
- Inflammation is designed to deliver additional effector molecules and cells to sites of infection.



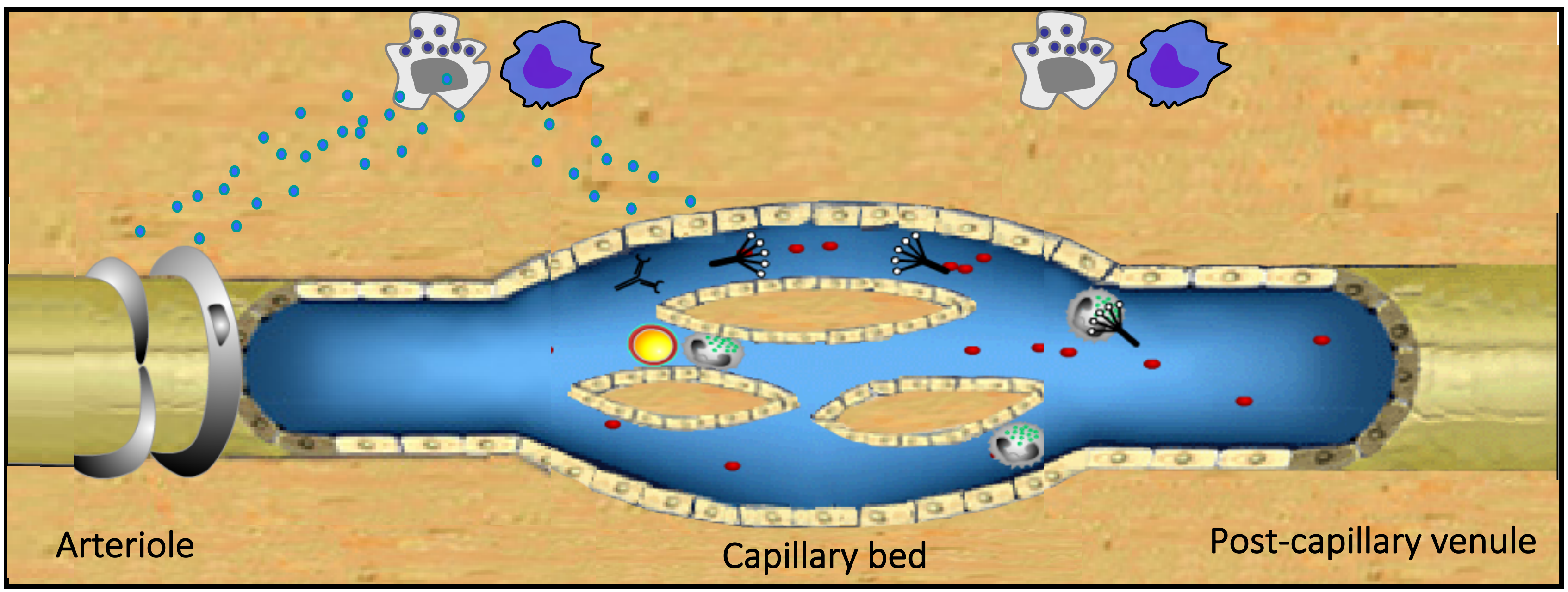
Local inflammation: role of epithelial cells

- First cells to encounter pathogens
- Secrete a **battery of antimicrobial factors** at their apical surface
- Send out **pro-inflammatory molecules** at their basolateral surface to alert underlying immune cells
- Cause macrophages and mast cells to release soluble mediators that set up a local inflammation



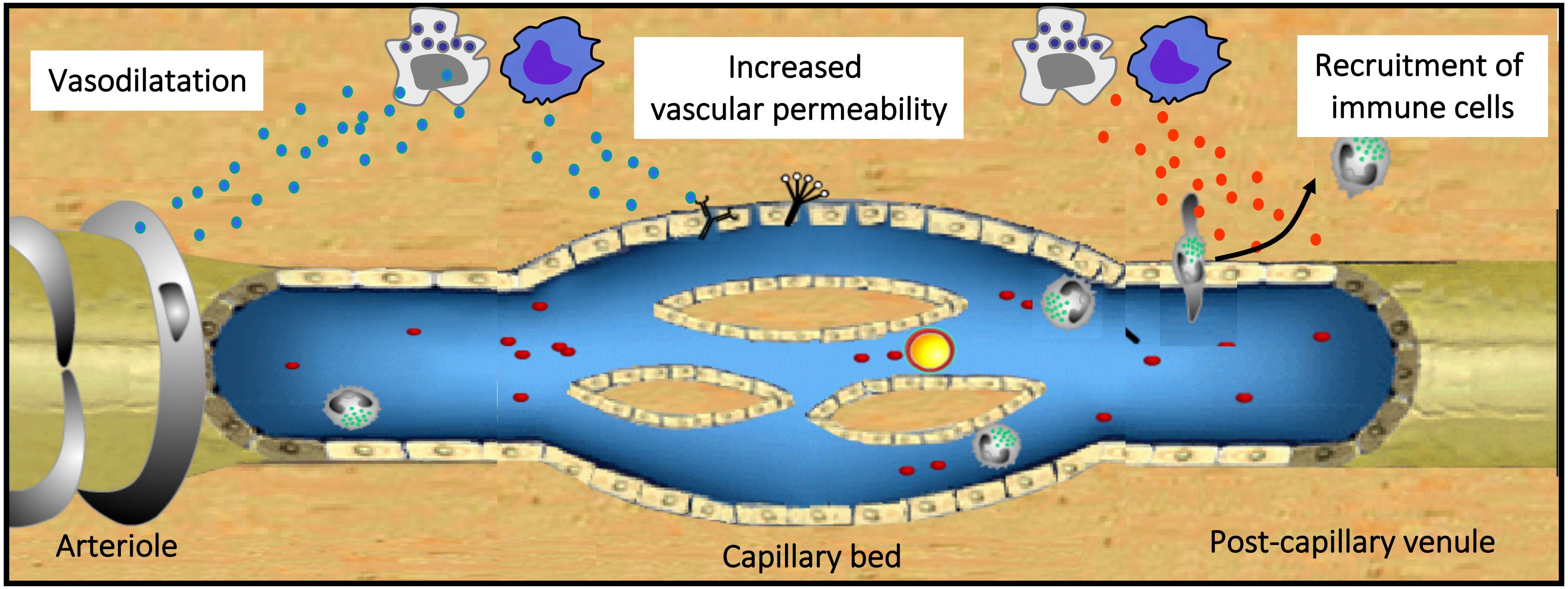
Local inflammation

- Inflammation involves **vascular changes** designed to deliver additional effector molecules and cells from the blood to sites of infection.
- Mast cells release **vasoactive mediators** (histamine, substance P, leukotrienes, prostaglandins) that cause:
  - dilatation of arterioles, leading to increased local blood flow and reduced velocity
  - increased permeability of capillary beds, allowing for the entry of complement.



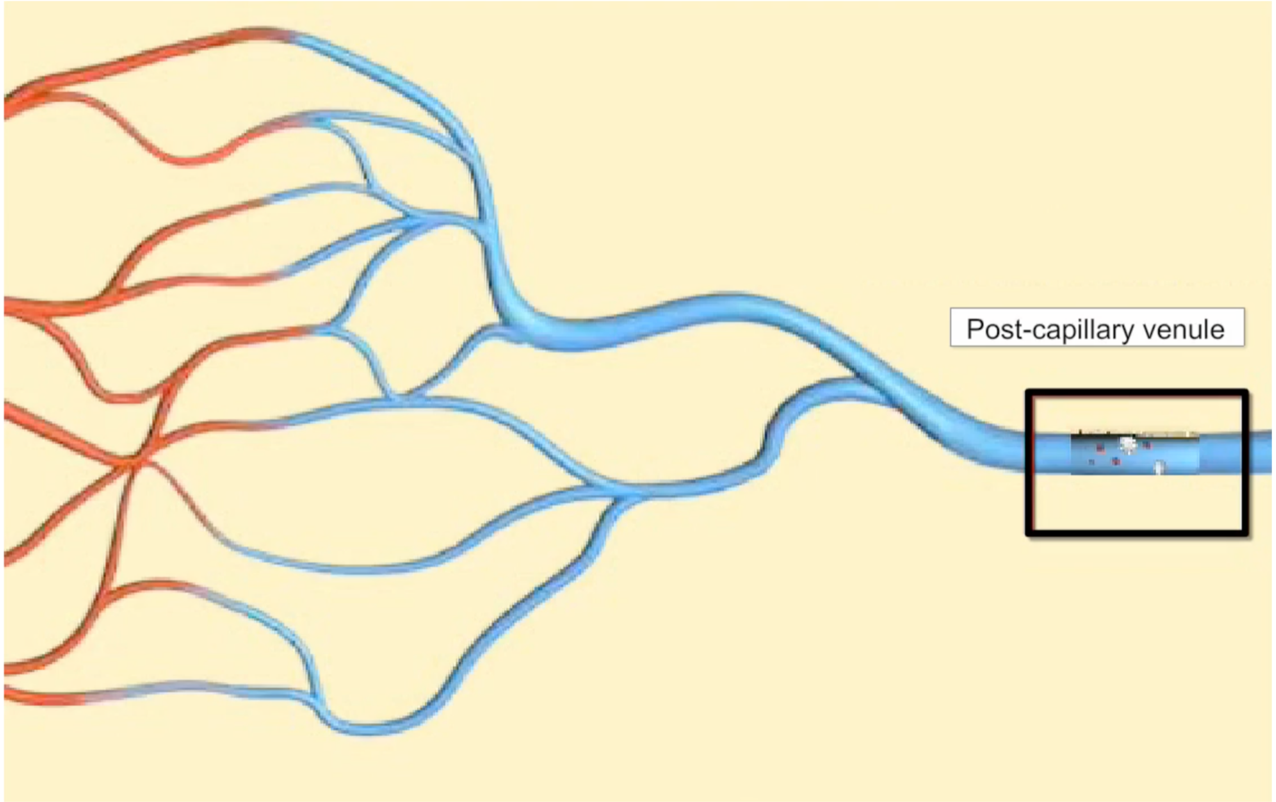
Local inflammation

- Inflammation involves **vascular changes** designed to deliver additional effector molecules and cells from the blood to sites of infection.
- **Vasoactive mediators**:
  - o dilatation of arterioles, leading to increased local blood flow and reduced velocity
  - o increased permeability of capillary beds, allowing for the entry of complement.
- **Proinflammatory cytokines and chemokines**:
  - o ↑adhesion molecules on endothelial cells to promote binding of circulating effector cells
  - o recruitment of additional effector cells (neutrophils, monocytes)



Local inflammation: recruitment of circulating leukocytes

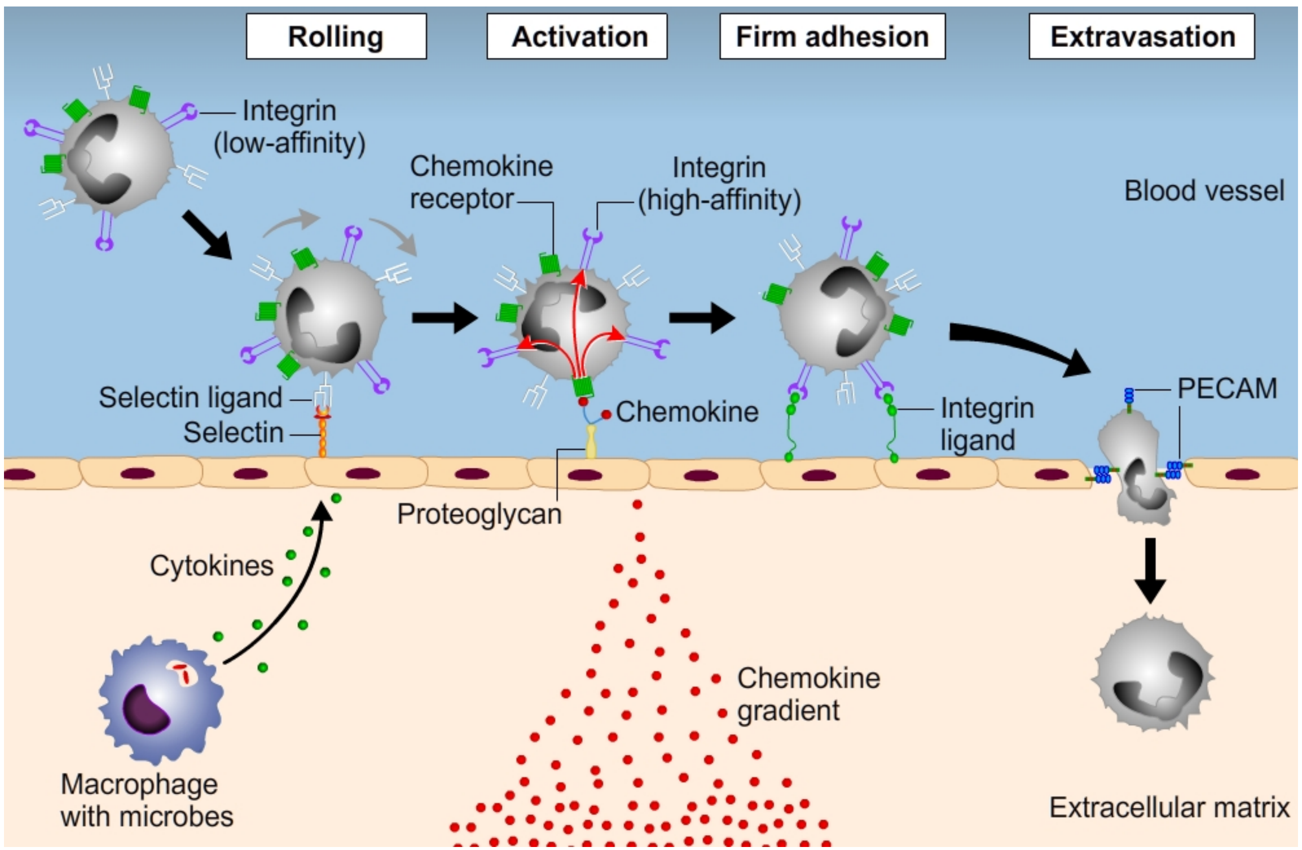
Migration of circulating leukocytes takes place in post-capillary venules.



Local inflammation: recruitment of circulating leukocytes

Four different phases of extravasation:

1. **Rolling:** low adherence of leukocytes in vessels
2. **Integrin activation**
3. **Strong adhesion:** strong adherence to endothelial cells (>30sec, involvement of adhesion molecules)
4. **Diapedesis:** crossing of endothelium by leukocytes

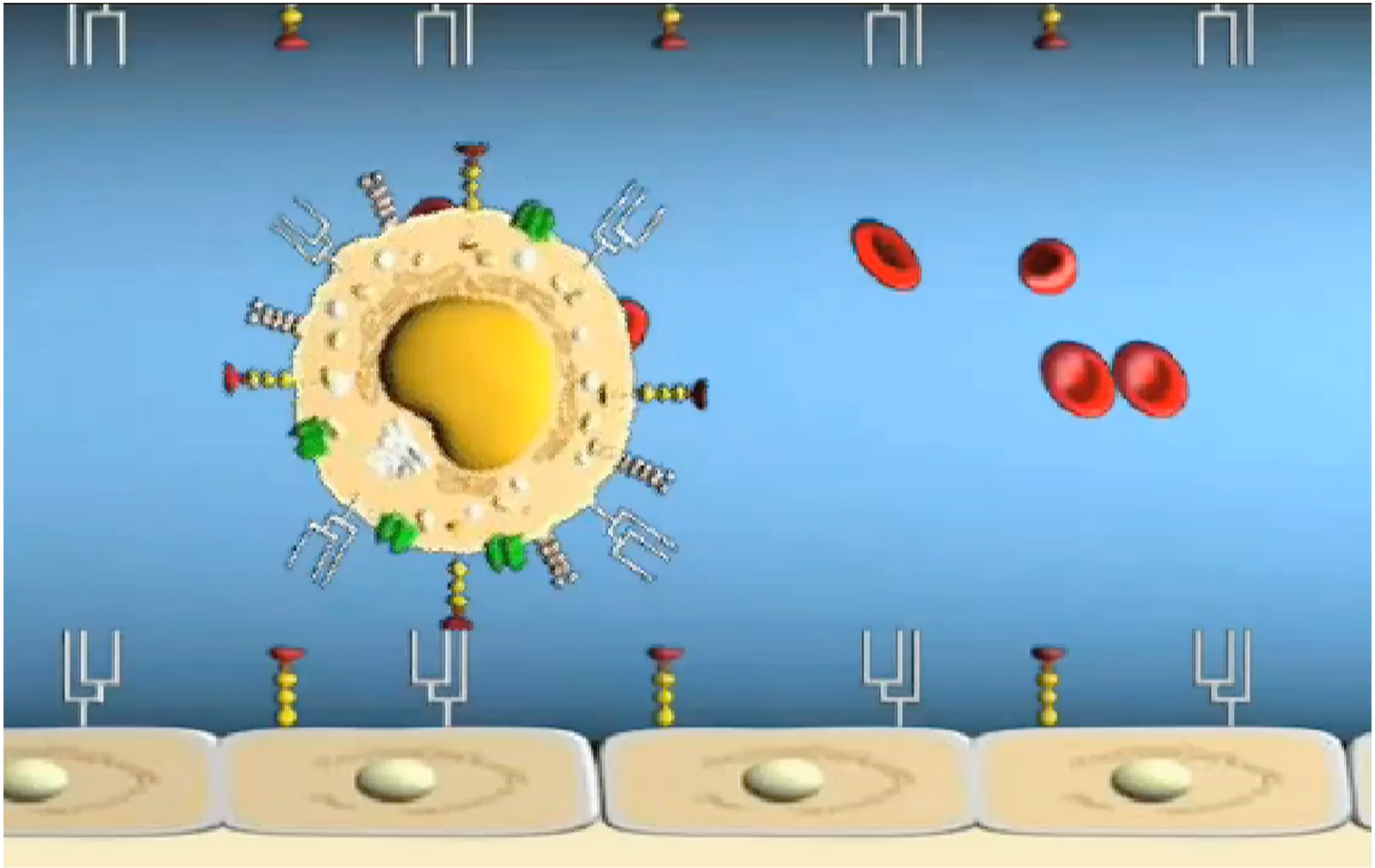


E-Selectin binds **carbohydrates**

LFA-1 (integrin) binds to **ICAM-1** (Ig superfamily)

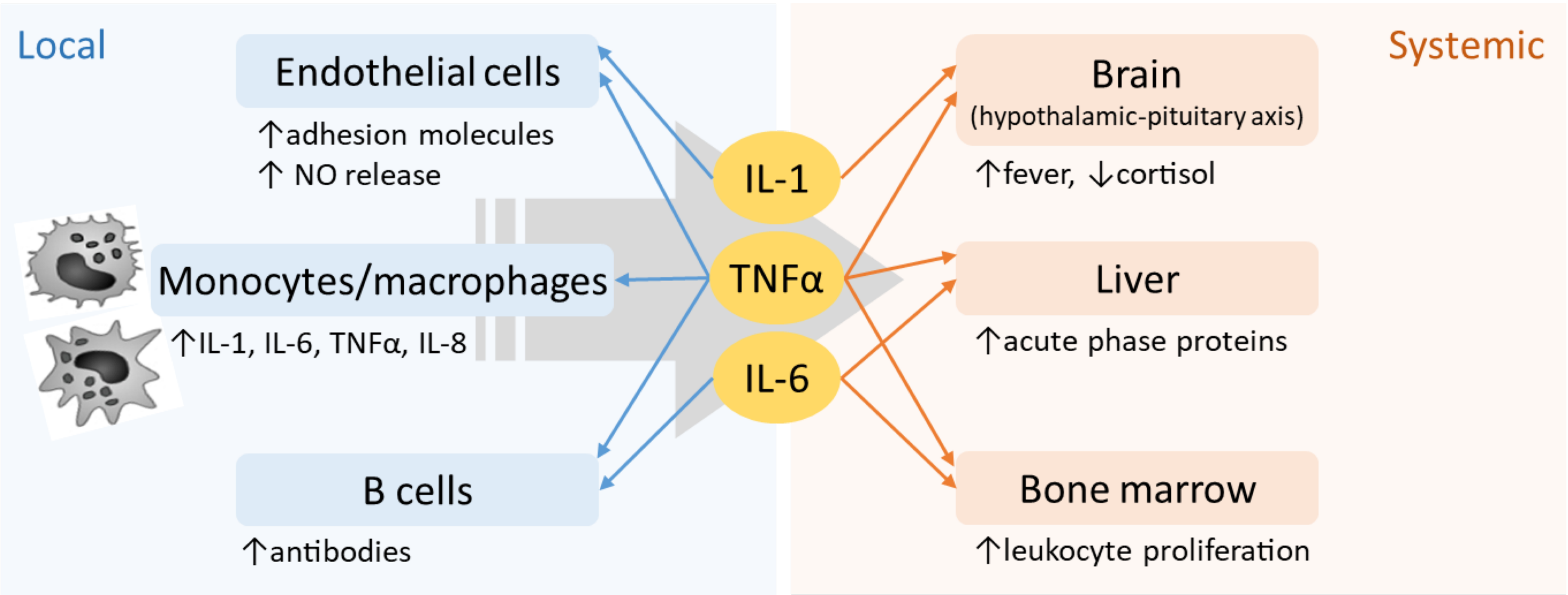
Local inflammation: Recruitement of circulating leukocytes

A neutrophil extravasating between endothelial cells

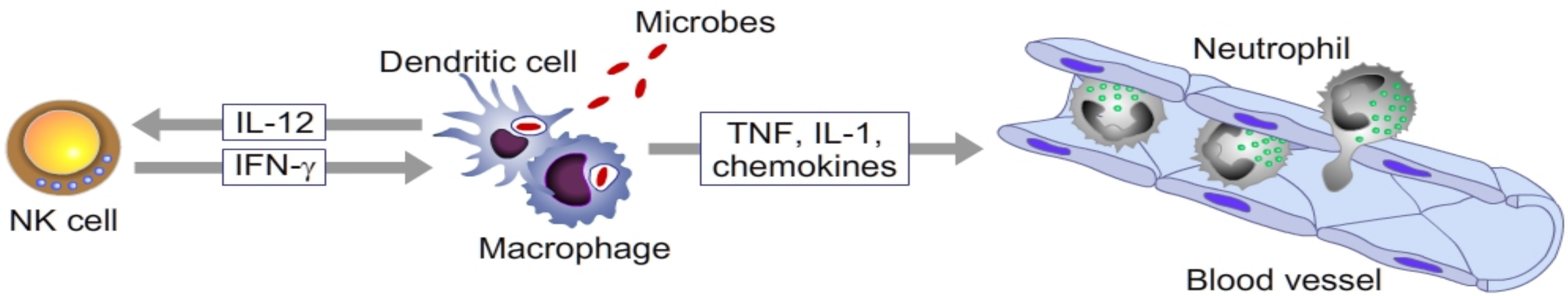


Local inflammation: critical role of cytokines

- Cytokines are **secreted small proteins** (<25kDa) produced by immune cells that orchestrate the immune response **locally and systemically**.
- Structurally diverse
- The **three major pro-inflammatory cytokines** are **IL-1, TNFα, and IL-6** (produced by macrophages and mastocytes)



Summary: innate immune cytokines



- **IL1, IL6, TNFα**: Inflammation
- **IL-12**: activates NK and T cells (Th1 response)
- Type I interferon: **IFNα, IFNβ** (antiviral response)
- Type II interferon: **IFNγ** (activates macrophages)
- **IL-10**: anti-inflammatory

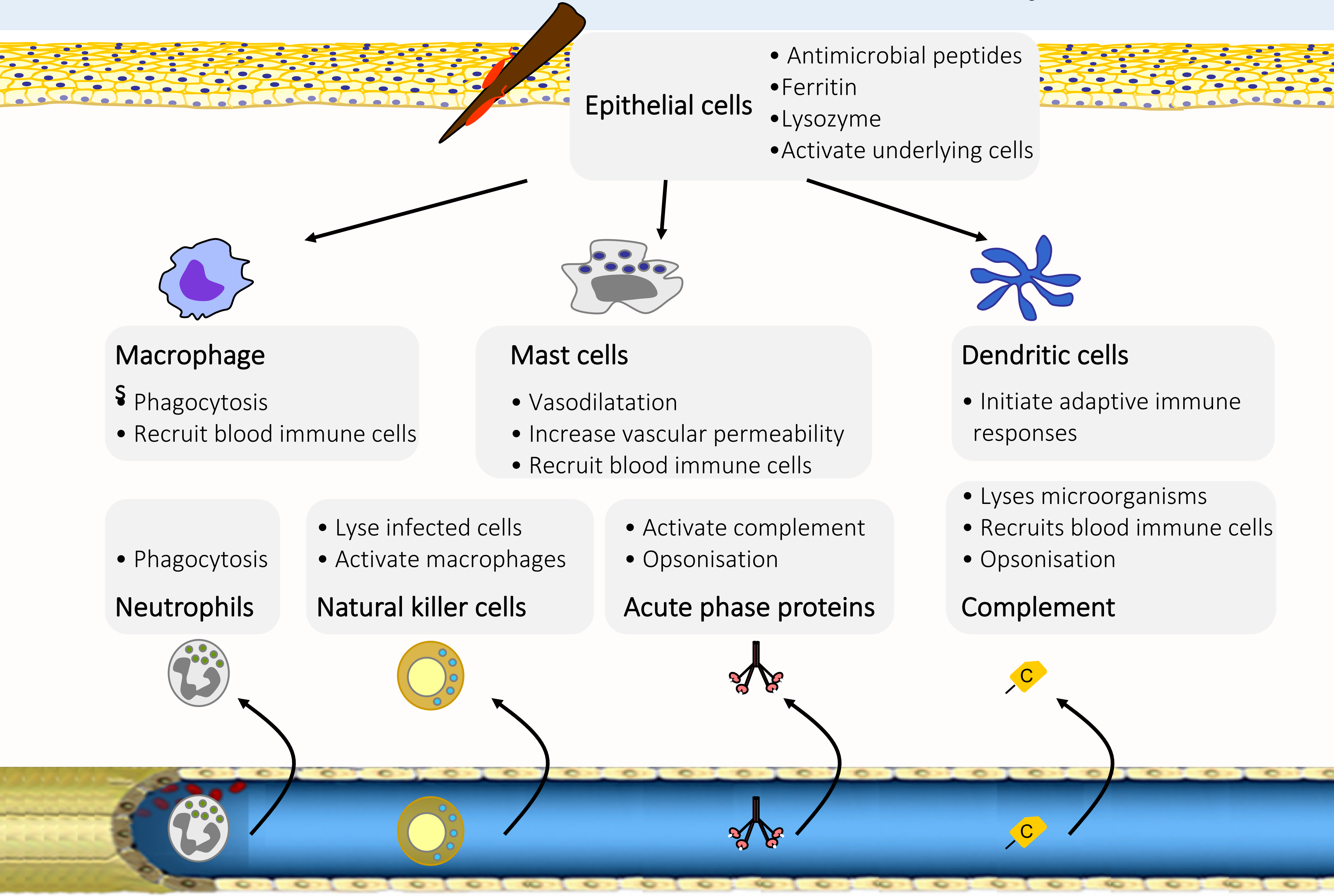
IFN, interferon; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NK, natural killer.

Summary: innate immune cytokines

Cytokine	Source	Target	Effect
TNF	Macrophages T cells	• Endothelial cells • Neutrophils • Brain (hypothalamus) • Liver • Muscle, fat • Various cell types	• ↑adhesion, ↑NO • Activation • Fever • ↑Acute phase proteins • Cachexia • apoptosis
IL-1	Macrophages Endothelial cells Epithelial cells	• Endothelial cells • Brain (hypothalamus) • Liver	• ↑adhesion, ↑NO • Fever • ↑Acute phase proteins
Chemokines	Macrophages DCs Endothelial cells T cells Fibroblasts platelets	• leukocytes	• ↑integrin affinity • Chemotaxis • Activation
IL-12	DCs Macrophages	• NK cells, T cells • T cells	• ↑IFNγ, cytotoxic activity • T_H1 differentiation
IFNγ	NK cells T cells	• Macrophages	• activation
IFNα **IFNβ**	DCs, macrophages fibroblasts	• All cells • NK cells	• Antiviral state, ↑MHCI • Activation
IL-10	Macrophages DCs T cells	• Macrophages, DCs	• ↓IL-12, ↓co-stimulators, ↓MHCII
IL-6	Macrophages Endothelial cells T cells	• Liver • B cells	• ↑Acute phase proteins • ↑antibodies

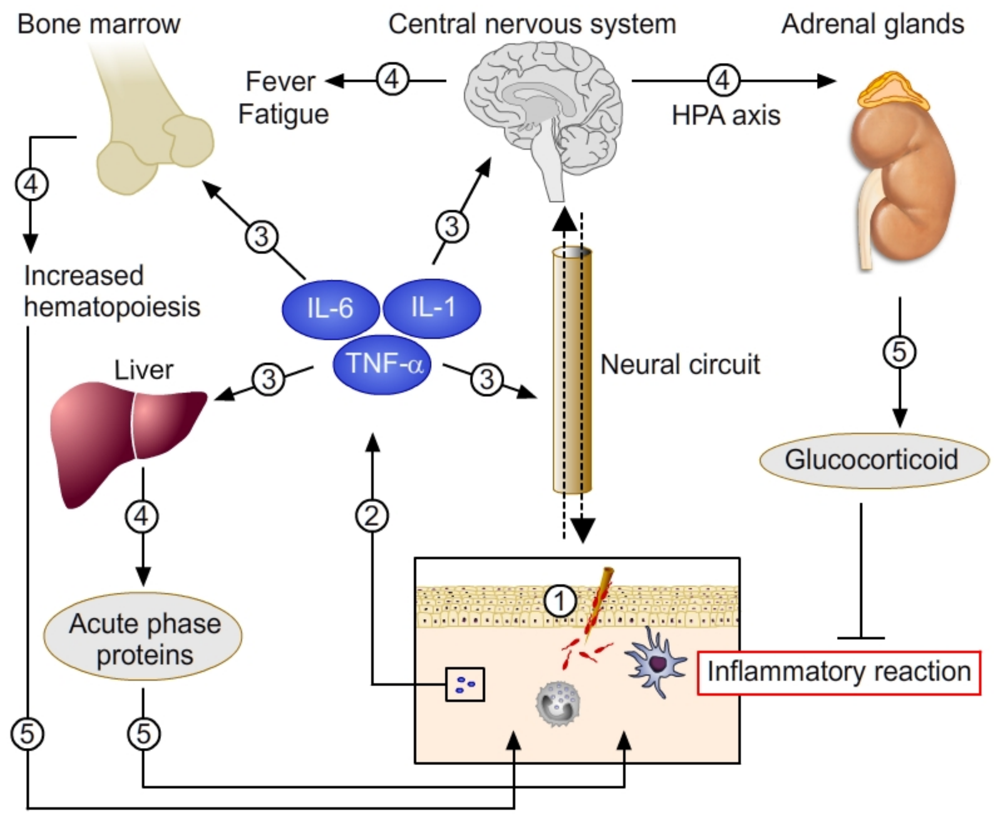
IFN, interferon; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NK, natural killer.

Local inflammation: A summary



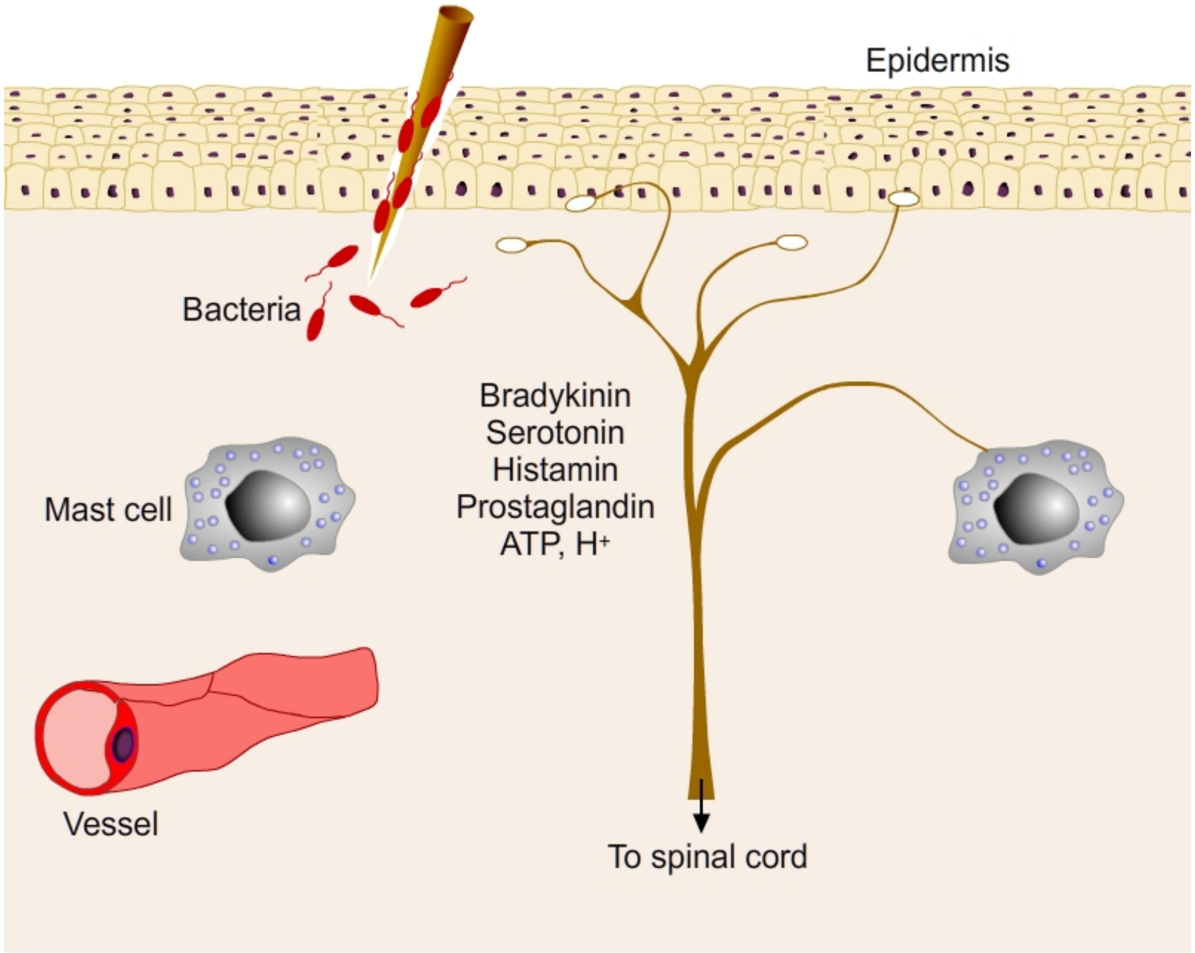
Systemic inflammation: Role of the liver and the nervous system

- Induced by **cytokines (IL-1, IL-6, TNFα)**
- Induces **symptoms of illness** (fever, anorexia, fatigue, withdrawal)
- Involves both **neural and hormonal** circuits (hypothalamic-pituitary-adrenal axis)
- Provides an important **negative regulatory feedback** through the production of **glucocorticoids**
- **Acute phase proteins** replenish (and increase) immune serum proteins
- Cytokines stimulate **hematopoiesis**



Inflammation and the nervous system

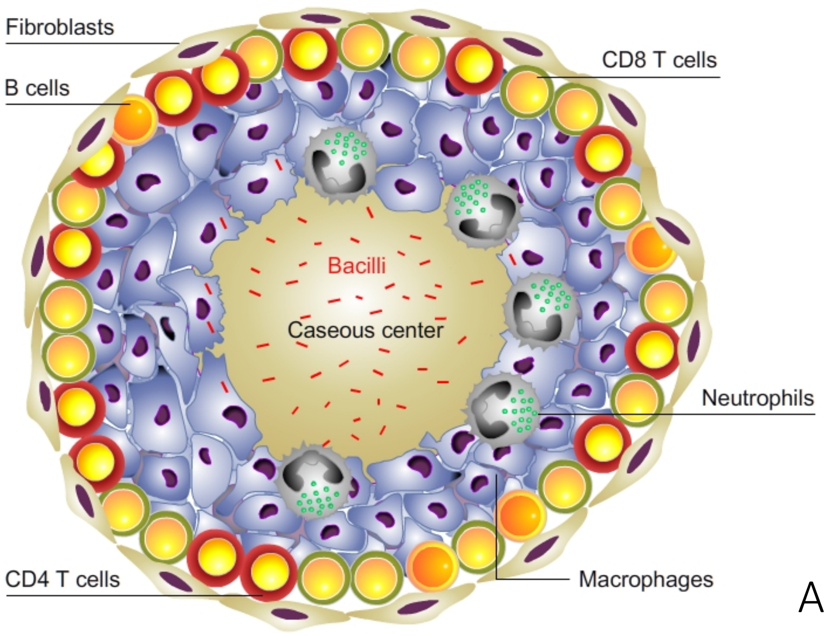
- Inflammatory molecules sensitize neuronal dendrites → ‘dolor’
- Neurons release substance P and CGRP which promote inflammation

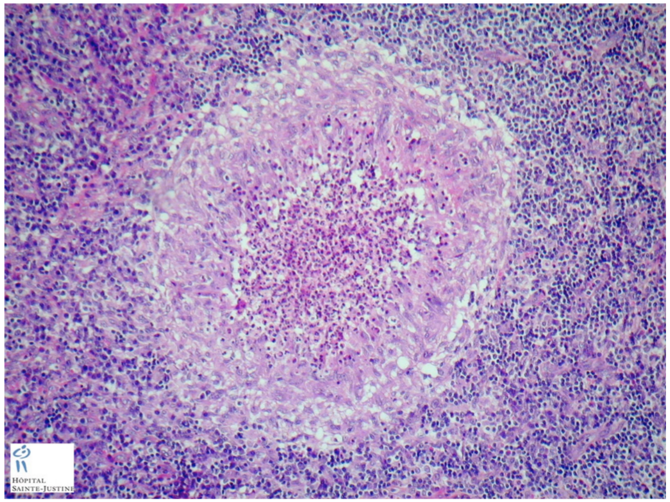


Resolution of inflammation

4 outcomes:

- **Resolution** (absence of damage, regeneration)
- **Wound healing** (→ fibrosis: increase of accumulation of extra-cellular matrix components that replace cells or tissue that cannot be replaced)
- **Chronic inflammation** (can lead to a granuloma, e.g. *Mycobacterium tuberculosis*)
- **Septicemia** (can lead to septic shock due to the massive production of TNF-α : fever, tachycardia, hyperventilation… →multiple organ failure, loss of blood pressure → death)





A granuloma

Conclusion 2D: Inflammation

- Reaction that takes place after damage/infection of a tissue. It involves local activation of innate immune cells, accumulation of fluid, plasma proteins, and recruitment of leukocytes
- Orchestrated by cytokines, notably the inflammatory trio IL1, IL6 and TNFα
- Systemic effects
  - nervous system (fever, sickness)
  - liver (synthesis of acute phase proteins)
  - bone marrow (increased hematopoeisis)
- Inflammatory reactions can be acute or chronic
- Deleterious side effects (damage to the host)
  - Existence of negative feedback control (glucorticoids)
  - Importance of anti-inflammatory molecules

II.E. Recognition and Role

The innate immune system

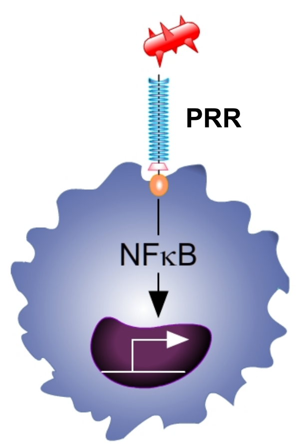
Innate Immune Recognition

How does the innate immune system detect infection?

- direct recognition of **pathogens**
  (Pattern recognition receptors/PAMPs, Charles Janeway, 1989)
- **Danger** signals from damaged tissue (Polly Matzinger 1994)
- recognition of **missing or altered self** (NK, complement)

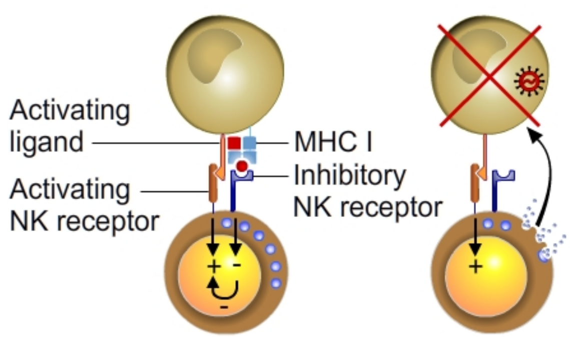
Recognition of

"microbial non-self"

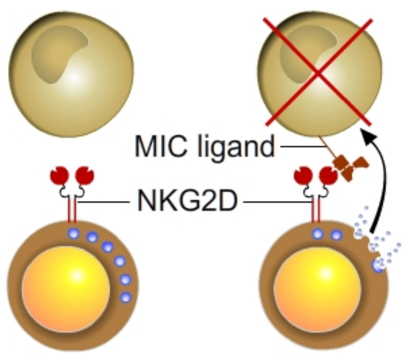


Macrophages, neutrophils
mast cells, epithelial cells

"missing-self"



"altered-self"



Natural killer cells

Concept of Pattern recognition (Janeway 1989)

Microbial non-self : PAMP (pathogen-associated molecular patterns)

Molecular structures that are

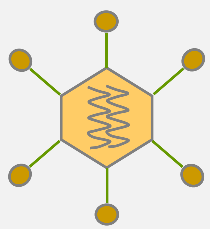
- unique to microbes and absent from mammalian cells
- essential for the metabolism, survival or pathogenicity of microbes, thus unlikely to mutate
- not unique to individual pathogens but shared by all the pathogens of a given class:
  - fungi
  - gram-positive bacteria
  - gram-negative bacteria
  - mycobacteria
  - viruses

PRRs (Pattern Recognition Receptors)

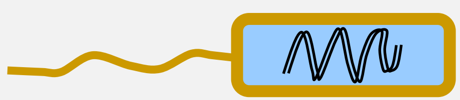
- <u>germline-encoded</u> receptors used to detect PAMPs
- recognize a class of microbes

Major PAMPs include

- **Nucleic acids** unique to microbes

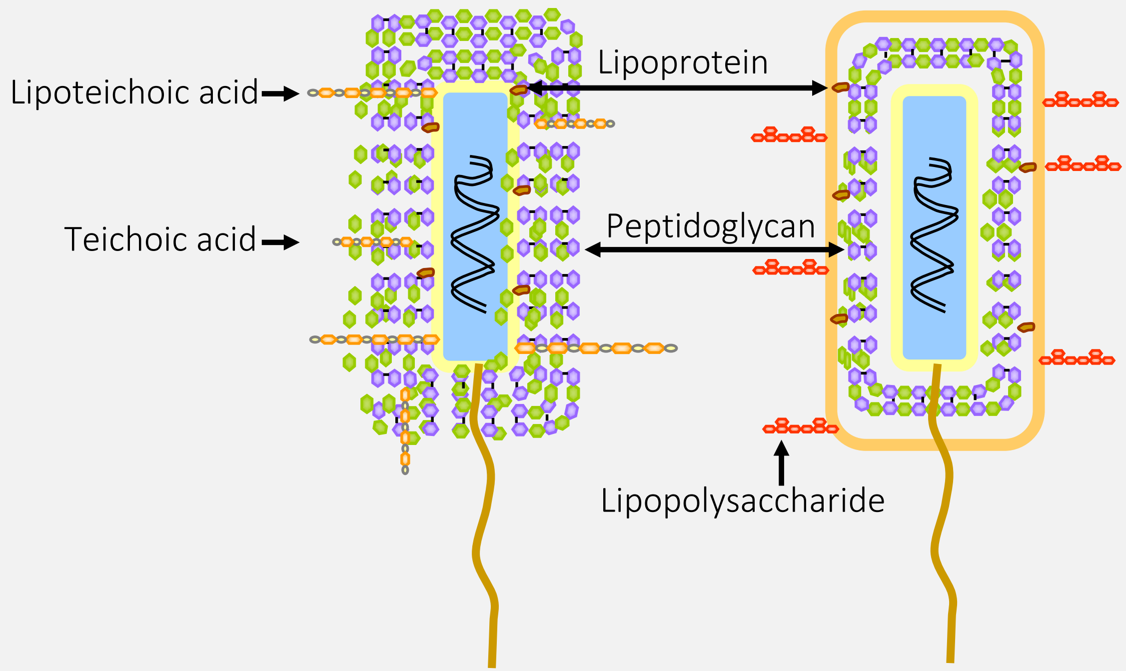


double-stranded RNA in viruses



unmethylated CpG DNA sequences in bacteria

- **Complex lipids and carbohydrates** synthesized by bacteria but not mammalian cells



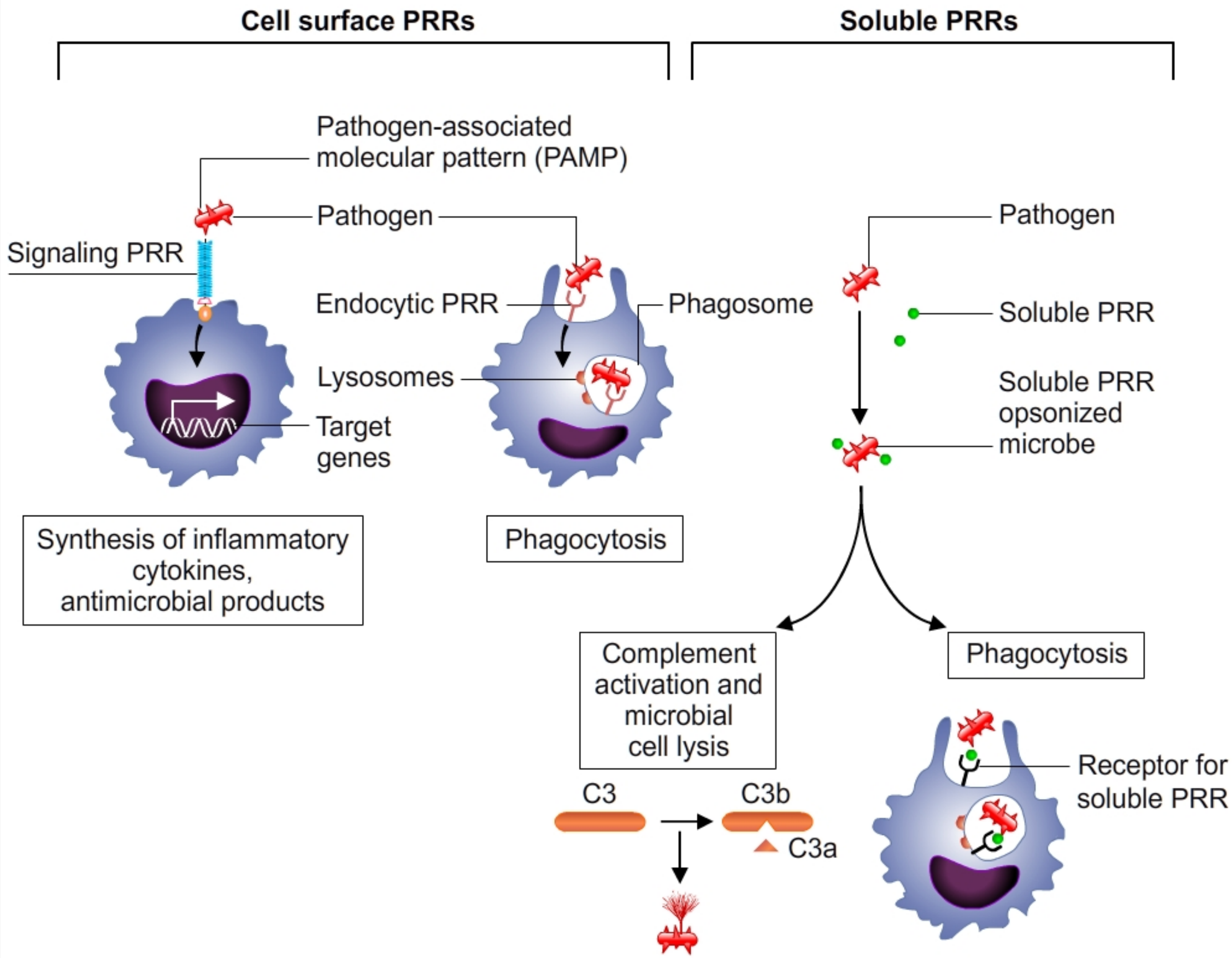
Gram-positive bacteria
(*Staphylococcus aureus*)
(*Streptococcus pneumonia*)

Gram-negative bacteria
(*Salmonella typhimurium*)

Recognition of microbial non-self

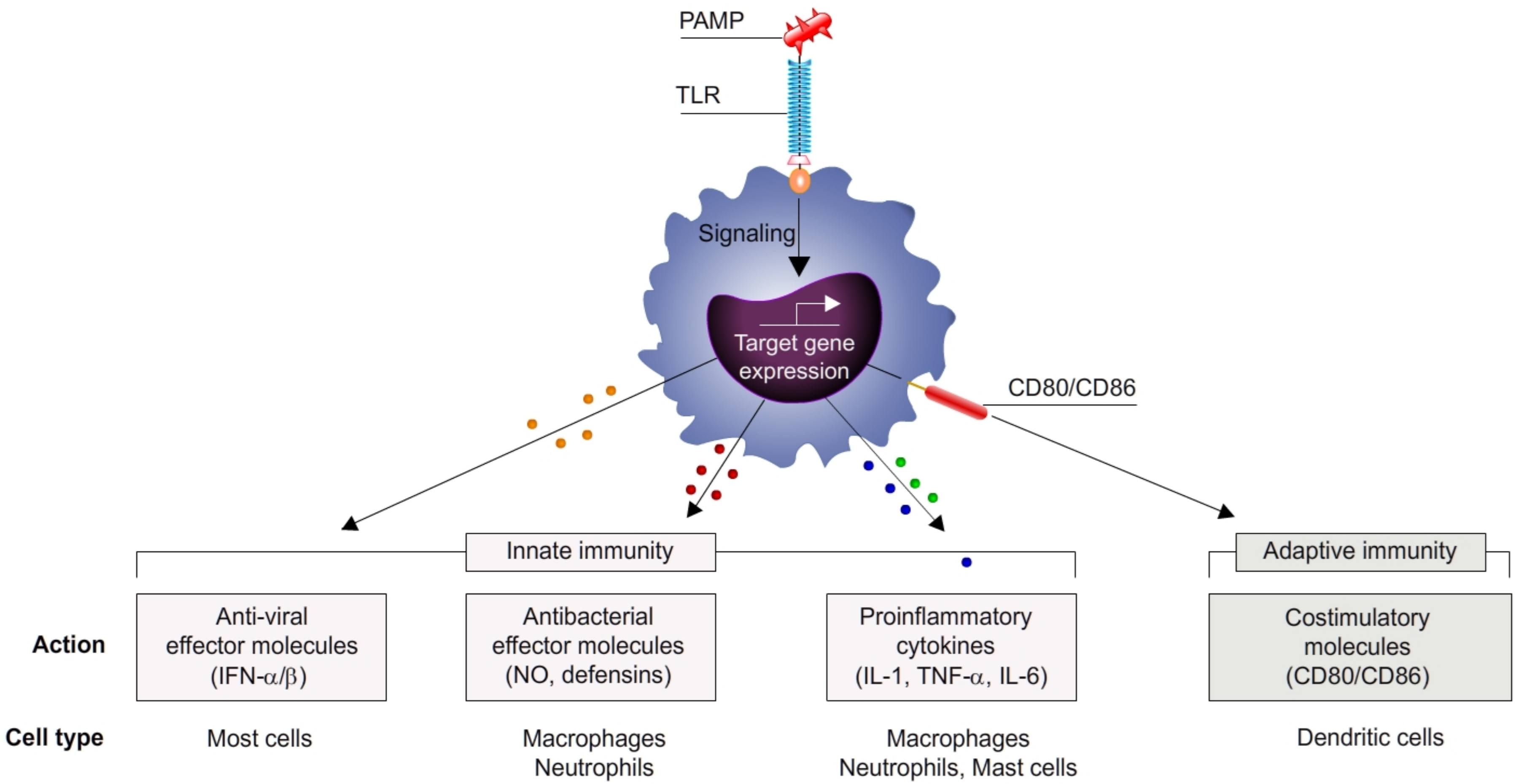
Three **classes** of Pattern recognition receptors:

- Signaling PRRs
- Phagocytic PRRs
- Soluble PRRs



Signaling receptors

All innate cells and epithelial cells express signalling PRRs, either at the cell surface or intracellularly.

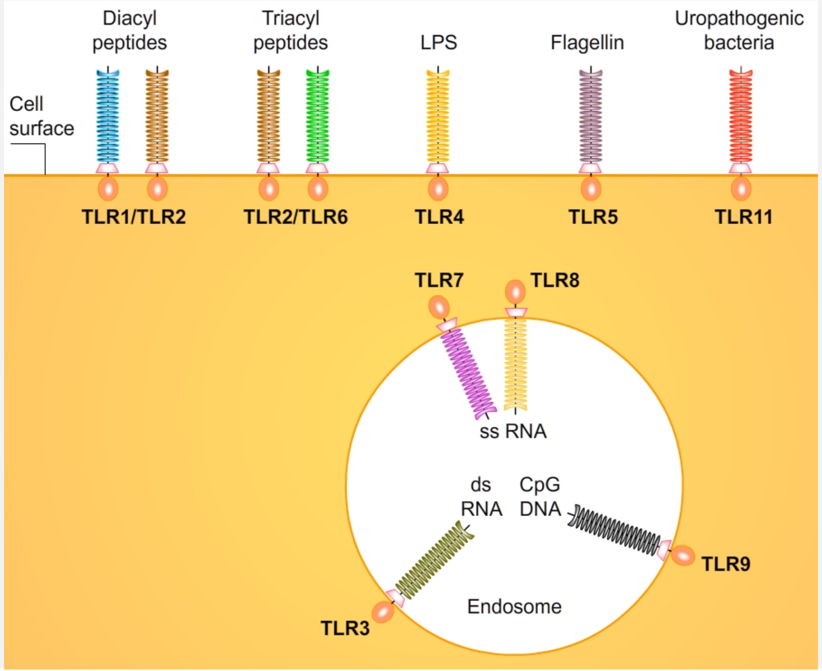


Major PRR signaling receptors

Cell membrane / endosome

Toll-like receptors (TLRs):

- 11 TLRs identified
- recognize various PAMPS (LPS, lipoproteins, dsRNA, sd RNA, bacteria DNA)



Cytoplasm

NOD-like receptors (NLRs):

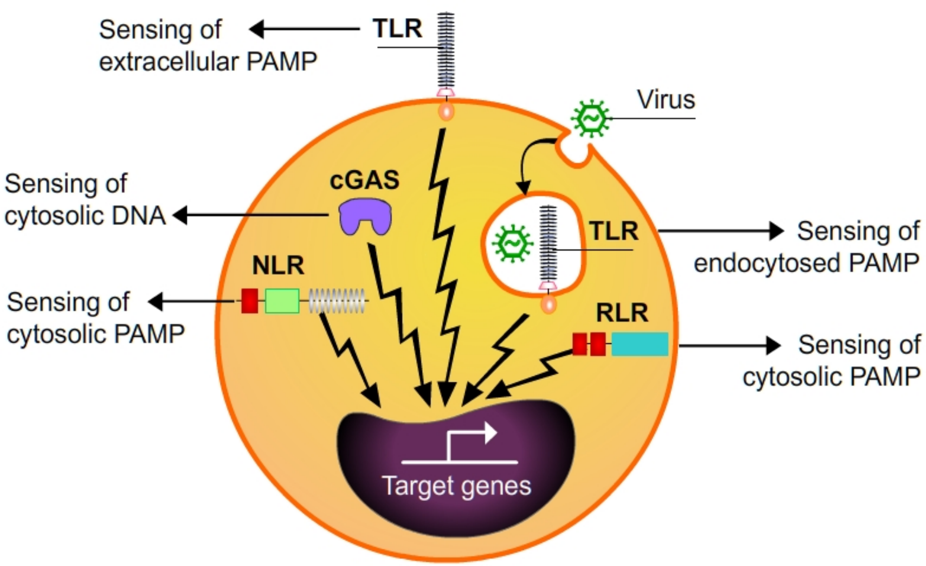
- NOD1, NOD2
- recognize bacterial peptidoglycan

RIG-I and MDA5 helicases (RLRs):

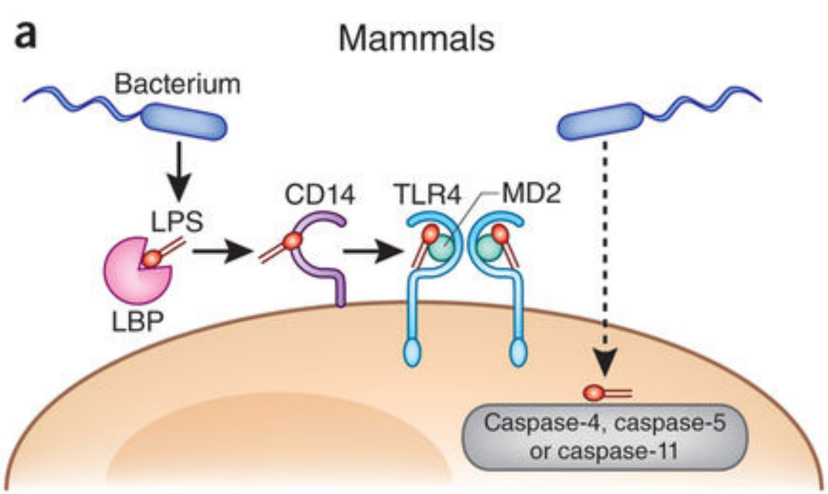
- recognize RNA

cGAS (Via cGMP and STING)

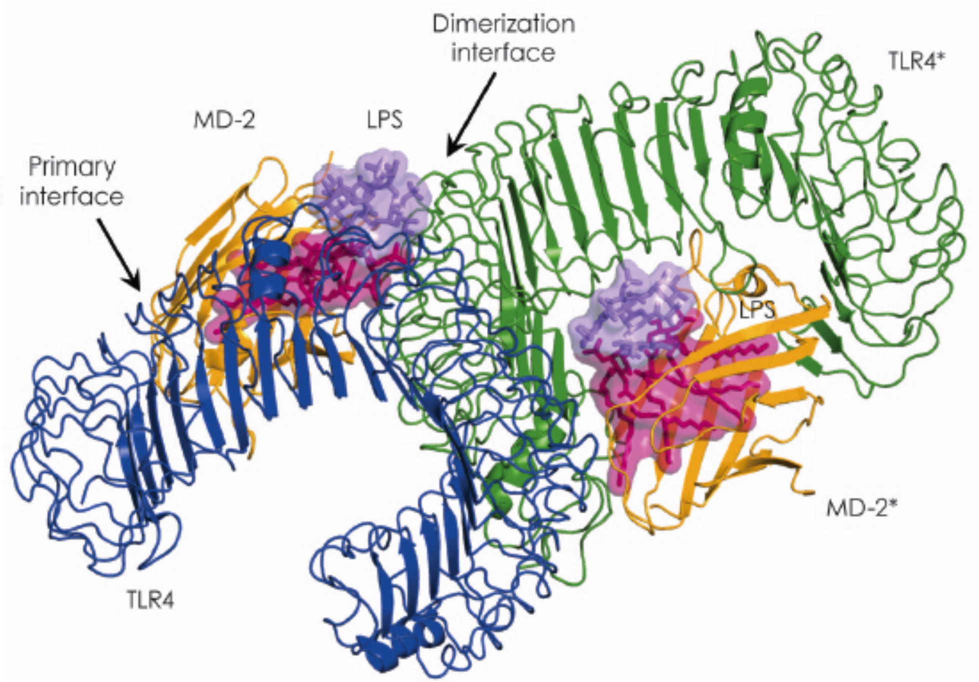
- recognize dsDNA



Pattern recognition receptor: TLR4



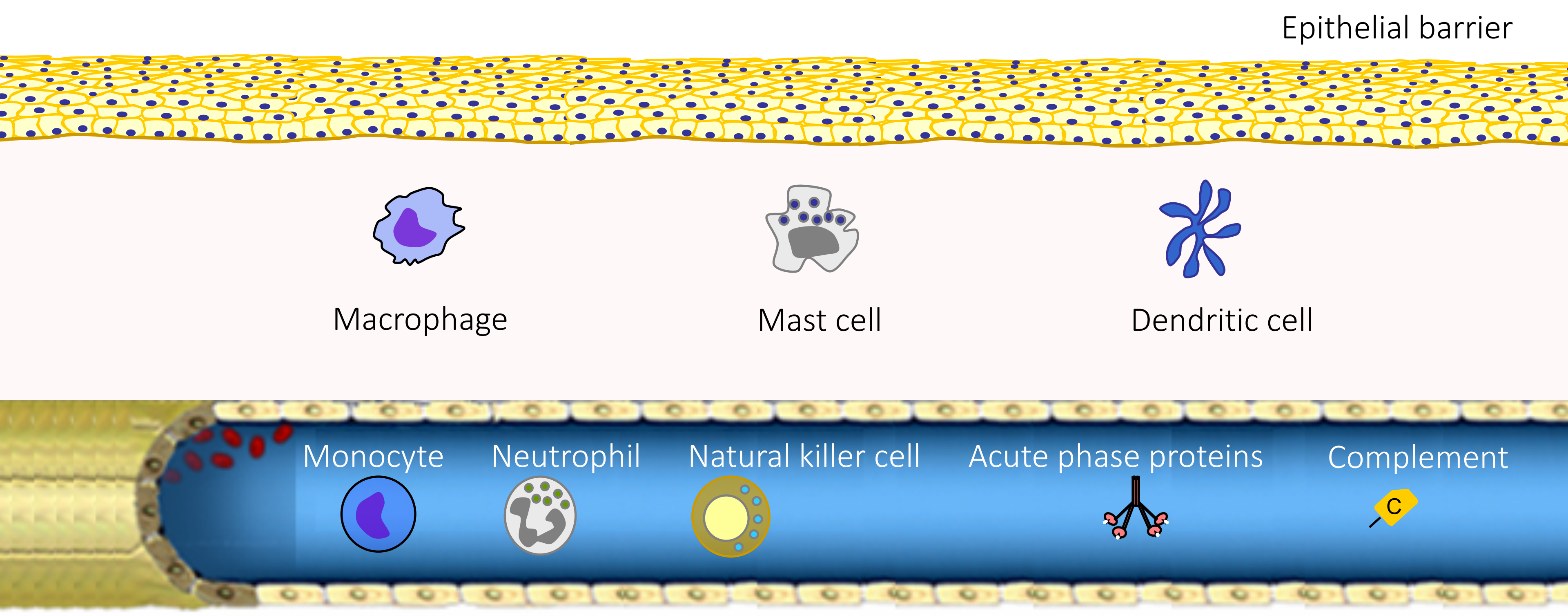
From C. Zypfel, Nature Immunology



From the structural basis of LPS recognition by the TLR4-MD-2 complex, ESRF

Roles of innate immunity

- Prevent invading microbes that have breached epithelial barriers from establishing infection foci
- Activate the adaptive immune system if infection reaches a critical threshold
- Cooperate with adaptive defense mechanisms to eliminate pathogens

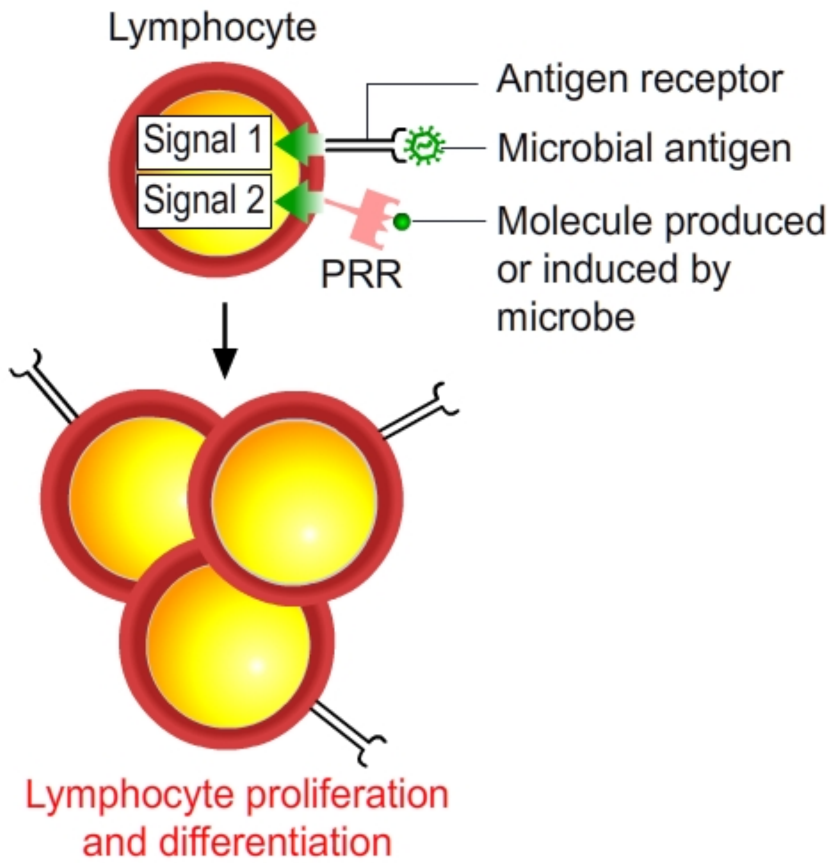


The role of innate immunity in stimulating adaptive immune responses: The two-signal theory

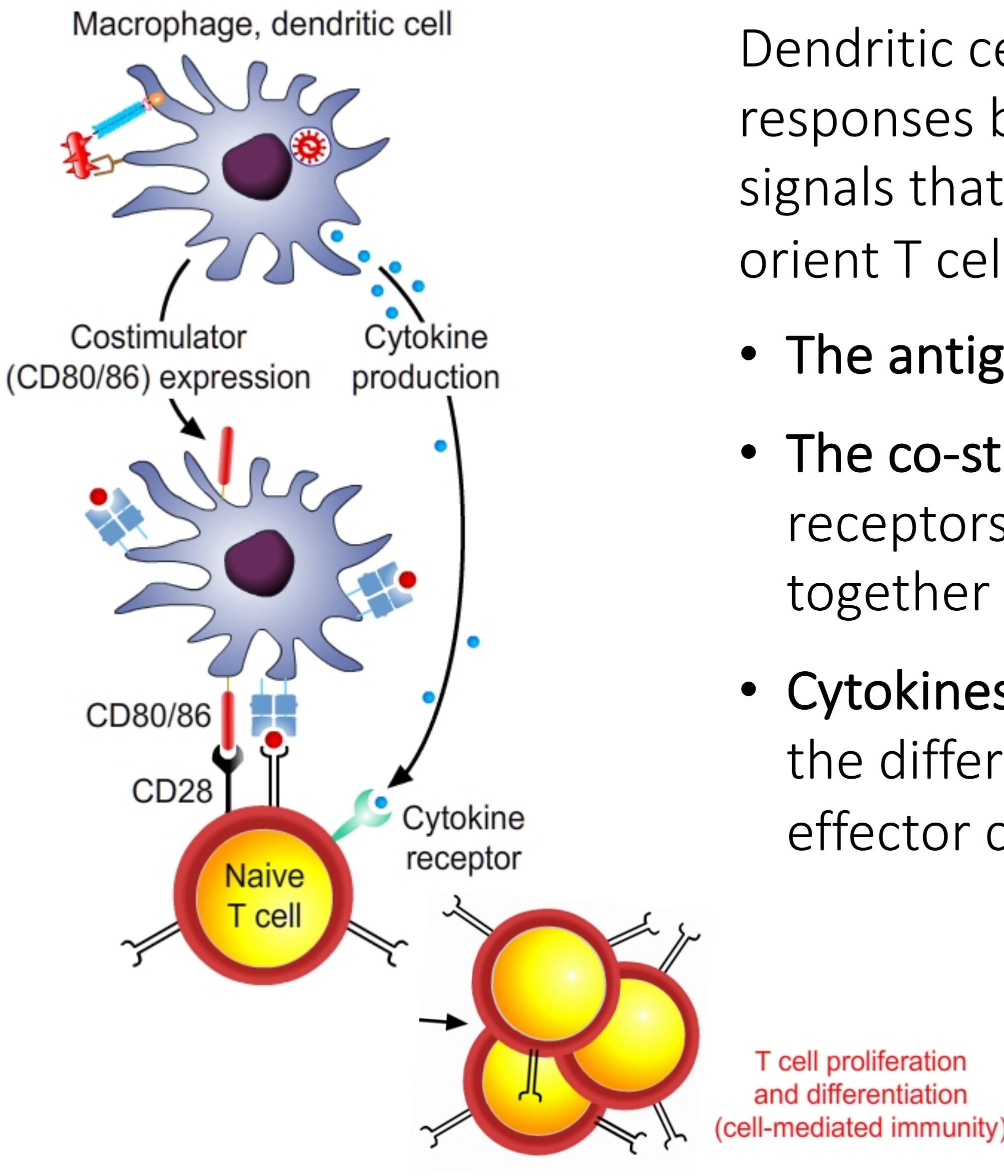
Full activation of antigen-specific lymphocytes requires two signals:
 "signal 1" : the antigen itself
 "signal 2" : innate immune responses

This requirement for microbe-dependent second signals **ensures that lymphocytes respond to infectious agents and not to harmless, noninfectious substances.**

For vaccines that contain antigens rather than whole microbes, substances called **adjuvants** have to be added to elicit innate immune reactions in the same way as microbes do.



The role of innate immunity in stimulating adaptive immune responses: Dendritic cells



Dendritic cells initiate adaptive immune responses by providing three types of signals that activate T lymphocytes and orient T cell differentiation:

- **The antigen** on a MHC molecule
- **The co-stimulators**, which bind to receptors on naive T cells and function together with antigen recognition
- **Cytokines,** which stimulate and orient the differentiation of naive T cells into effector cells.

Conclusion II: Features of Innate Immunity

- **Induced by danger signals:**
  - **Infectious non-self**: molecules specific to microbes (LPS, peptidoglycan, ß1-3 glucan, dsRNA) are recognized by «**Pattern Recognition Receptors**»
  - **Damage signals**: endogenous factors displayed or released by host cells
  - **Absence of self**
- Displays a certain **degree of specificity**
- **Immediately active** (minutes to hours after infection)
- **No memory** (does not improve after repeated encounters with the same pathogen) **but sometimes long-term effect** (Priming - Trained Immunity)*
- **Two roles**
  - first line of immune defense
  - stimulate the adaptive immune system
- **Conserved throughout evolution** (e.g. invertebrates)

Innate Immunity: Learning Objectives

- Describe the molecular and cellular components that mediate innate immunity
- Describe how components of the innate immune system recognize infectious agents. Define Pattern recognition receptors.
- Mention the differences between innate and adaptive immune systems. Indicate interactions between innate and adaptive immunity.
- Describe how NK cells become activated and how they kill target cells.
- Describe the sequence of events of an inflammatory reaction.