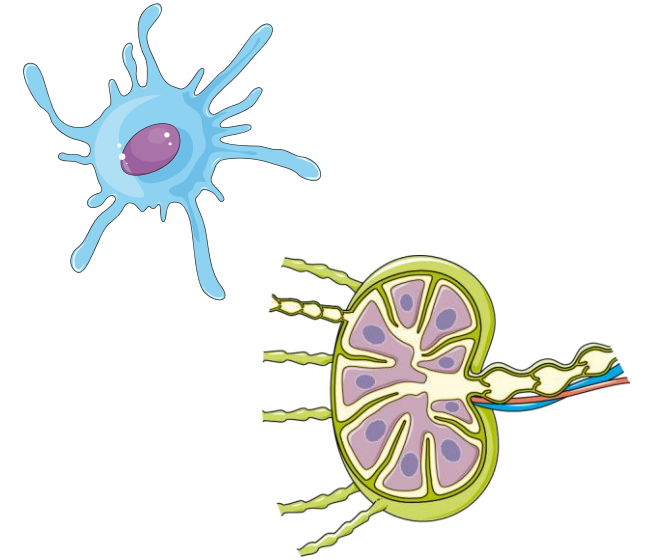
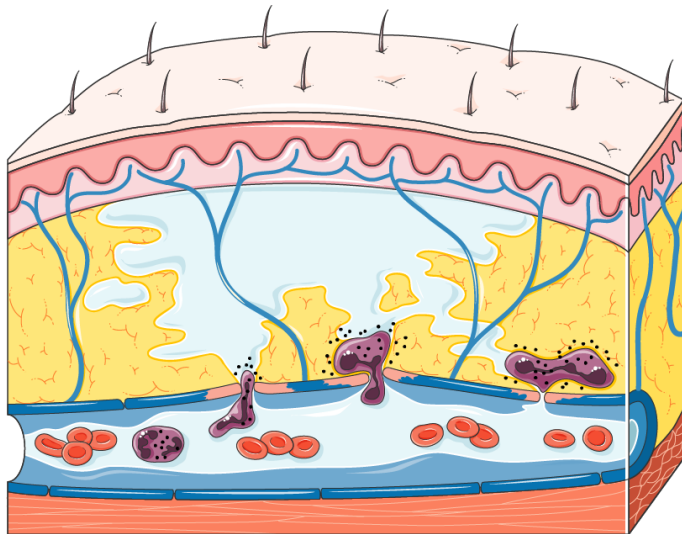


Basics of Immunology



Introduction Master D2HP

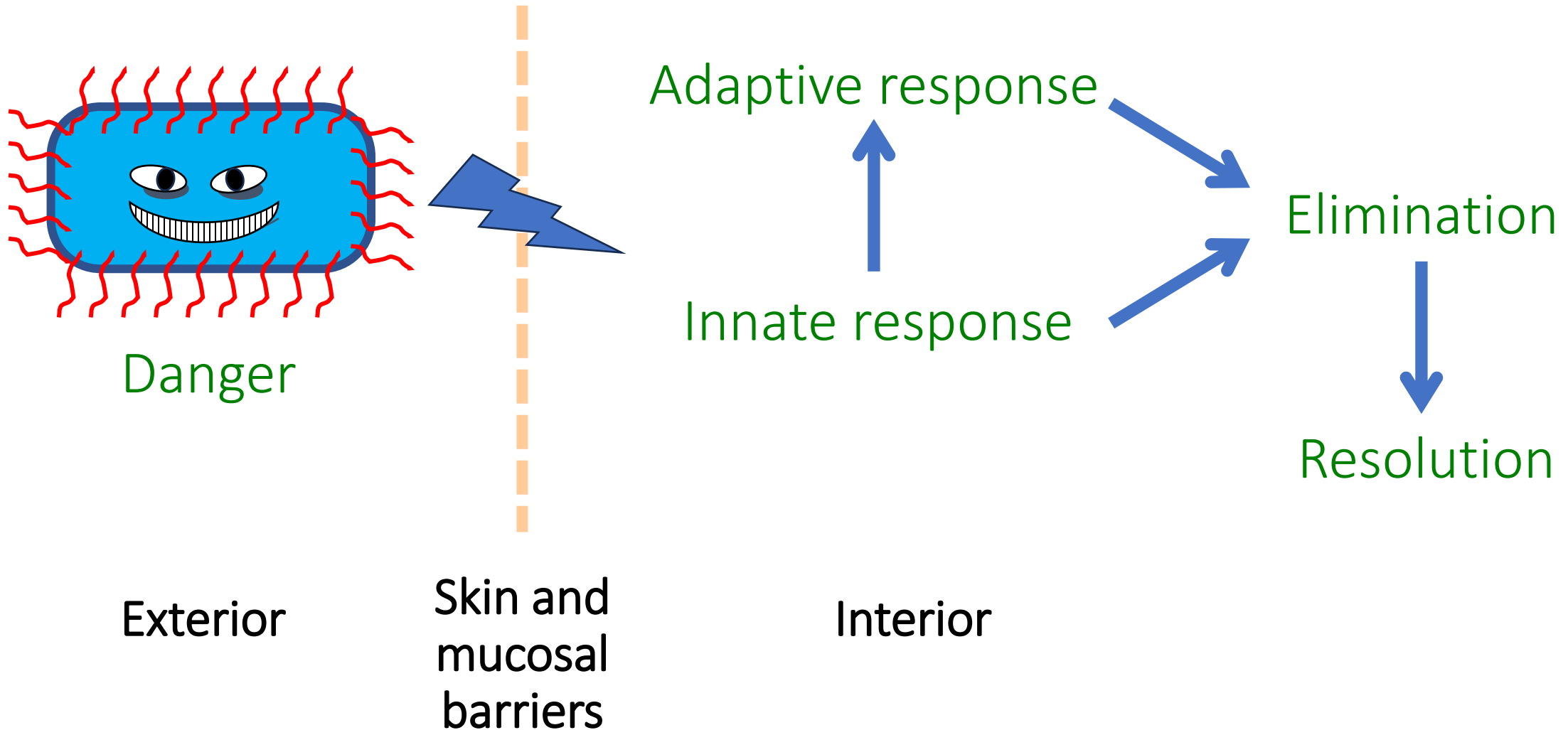


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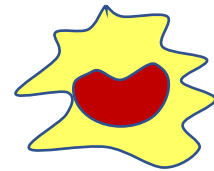
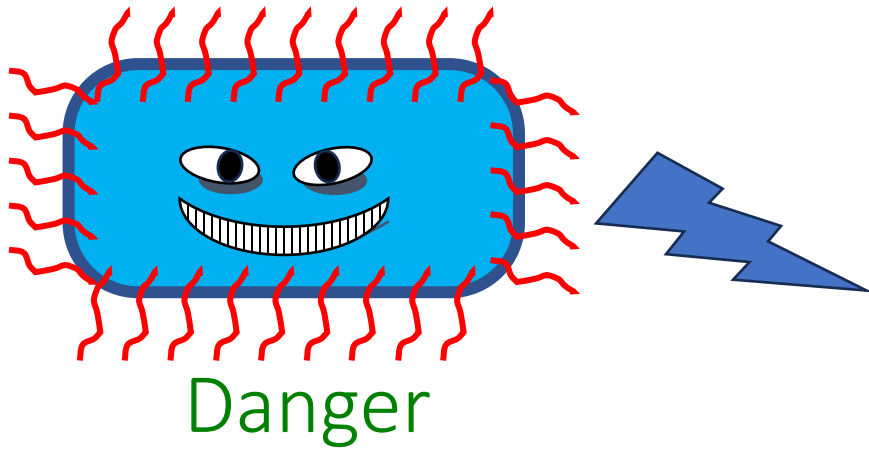
Immunology- Host defense against pathogens

Immune response mechanisms

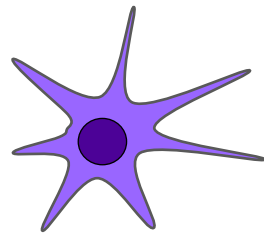


Innate response

Detection of danger



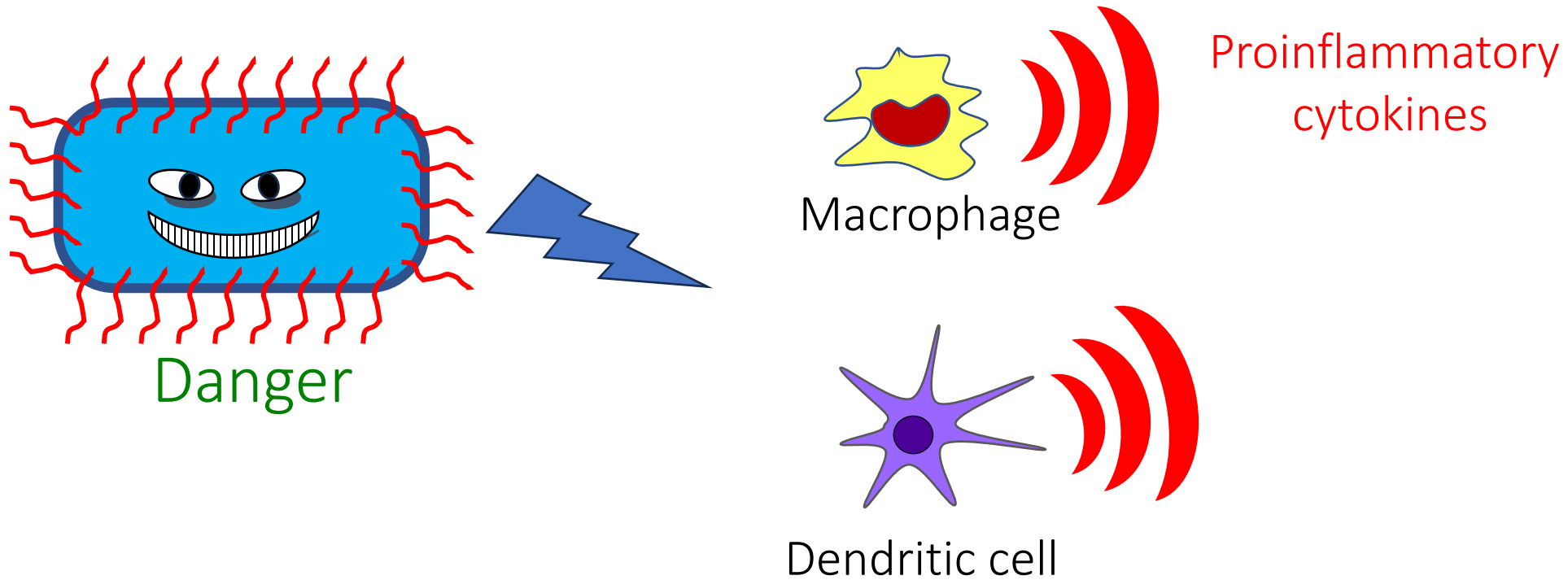
Macrophage



Dendritic cell

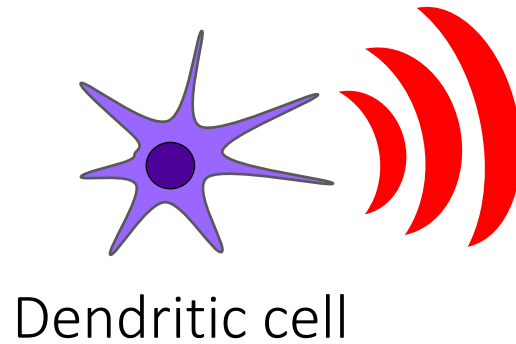
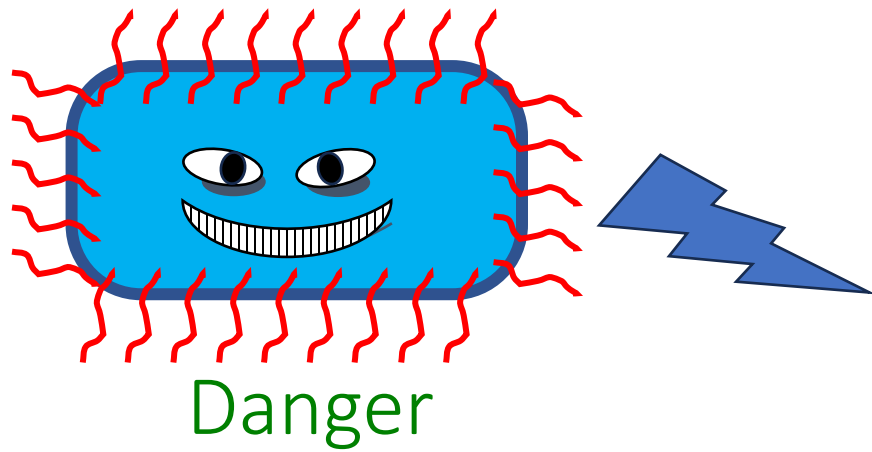
Innate response

Detection of danger Activation of inflammation

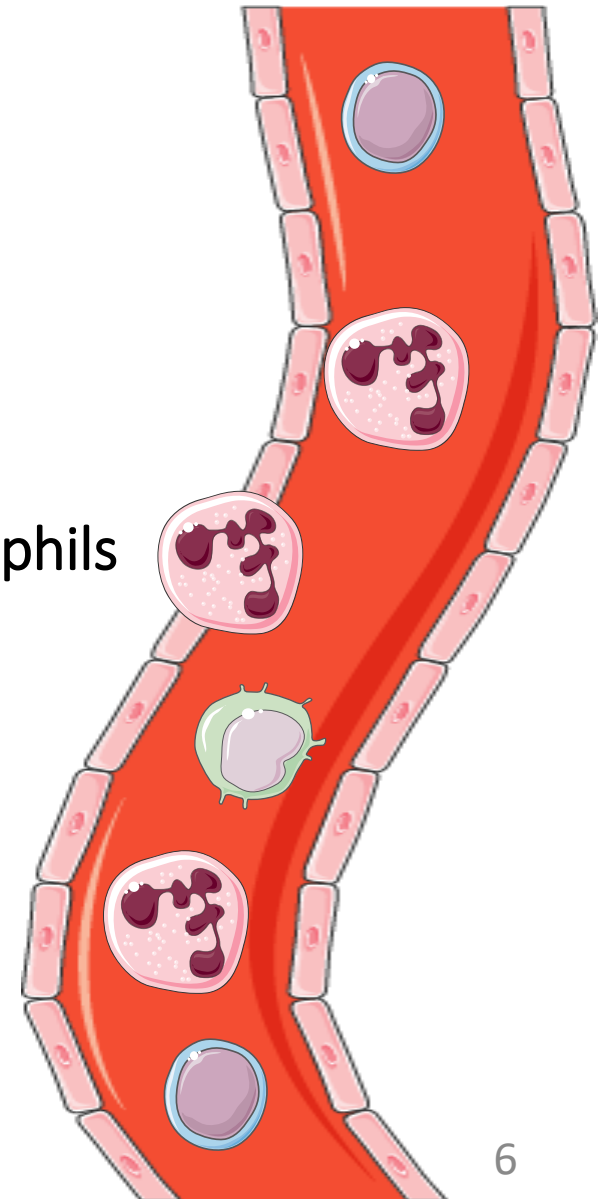


Innate response

Recruitment of circulating cells

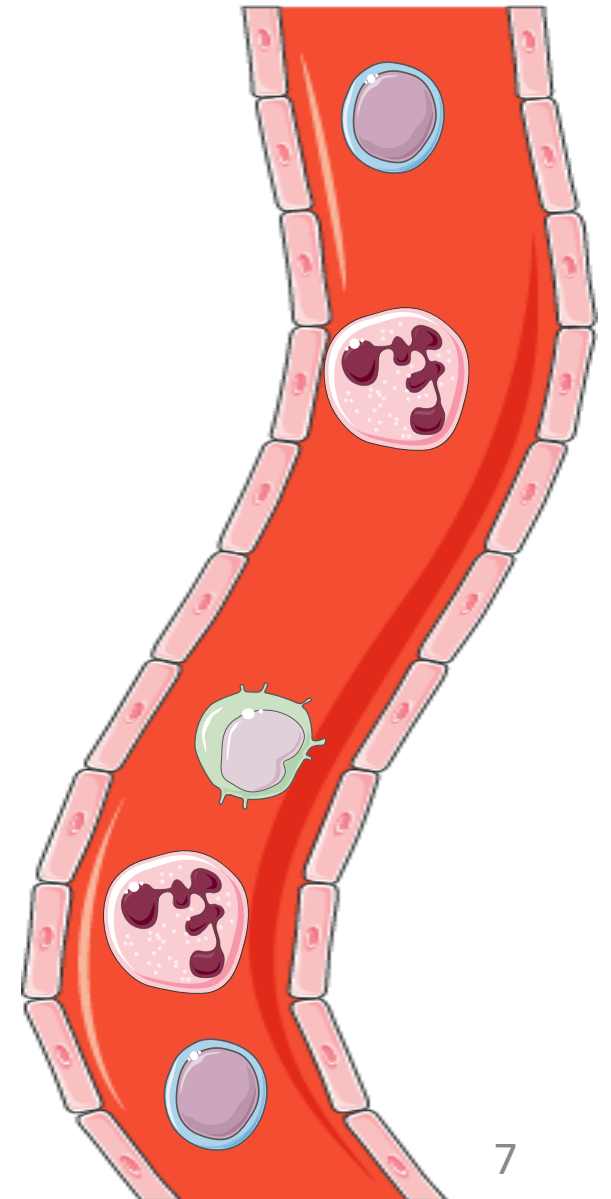
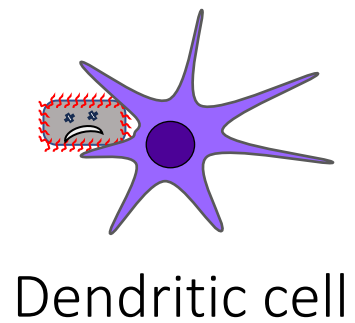
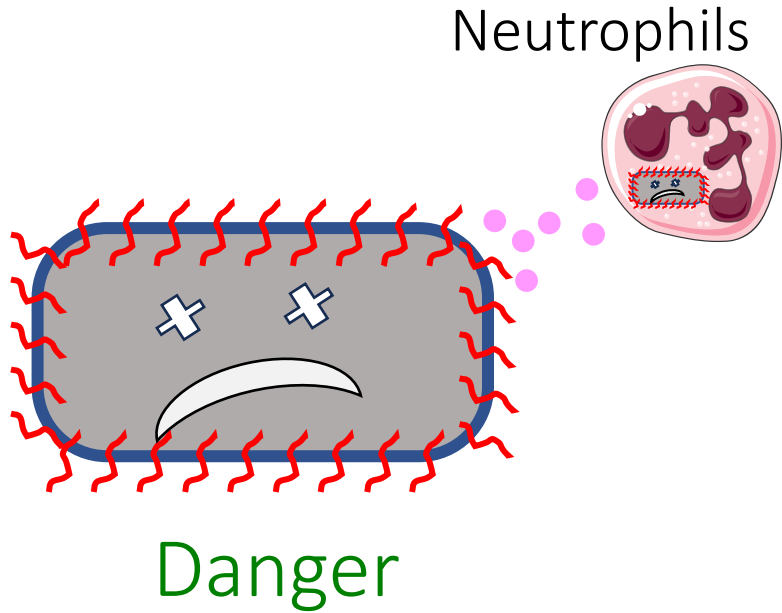


Neutrophils



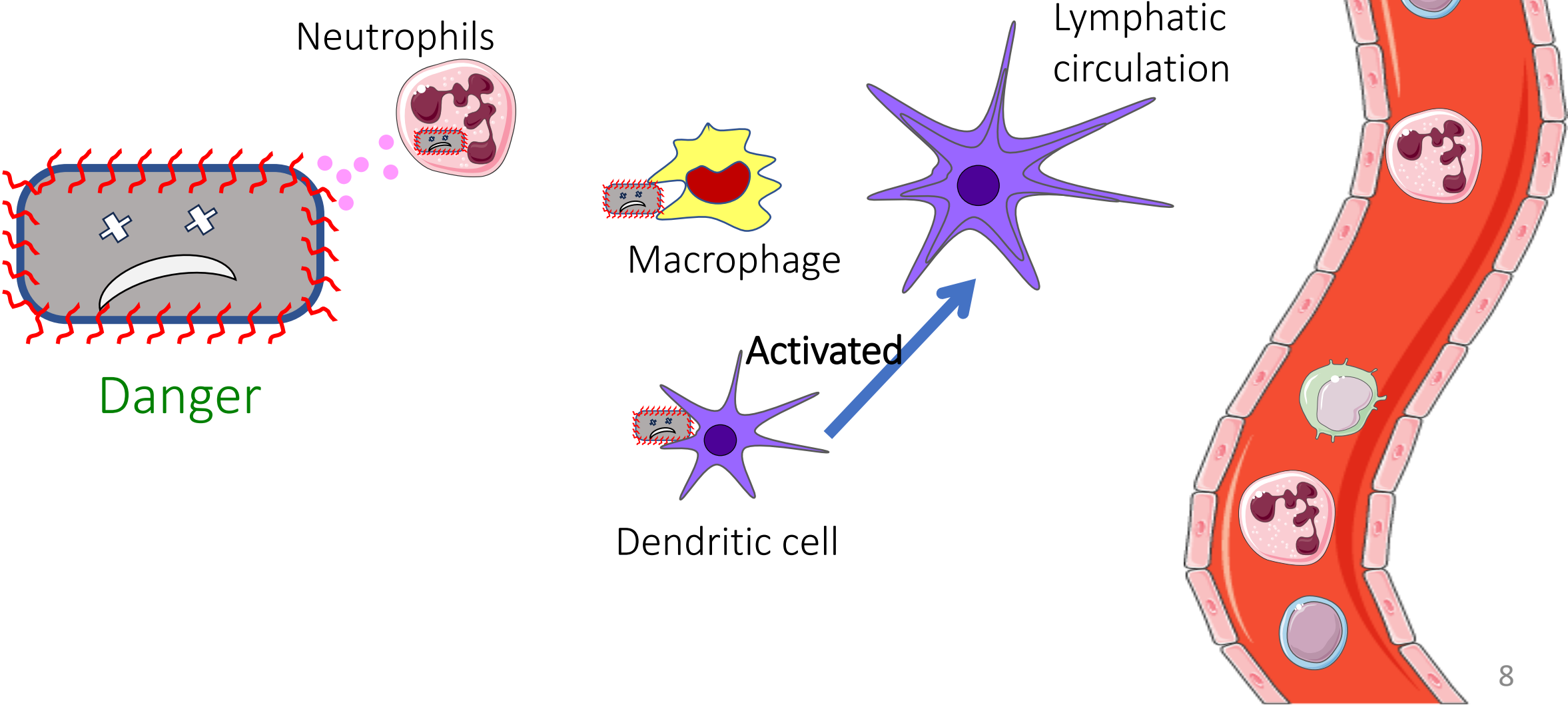
Innate response

Destruction of the pathogen



Innate response

Starting adaptive response



Innate response



In a nutshell

- Immediate response
- Not antigen-specific
- No memory
- 3 goals :
 - Trigger inflammation
 - Destroy the pathogen
 - Initiate adaptative response

Adaptive response components

Cells

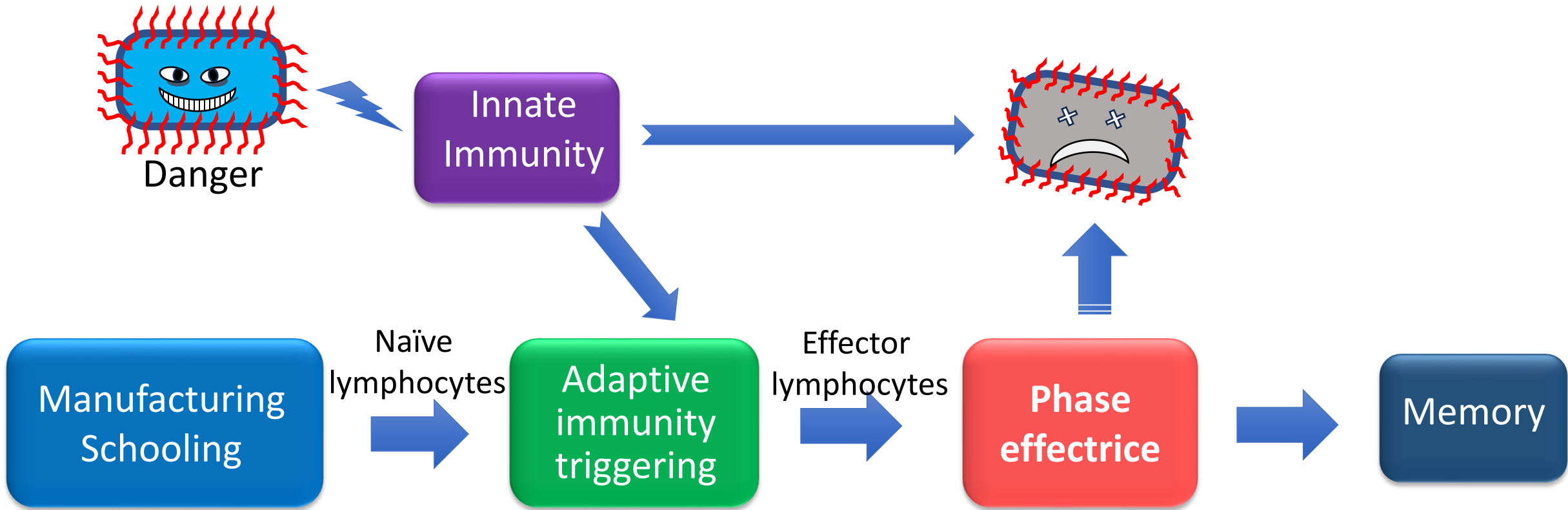
Lymphocytes

- T lymphocytes
 - CD4+ helper T cells
 - CD8+ cytotoxic T cells
- B Lymphocytes
 - Plasma cells

Molecules

- Cytokines (helper T lymphocytes)
- Antibodies (plasma cells)
- Cytotoxic molecules (cytotoxic T lymphocytes)

Adaptive response



- Lymphopoïesis
- BCR and TCR gene arrangement and expression
- Sélections - Elimination of autoreactive repertoire

- Antigen presentation
- Lymphocyte activation
- Clonal expansion
- Differentiation into effectors

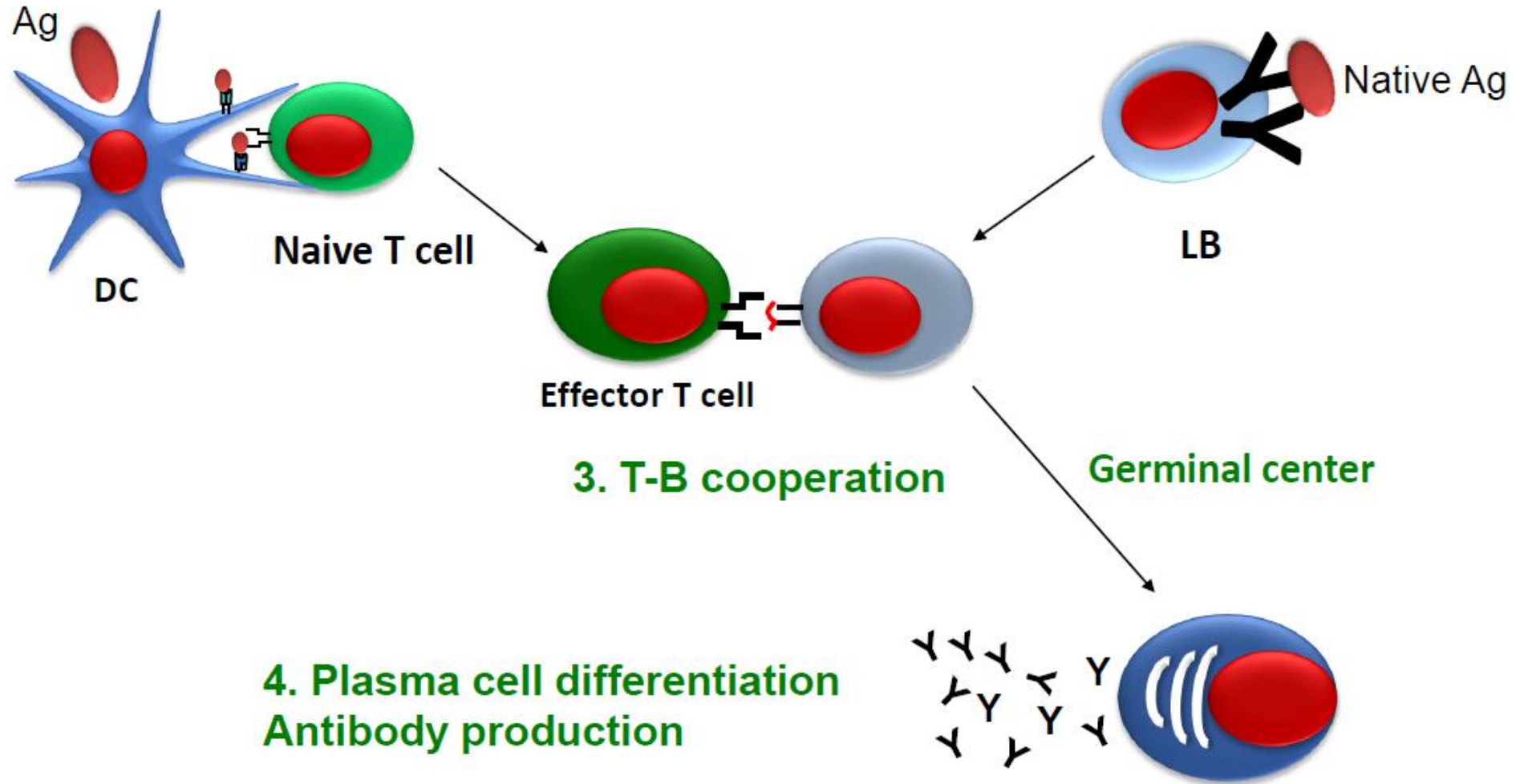
- Humoral response (antibodies)
- Cytotoxic response

Humoral adaptive response = B lymphocytes



1. T cell activation (antigen presentation)

2. B cell activation



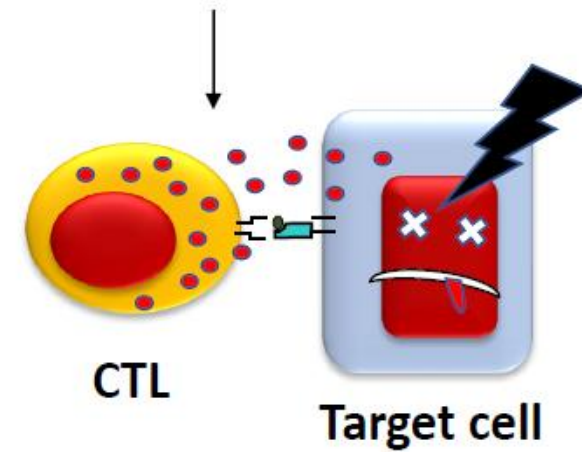
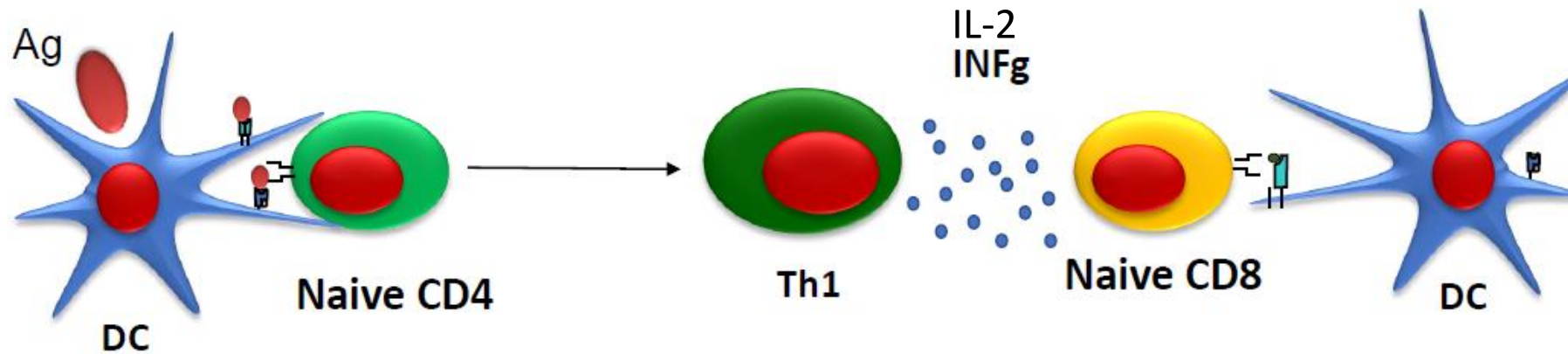
Cellular adaptive response = T lymphocytes



Helper and cytotoxic response

1. CD4 T cell activation

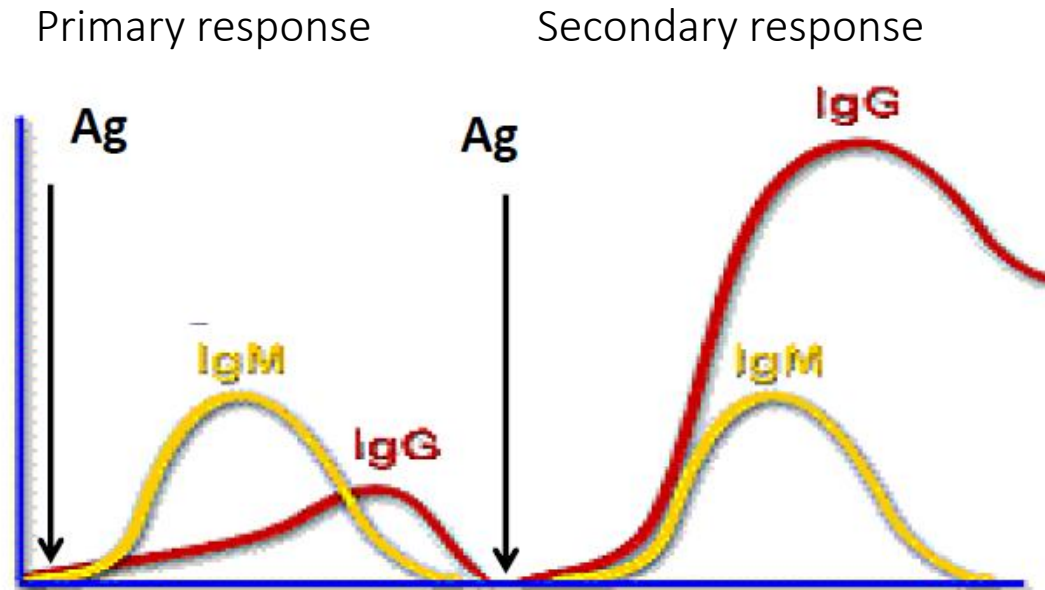
2. CD8 T cell activation



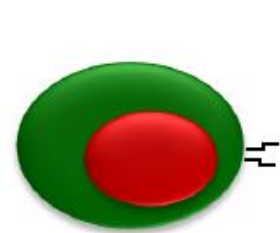
3. Target cell lysis

Memory response

Example of B-lymphocyte memory response illustrated by blood immunoglobulin levels



B and T lymphocytes benefit of memory response:



Helper T cell



B cell



CTL

Adaptive response



In a nutshell

- Delayed answer
- Antigen-specific
- Effectors: antibodies and cytotoxic T cells
- Memory capacity

- 2 Goals:
 - to destroy the pathogen, directly or via activation of immune mechanisms
 - to set up a protection against future infections (memory)

Differences in immune responses



Innate

- Immediate
- PRR not restrained to a unique antigen
- No memory

Deficiencies in innate response:
Bacterial or fungal infections

Adaptive

- Delayed
- Antigen-specific
- Memory capacity

Deficiency :
Humoral response: bacterial infections
Cellular response : viral infections,
fungal and parasite infections

Immunopathology

Not enough ■

- **Infections**

Immune system

+ Too much

- **Auto-immunity**
- **Allergy**
- **Graft rejection**
- **Monoclonal gammopathies**

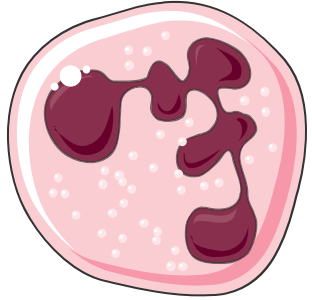
HEALTH

Clinical tools related with the immune system

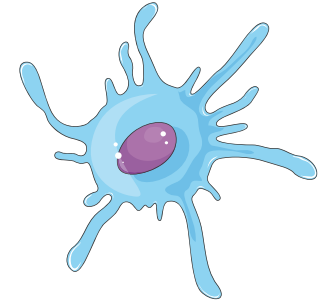
Function	Role	Clinical Tools
Antimicrobial	Defense against pathogens (innate/adaptive response)	Vaccines , vaccine adjuvants, monoclonal antibodies, immunoglobulin therapies
Antitumoral	Tumor surveillance and elimination	Immunotherapies (checkpoint inhibitors, CAR-T), cancer vaccines
Transplantation	Managing immune rejection	Immunosuppressants , tolerance induction therapies
HSCT	Immune system restoration	Hematopoietic stem cell transplantation (allogeneic/autologous)

Course outline

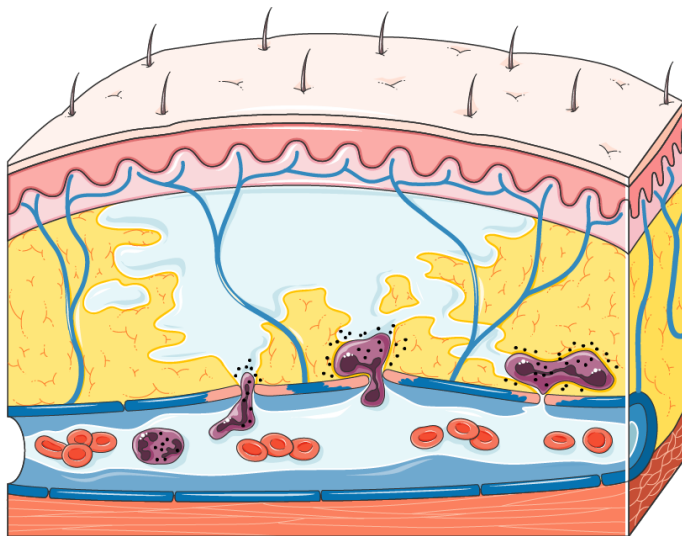
- **Basics**
 - Innate Immunity
 - Adaptive immunity
- **Immunopathology**
 - Allergy
 - Graft
 - Immune deficiencies (january 2025)
 - Auto-immune diseases (january 2025)
 - Diagnostic methods using antibodies



Basics of Immunology



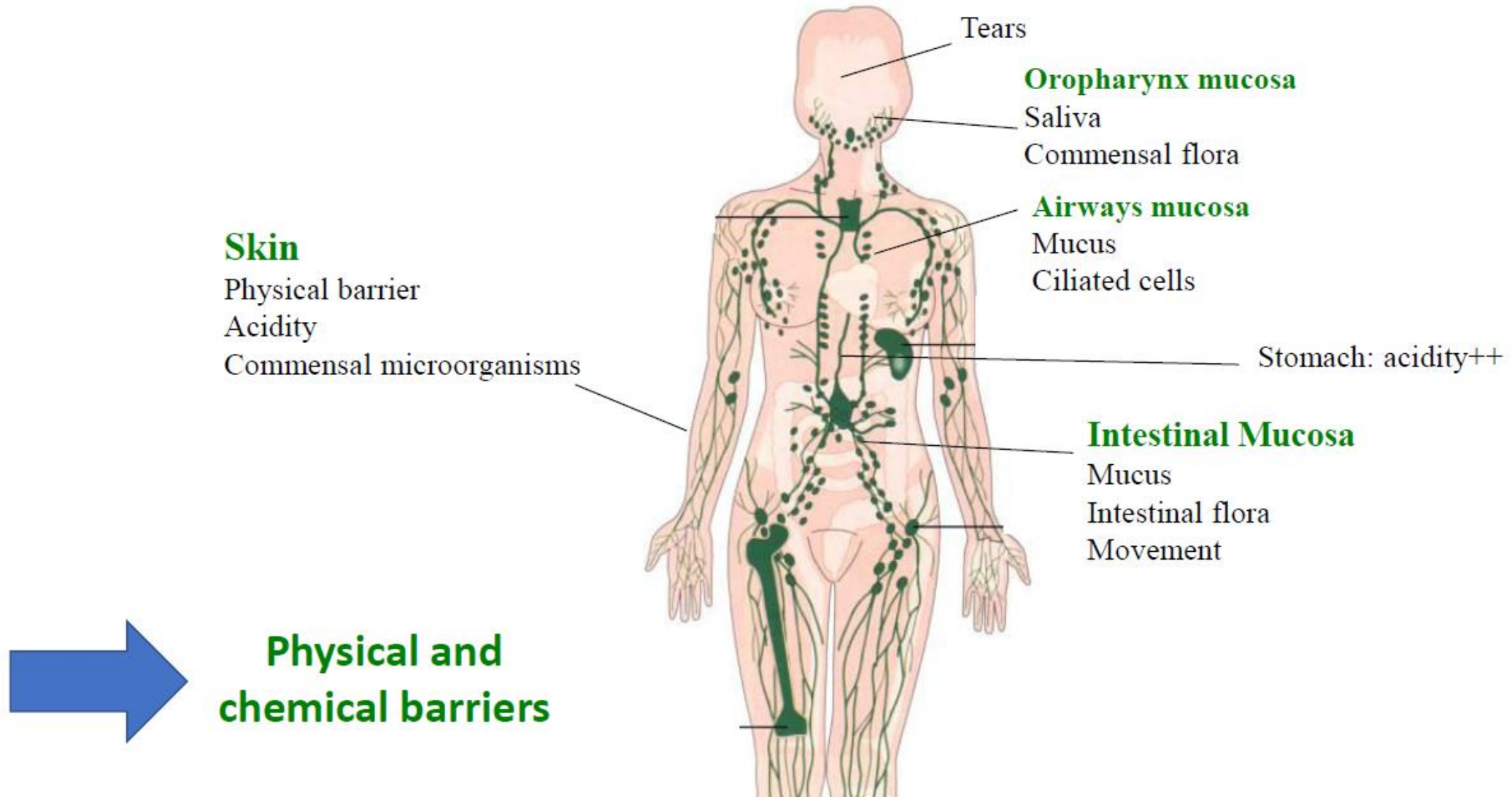
Innate response and inflammation Master D2HP



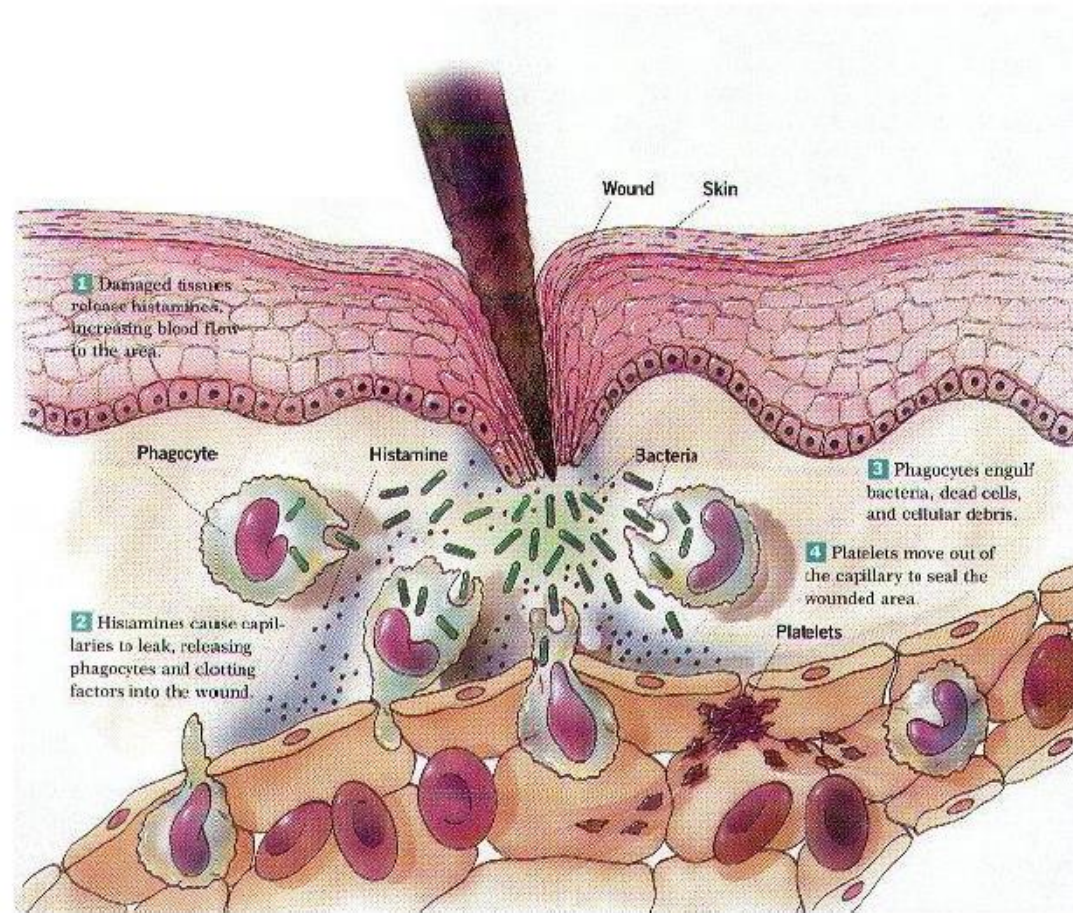
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First lines of defense

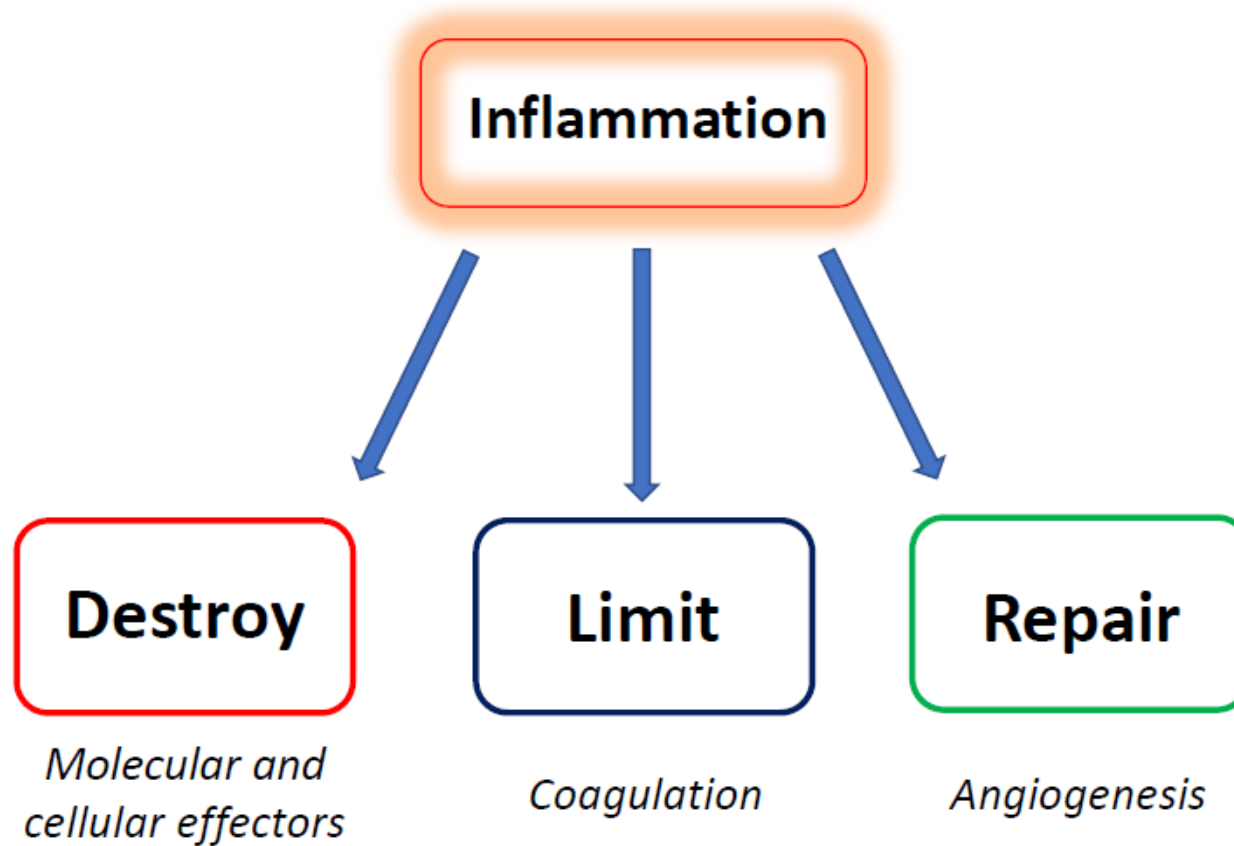


Infection = breach of muco-cutaneous barrier



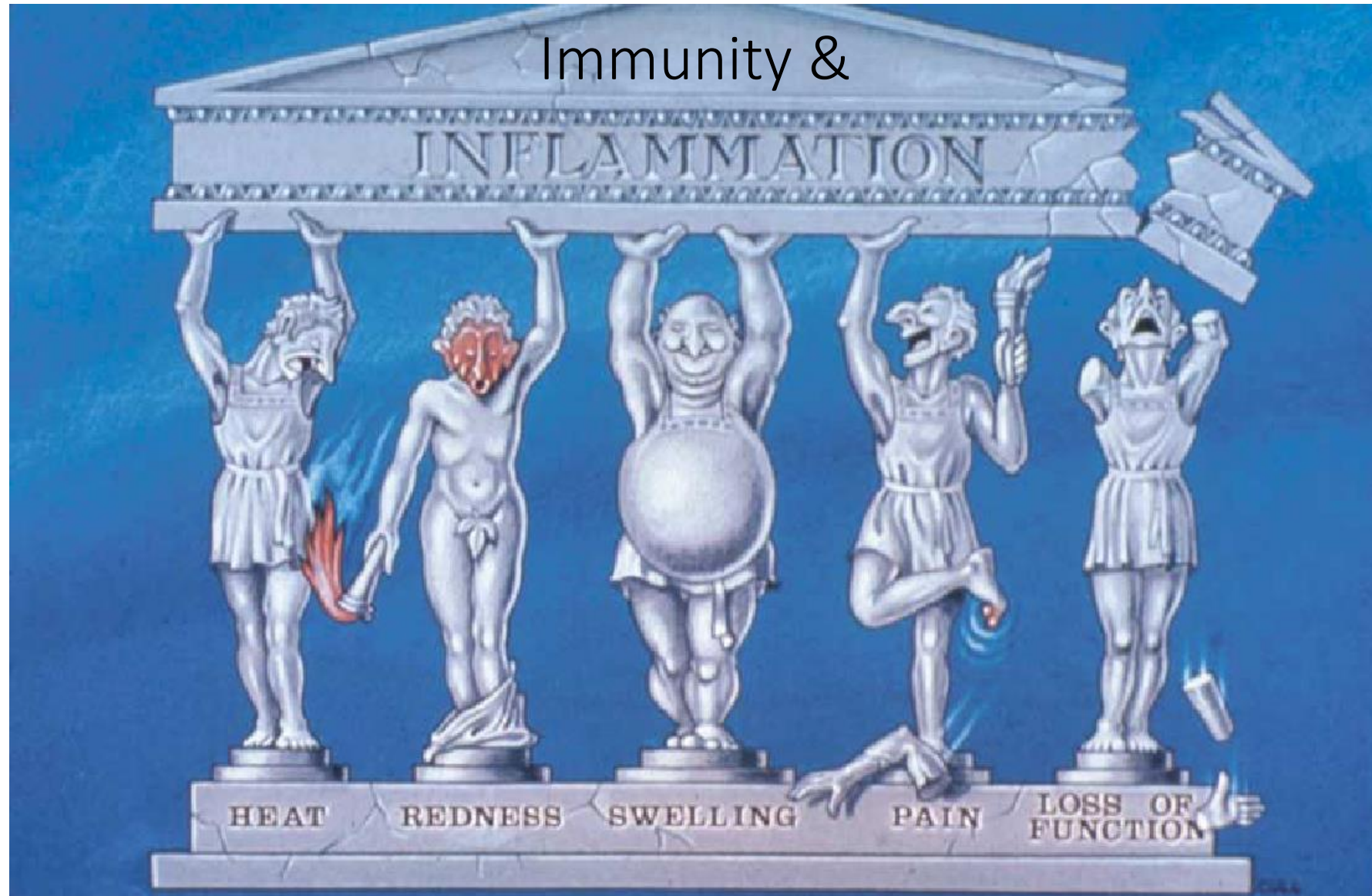
Intrusion alarm: inflammatory response

Roles of inflammation



If > 6 weeks: **chronic inflammation** => tissue lesions

Clinical manifestations



Innate response components



Cells

Tissue resident:

- Sentinel cells
Dendritic cells, macrophages
- Others: Mast cells, epithelial cells, endothelium, innate lymphoid cells

Recruited cells:

- Granulocytes (neutrophils ++)
- Monocytes
- NK lymphocytes

Molecules

- Complement
- Cytokines (pro-inflammatory. In resolution phase anti-inflammatory)
- Antimicrobial molecules
- Vasoactive molecules

How do innate cells recognize non-self?

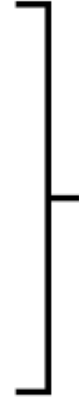
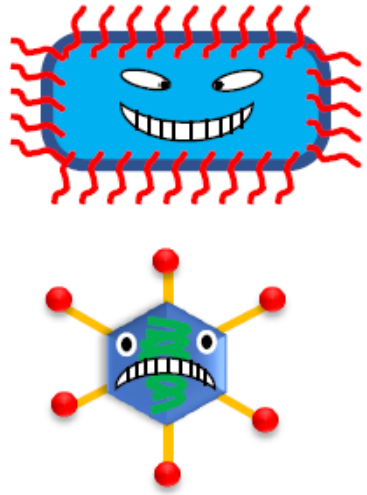


Self



Non-self

« Danger » signal



PAMP / MAMP
(Pathogen-Associated
Molecular Pattern)
Ex: LPS, viral RNA..

DAMP
(Damage-Associated
Molecular Pattern)
Ex: DNA, ATP, HMGB1..

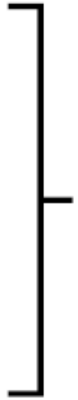
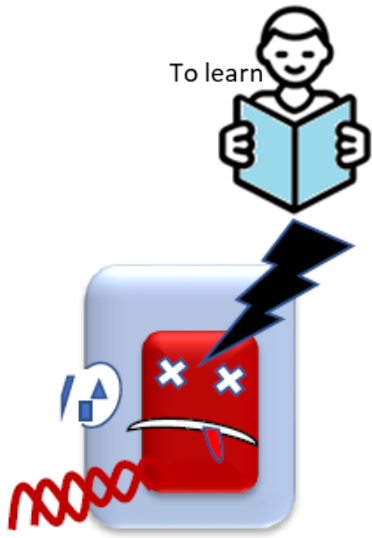


PRR: Pattern Recognition Receptor:

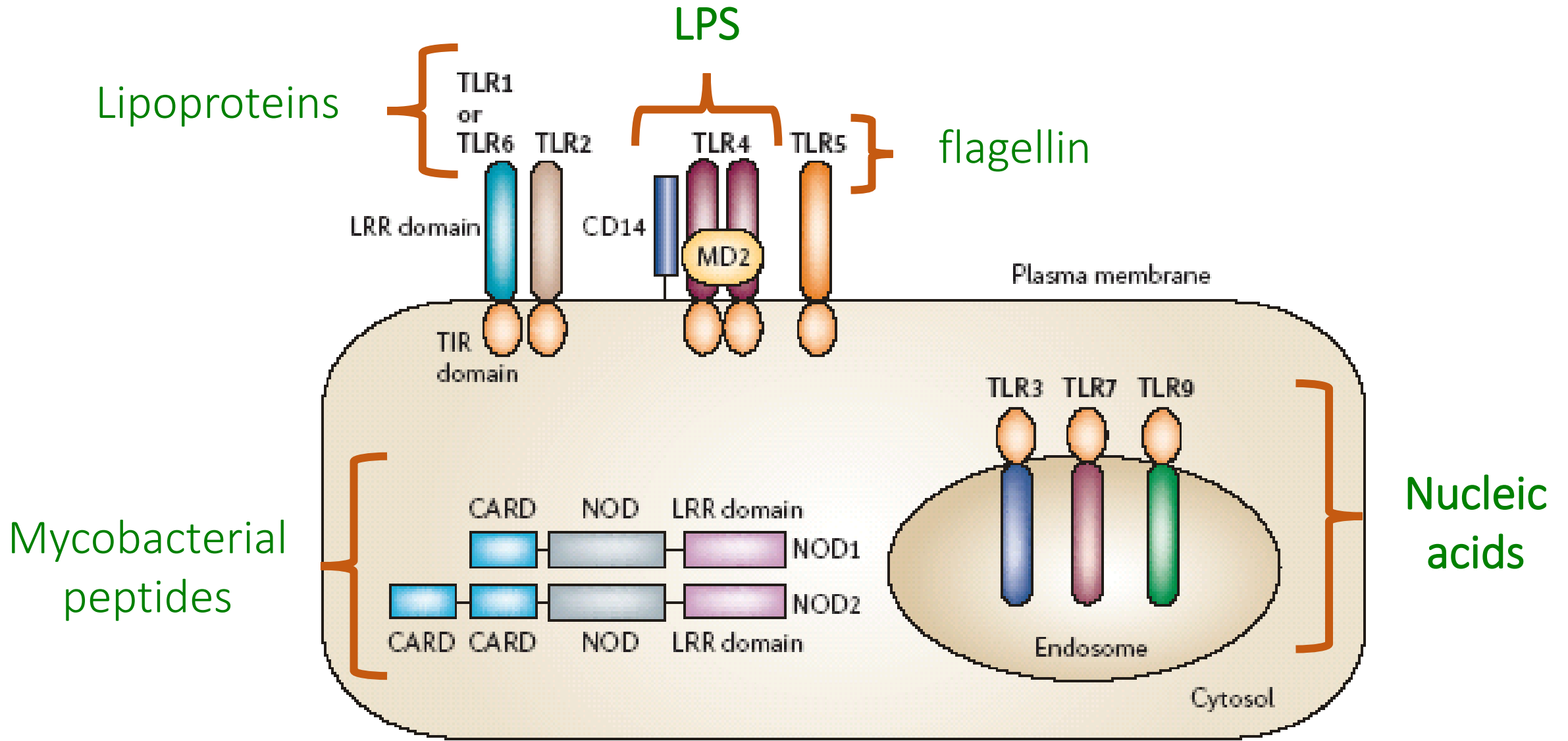
TLR (Toll-Like Receptor)	}	Membranes
C-type lectins		
NLR (NOD-Like Receptor)	}	Cytosol
RLR (RIG-like receptors)		



Cell activation
Cytokine secretion

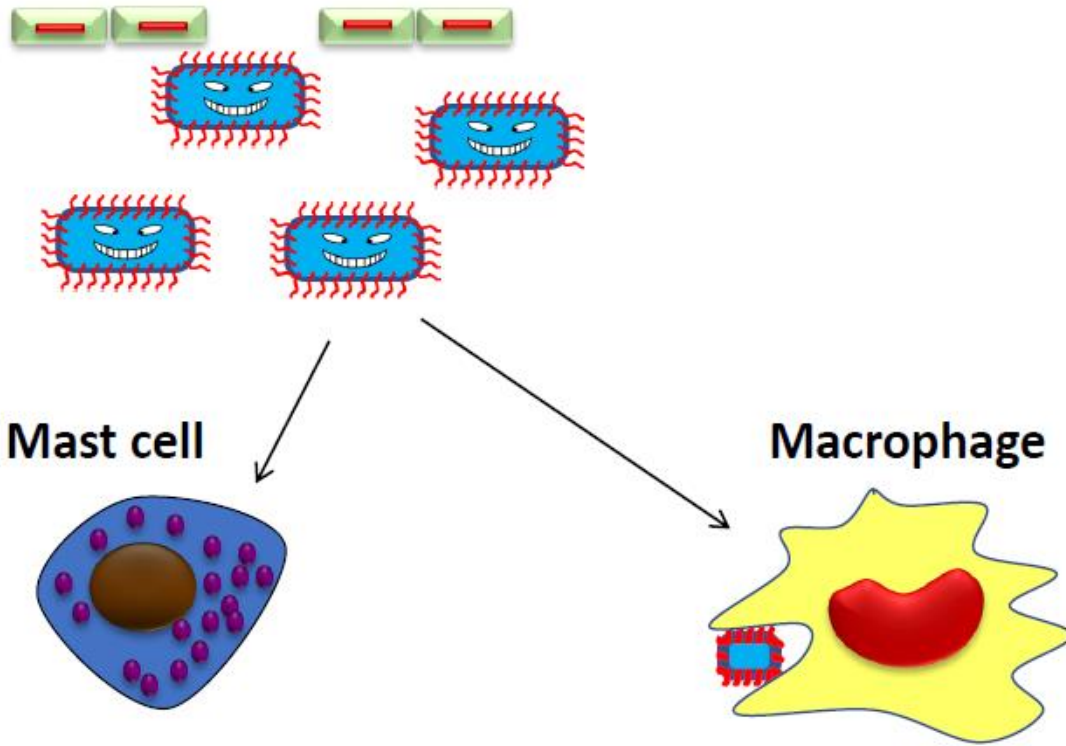


Examples of PRRs



Inflammatory response

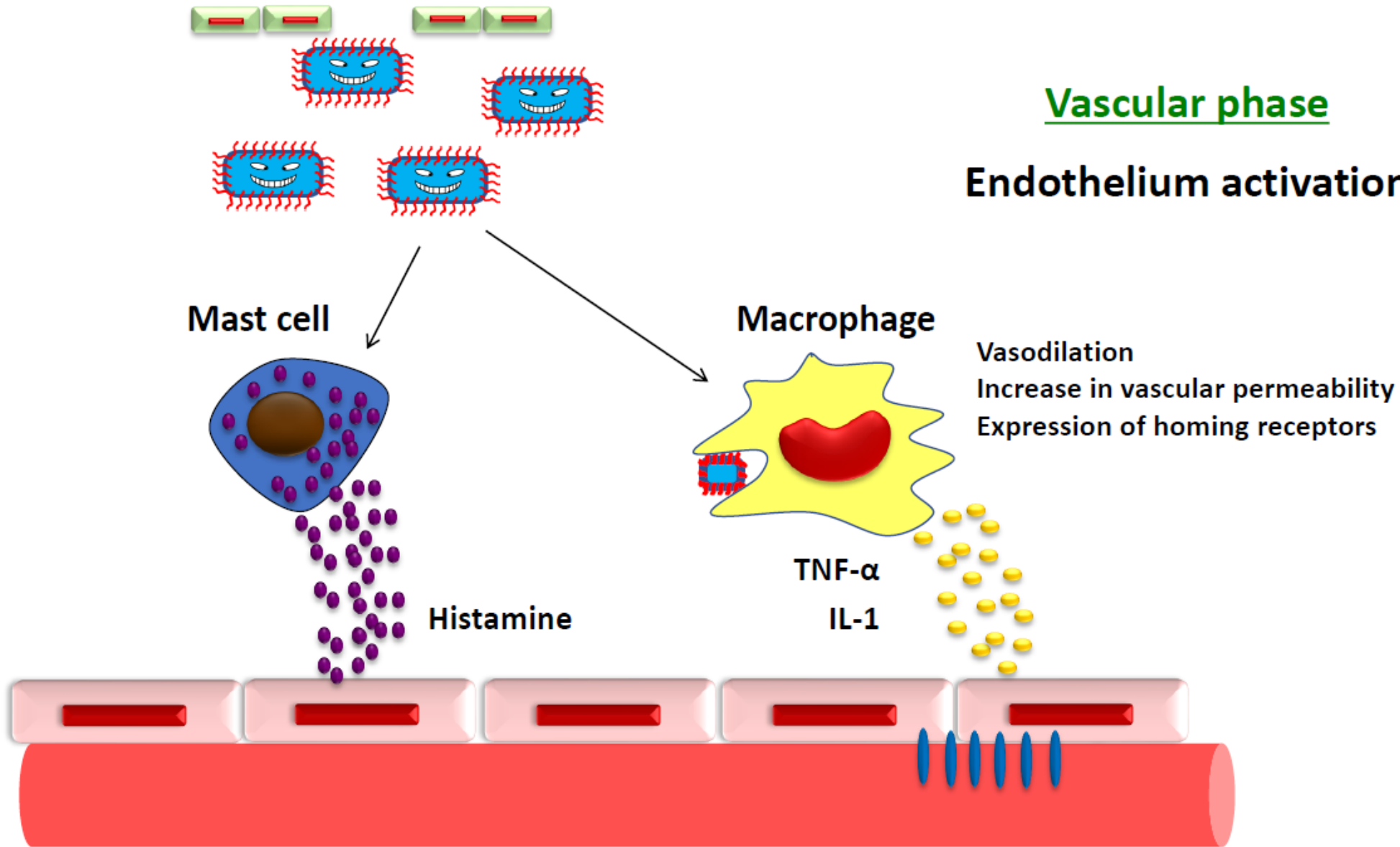
Tissue injury



Inflammatory response



Tissue injury



Cytokines and inflammation



Pro-inflammatory

IL-1 : activates endothelium, immune cells, causes fever

TNF α : activates endothelium, immune cells, raises vascular permeability

IL-6 : activates lymphocytes, causes production of inflammatory molecules by the liver

Chemokines

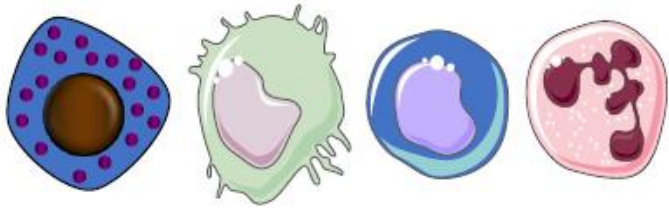
IL-8: Attracts neutrophils

Anti-inflammatory

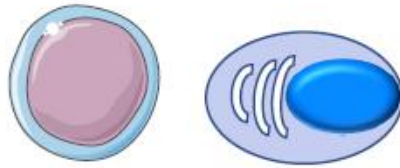
IL-10 Tissue repair, downregulates pro-inflammatory cytokines and

TGF β diminishes activation of cells

Pleiotropy of cytokine effects



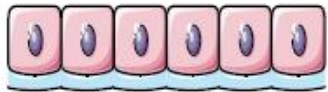
Innate cells activation



Activation LyT / LyB



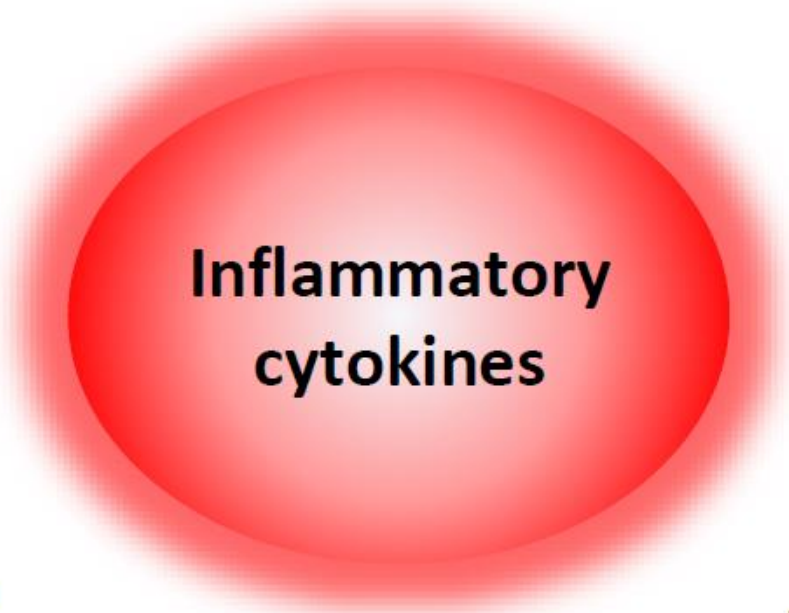
CNS: fever



Endothelium activation



Fibroblast activation



Inflammation protein
synthesis



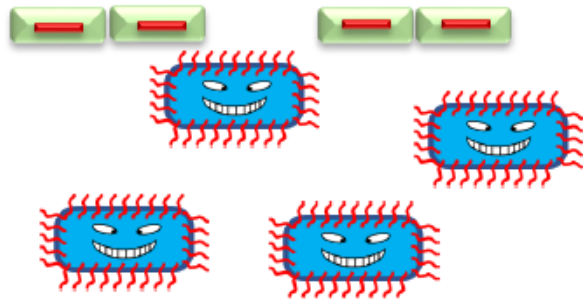
Hematopoiesis

TNF α , IL-1 and IL-6 are therapeutic targets in inflammatory diseases

Inflammatory response



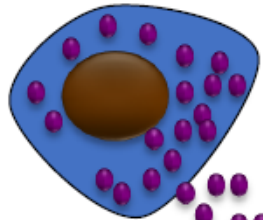
Tissue injury



Cellular phase

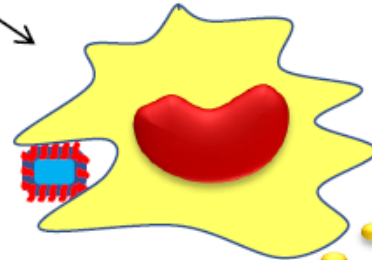
Phagocyte recruitment

Mast cell



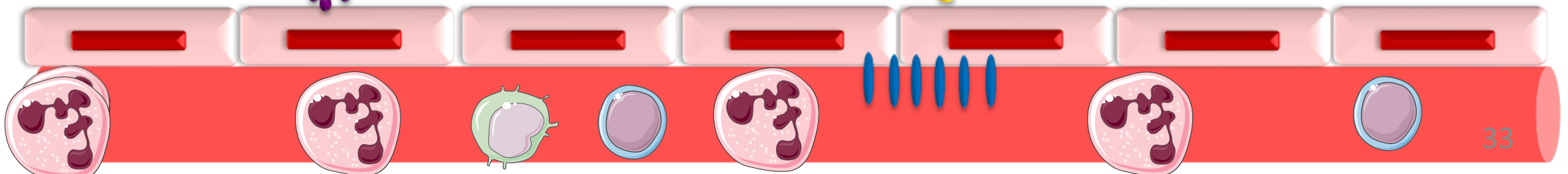
Histamine

Macrophage



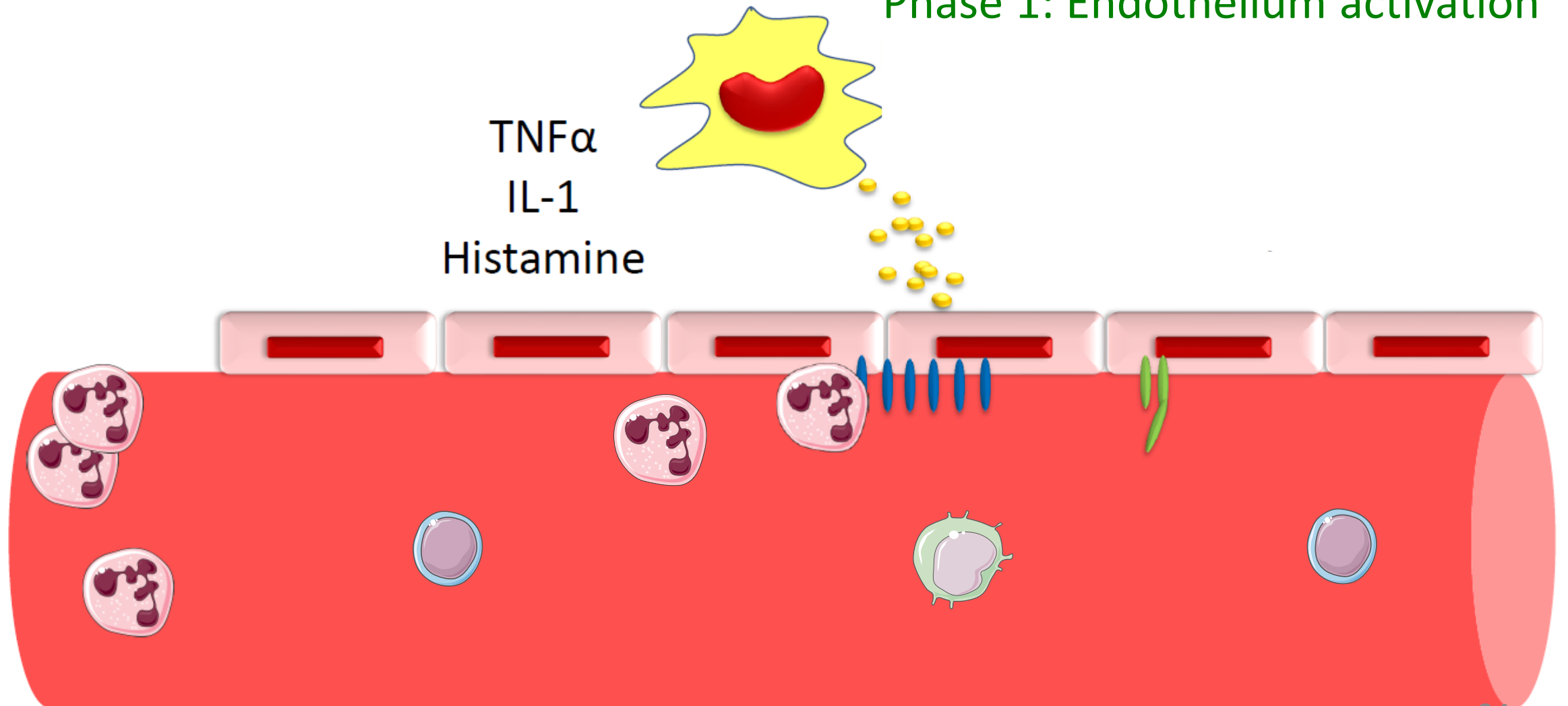
TNF- α
IL-1
IL-6

Neutrophils



Phagocyte recruitment

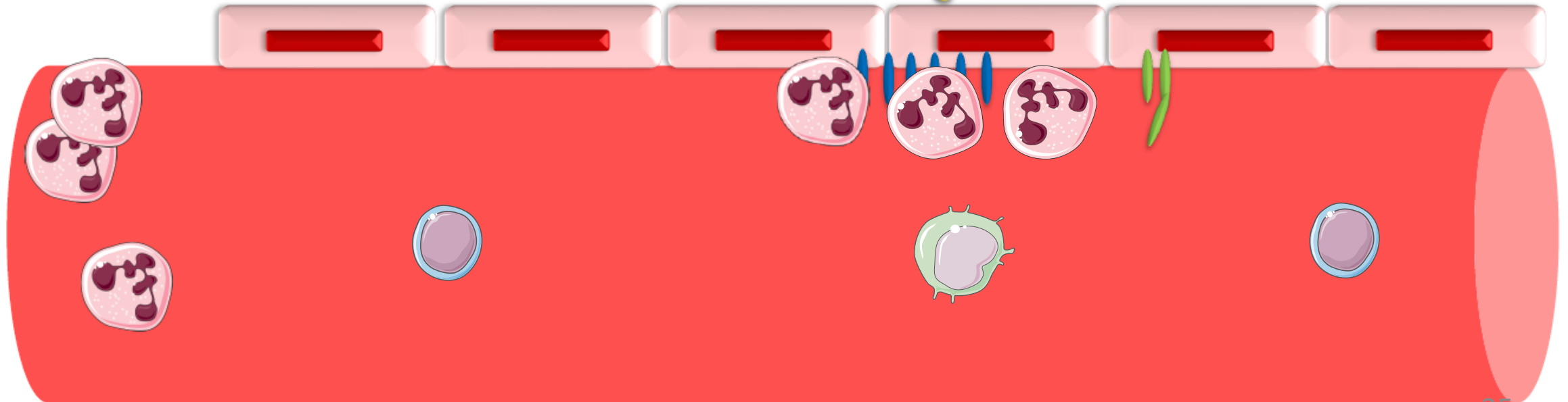
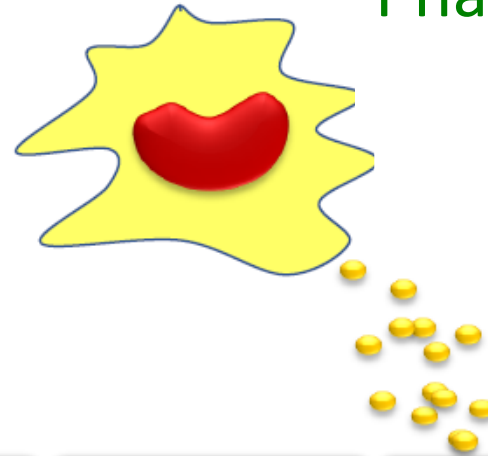
Phase 1: Endothelium activation



Phagocyte recruitment

L-selectin (CD62L)
Sialyl-Lewis X

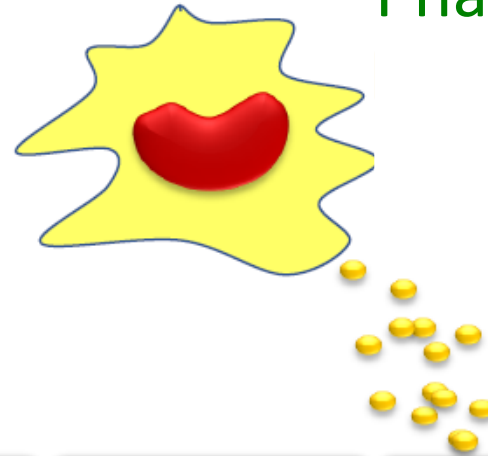
Phase 2: Rolling
Slowing down



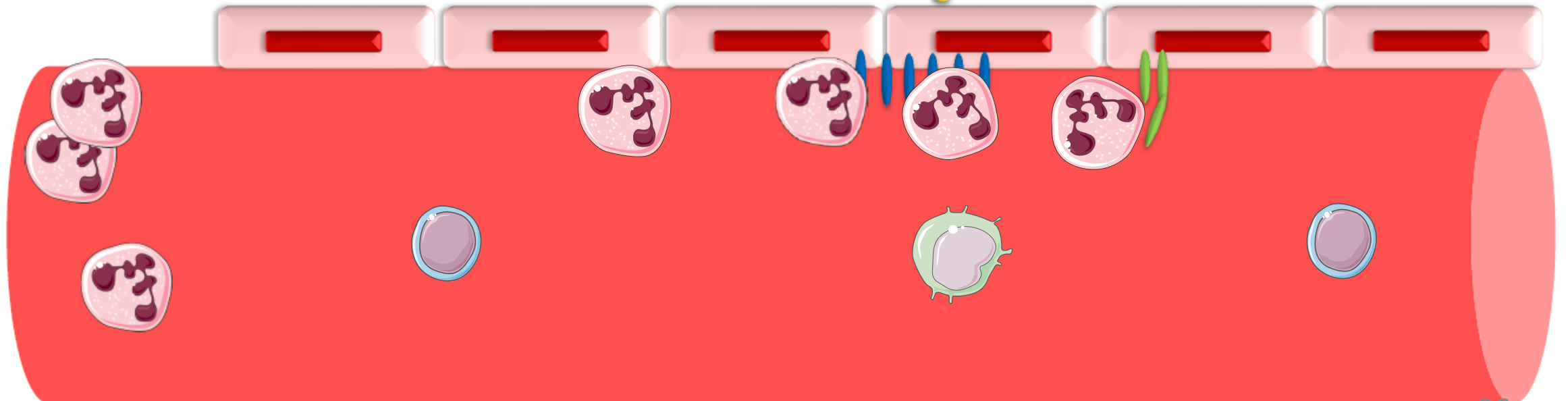
Phagocyte recruitment

Chemokines
Activation of integrins

Phase 3: Stopping



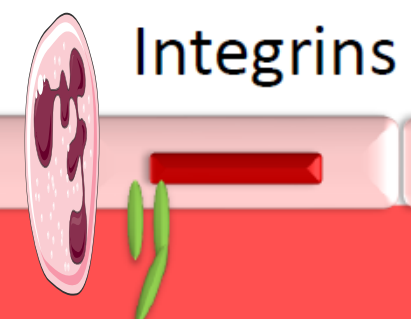
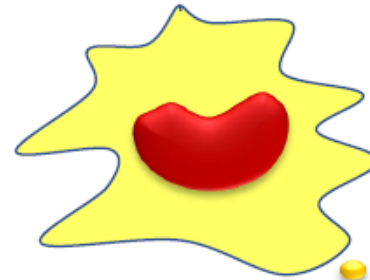
Integrins



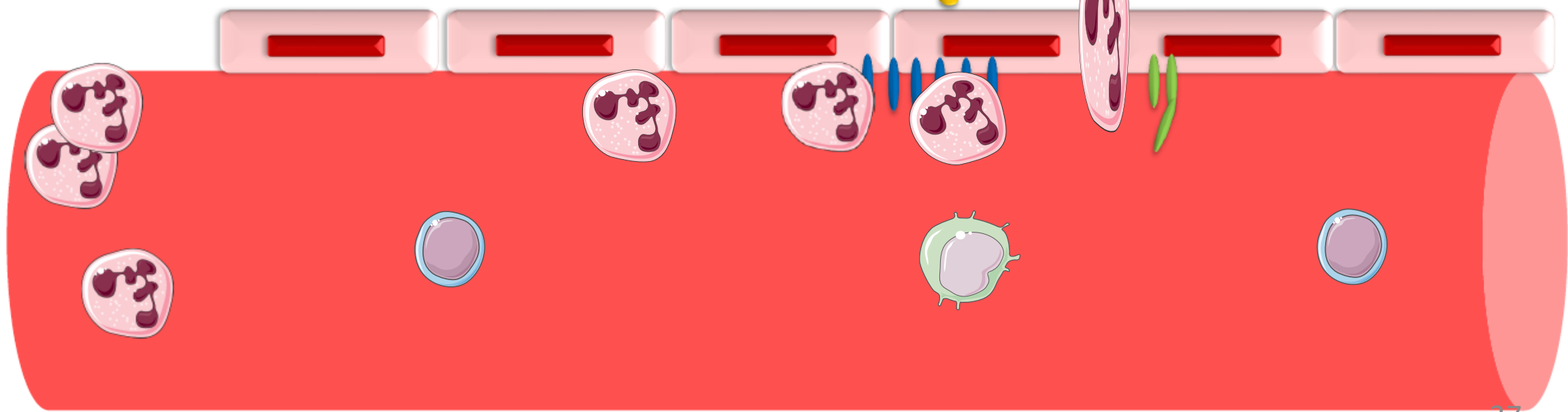
Phagocyte recruitment

Chemokines
Activation of integrins

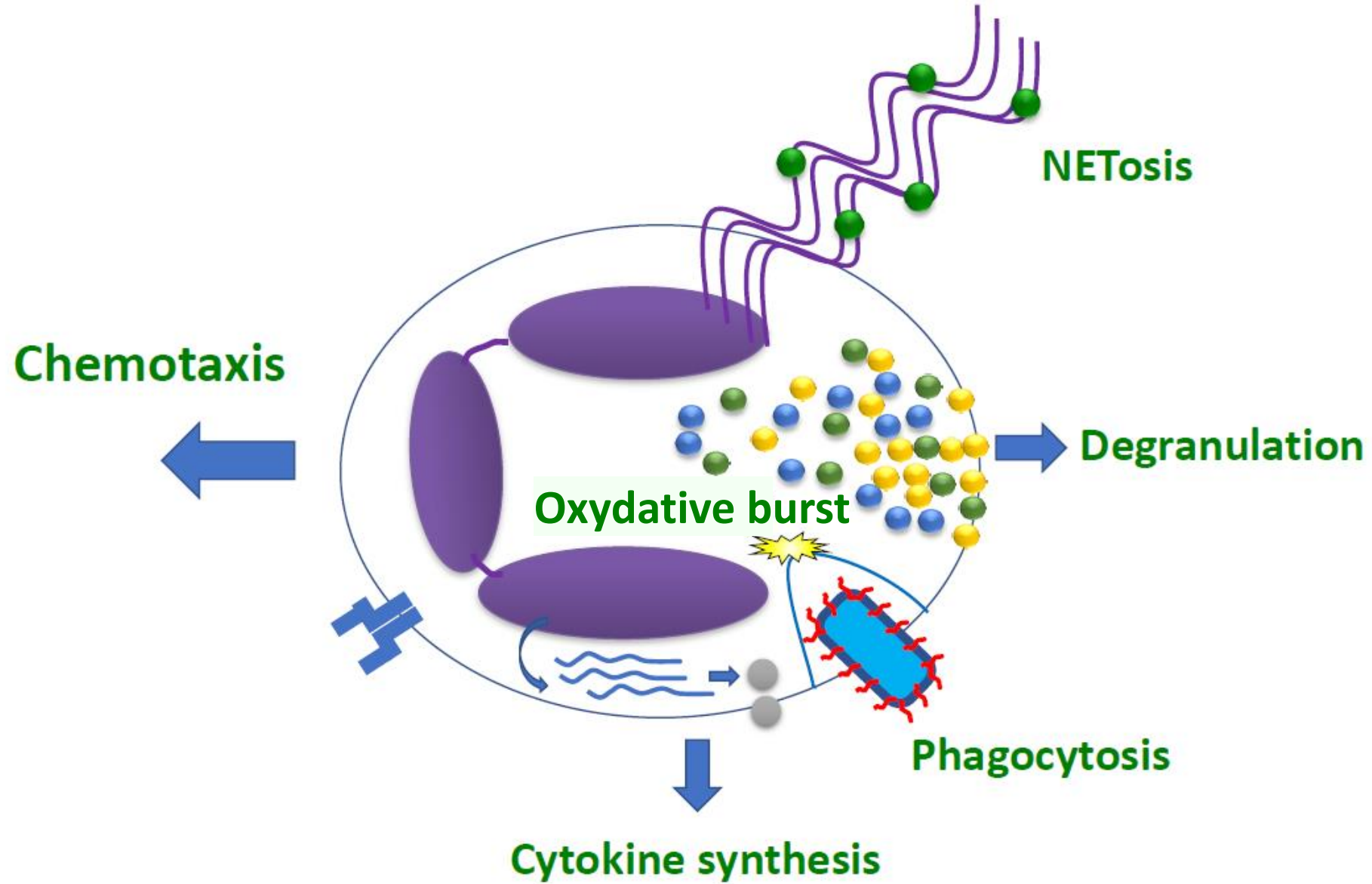
Phase 4: Diapedesis



Integrins

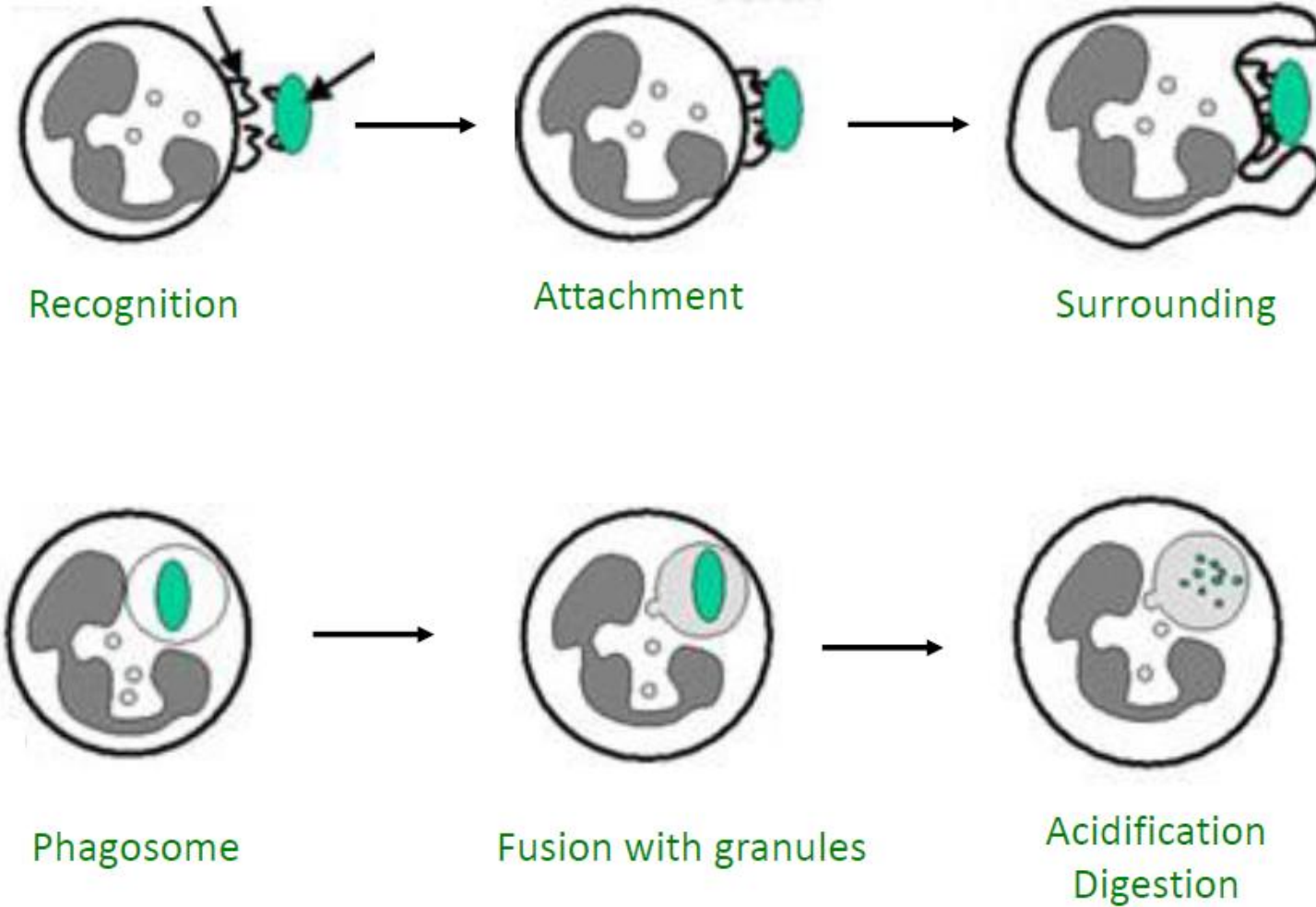


The multiple microbicidal strategies of the neutrophil

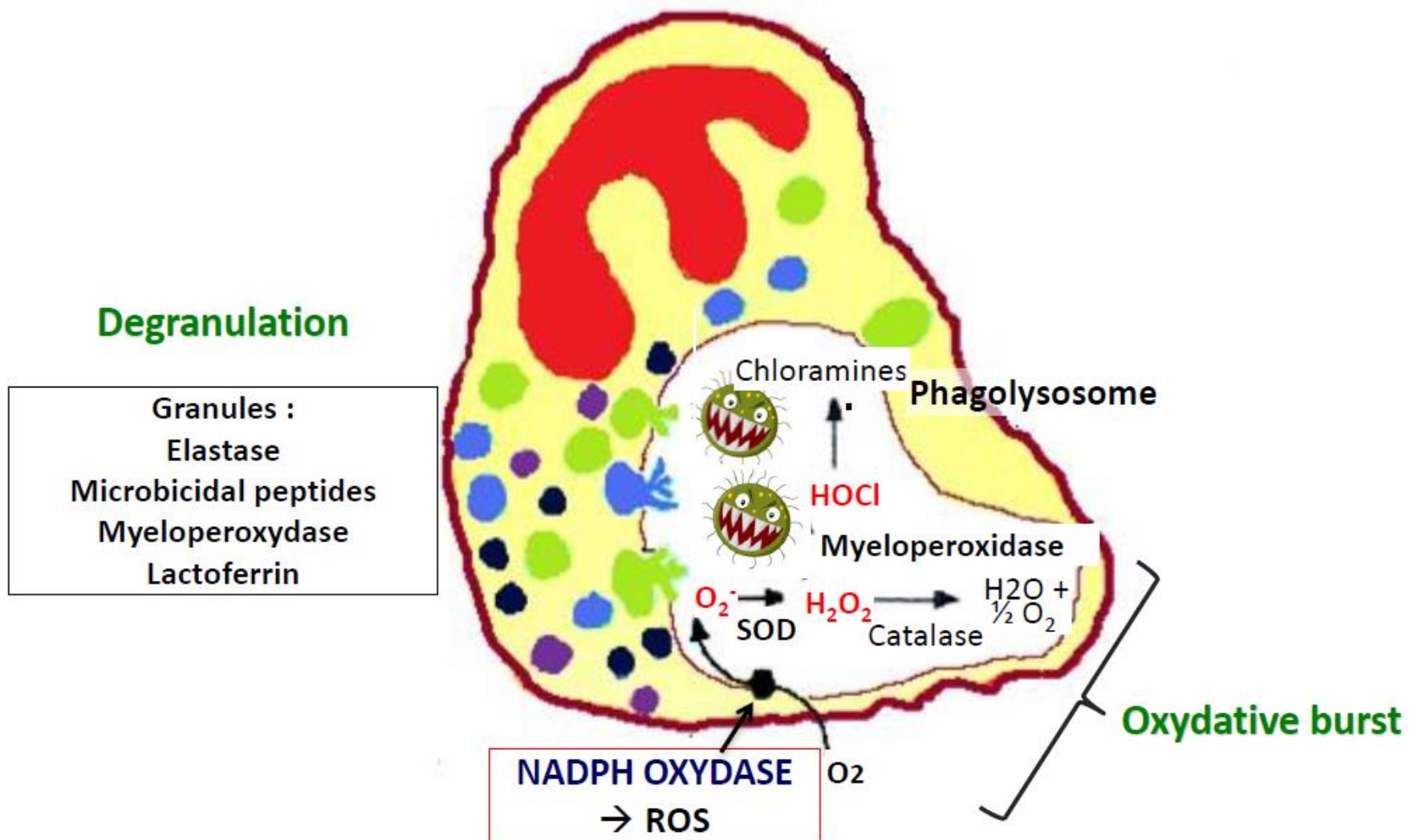


1- Phagocytosis

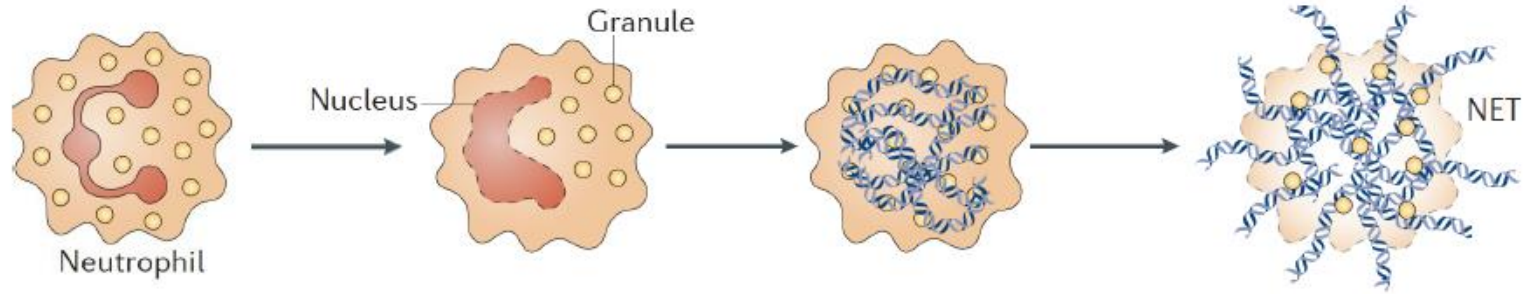
Opsonins:
IgG, C3b



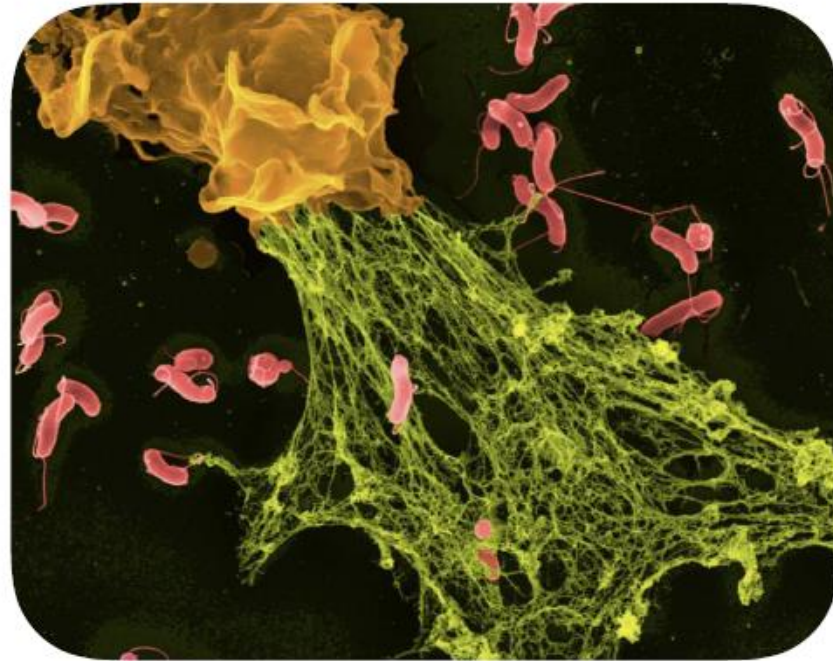
2- Degranulation and oxydative burst



3- NETosis



DNA ejection from neutrophil
Traps microorganisms

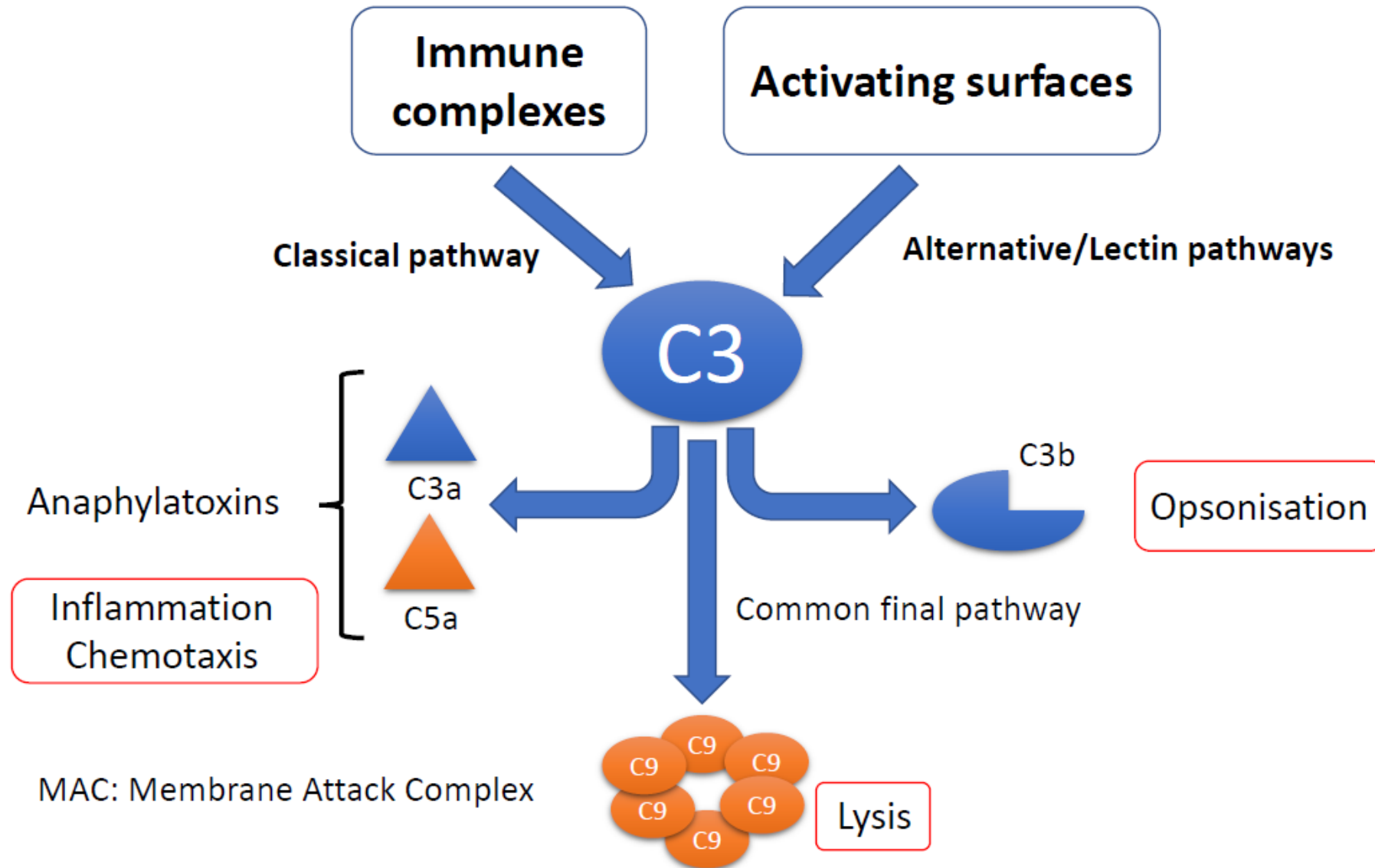


The complement system



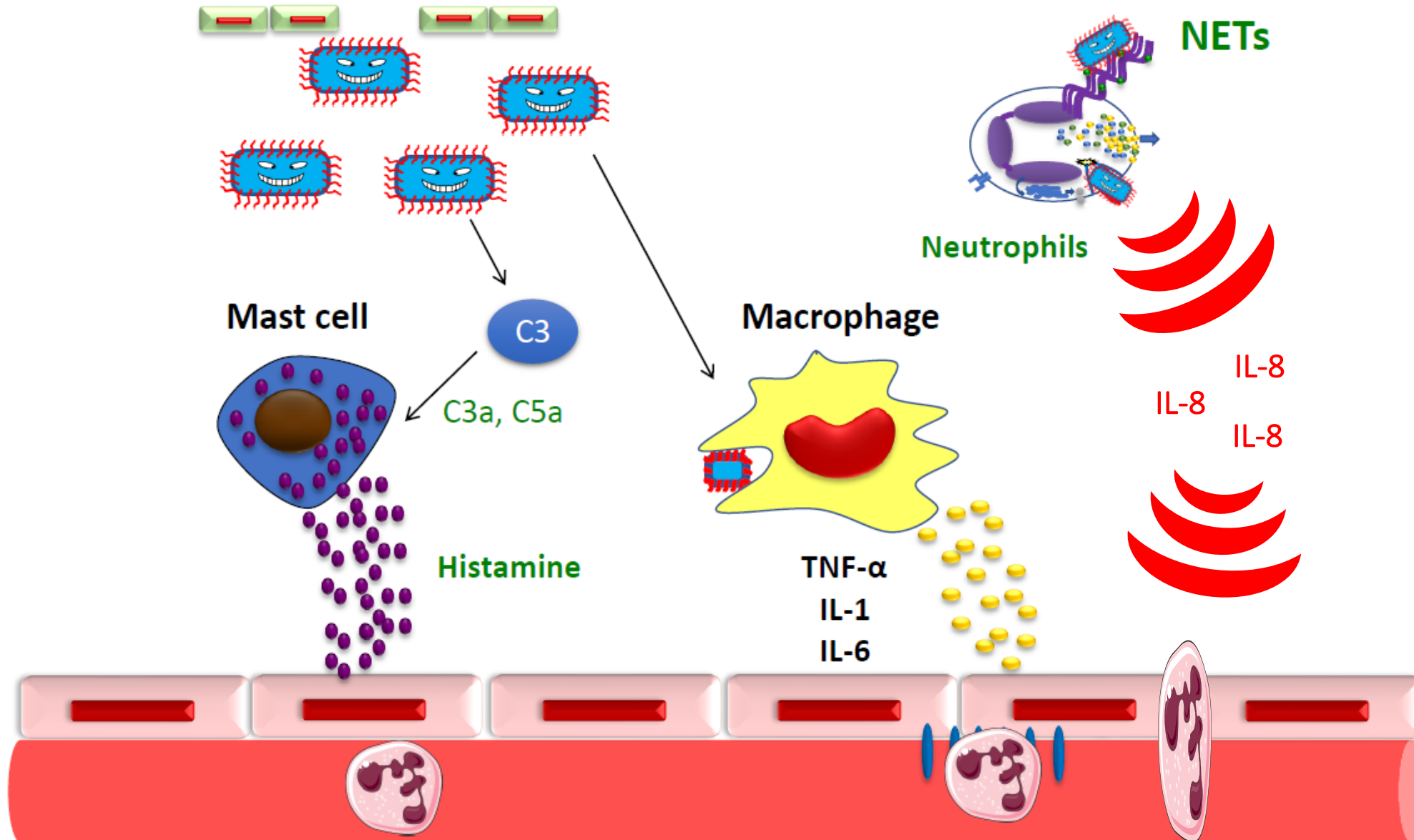
- About 30 plasma proteins (5%)
- Complex enzymatic activation cascades
- **3 activation ways**
- All leading to **C3 protein cleavage**
- Leads to **target cell destruction**

Complement overview



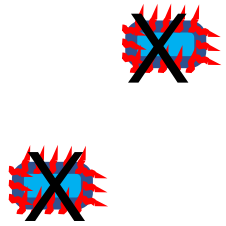
Inflammatory response

Tissue injury

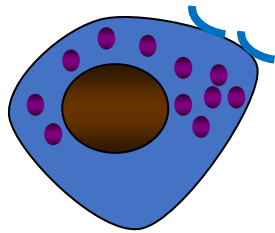


Inflammation resolution

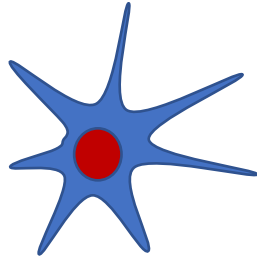
Tissue injury



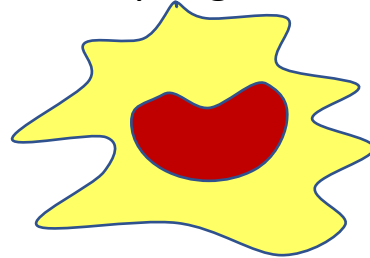
Mastocyte



Cellule dendritique



Macrophage

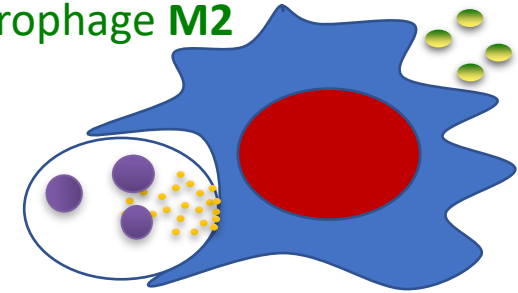


→ Tissue reparation

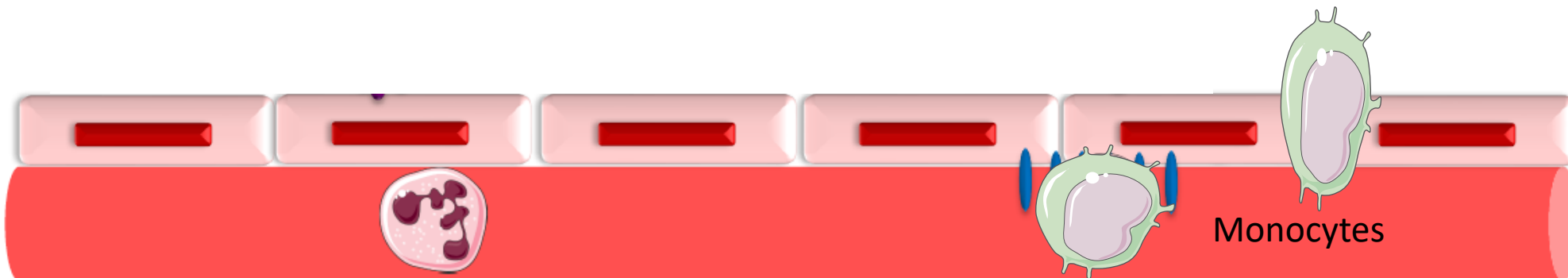


Resolution

Macrophage M2 $TGF\beta$, IL-10



Efferocytose
of apoptotic neutrophils



Key takeaways



- PRRs detect danger signals, either exogenous (MAMPs) or endogenous (DAMPs), extracellular or intracellular.
- PRRs recognize diverse microorganisms and different PRR are expressed on every innate immune cell.
- PRR interactions triggers the production of proinflammatory cytokines (TNF, IL-1, IL-6).
- Proinflammatory cytokines initiate the inflammatory response by activating local cells, including endothelial cells of nearby blood vessels, and inducing systemic responses such as fever.
- Neutrophils are the first cells recruited on inflammed tissues. They are highly effective at combating pathogens through phagocytosis, oxidative bursts, degranulation, and the release of NETs (DNA-based antimicrobial traps).
- As danger persists, neutrophils are activated and release IL-8, a chemokine that recruits additional neutrophils to the site of inflammationand.

Key takeaways

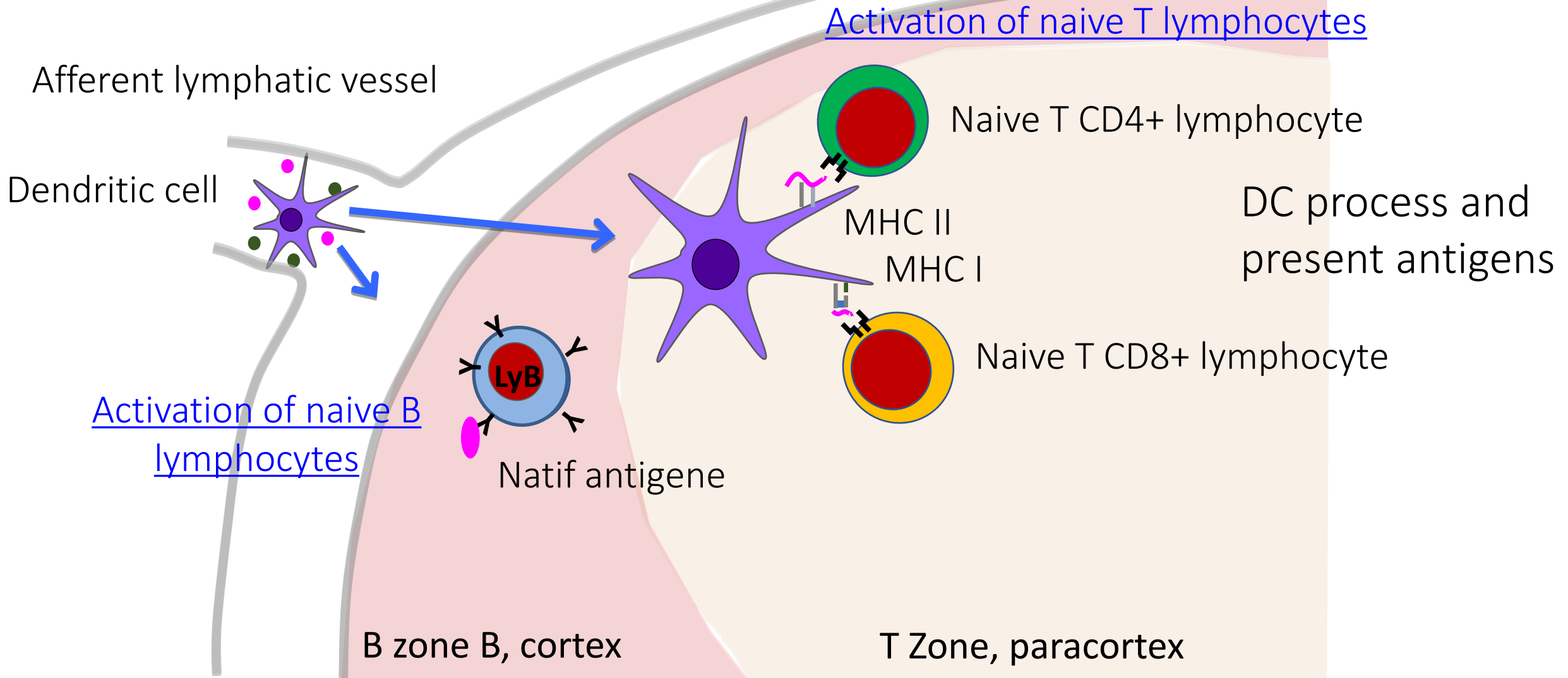


- Neutrophil activity can cause collateral tissue damage.
- Inflammation resolution: Apoptotic neutrophils are cleared by macrophages via efferocytosis, which switches macrophages to an anti-inflammatory (M2) state.
- Anti-inflammatory mediators: IL-10, TGF- β , and lipid mediators (resolvins, protectins) stop inflammation and promote tissue repair.
- Clinical relevance of cytokines: Cytokine dysregulation contributes to diseases like septic shock or chronic inflammation, making them therapeutic targets.

Starting adaptive response

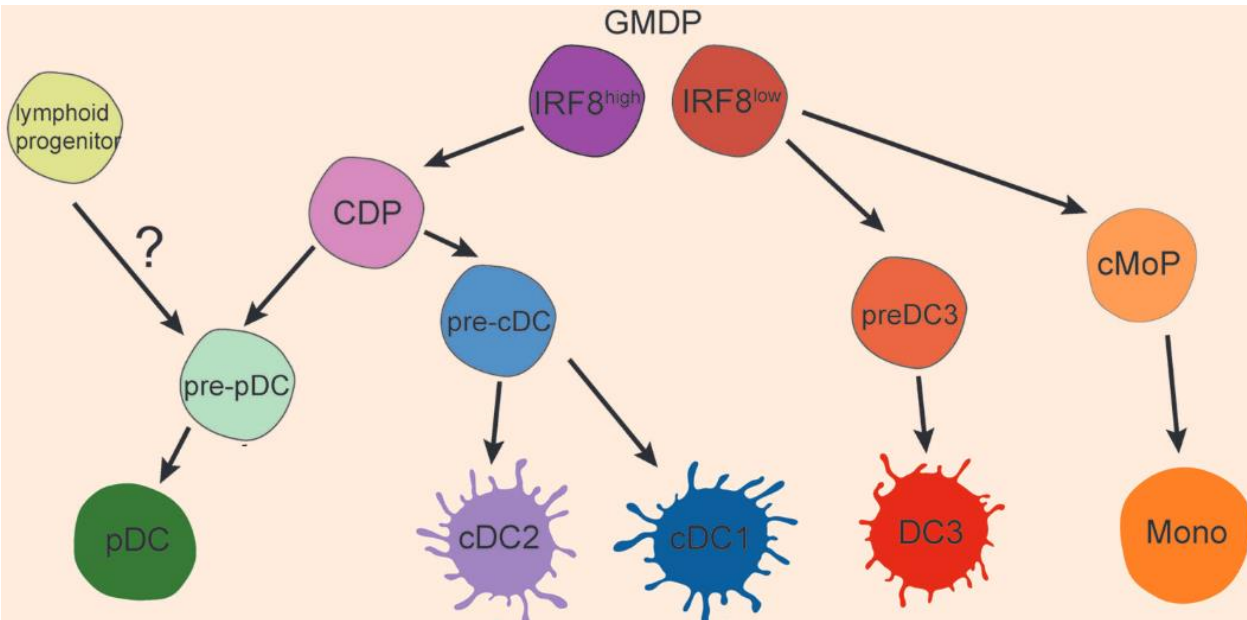


Secondary lymphoid organs: lymph nodes



Dendritic cells

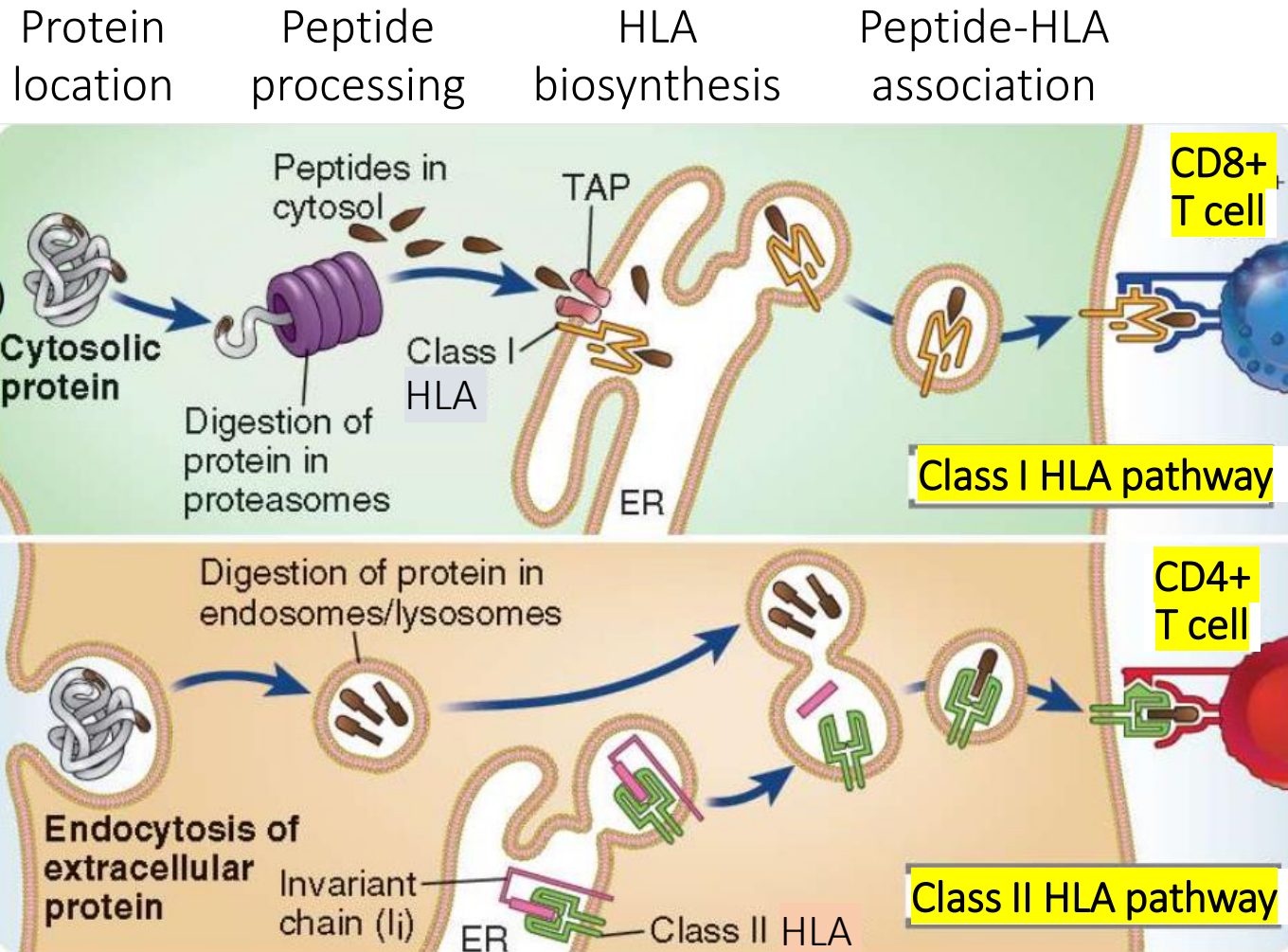
Different subsets with distinct phenotypes, including varying patterns of PRR expression
 → lead to distinct immune responses.



Segura, Eur J Immunol 2022

	cDC1	cDC2	pDC	cDC3	Mo-DC
Cross-presentation	Yes	Yes	Yes	?	Yes
Presentation on MHC II	Yes	Yes	Yes	Yes	Yes
Induction of cytotoxic CD8 T cells	Yes	Yes	Limited	?	Yes
Induction of Th1 cells	Yes	Yes	Yes	Yes	Yes
Induction of Th2 cells	Yes	Yes	No	No	?
Induction of Th17 cells	No	Yes	No	Yes	Yes
Induction of Tfh cells	No	Yes	No	?	Yes
Induction of Treg cells	No	Yes	Yes	?	?
Secretion IL-12	Limited	Yes	No	Yes	Yes
Secretion IL-23	No	Yes	No	Yes	Yes
Secretion type I IFN	No	No	Yes	No	No

Peptides associated to MHC / HLA molecules : Processing and presentation pathways



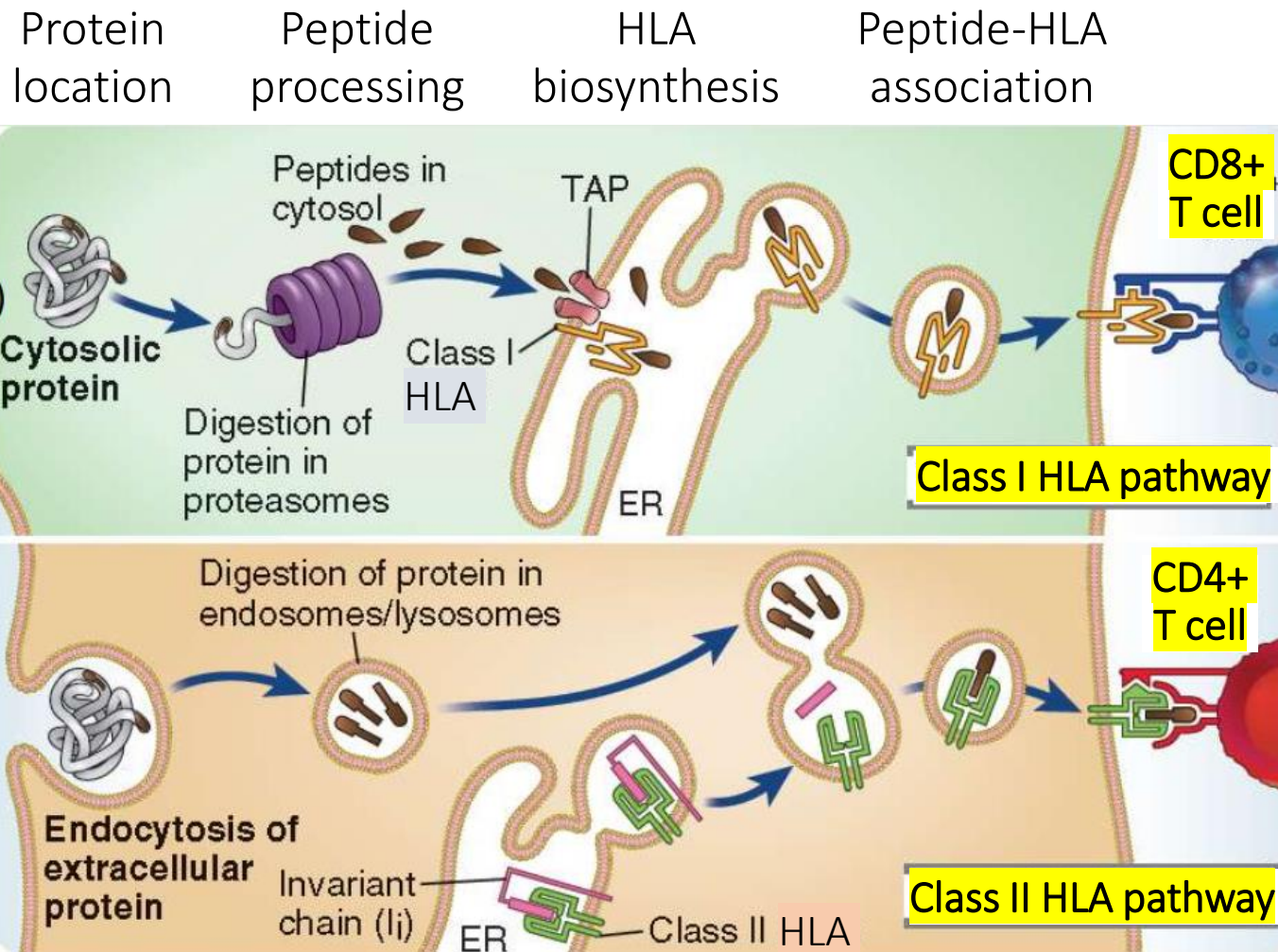
Class I HLA molecules :

- Present peptides mostly derived from endogenous / cytoplasmic proteins
- Peptides are presented to **CD8+ T lymphocytes** → **cytotoxic response**

Class II HLA molecules

- Present peptides mostly derived from exogenous proteins
- Peptides are presented to **CD4+ T lymphocytes** → **cytokine response**

Peptides associated to HLA molecules : Processing and presentation pathways



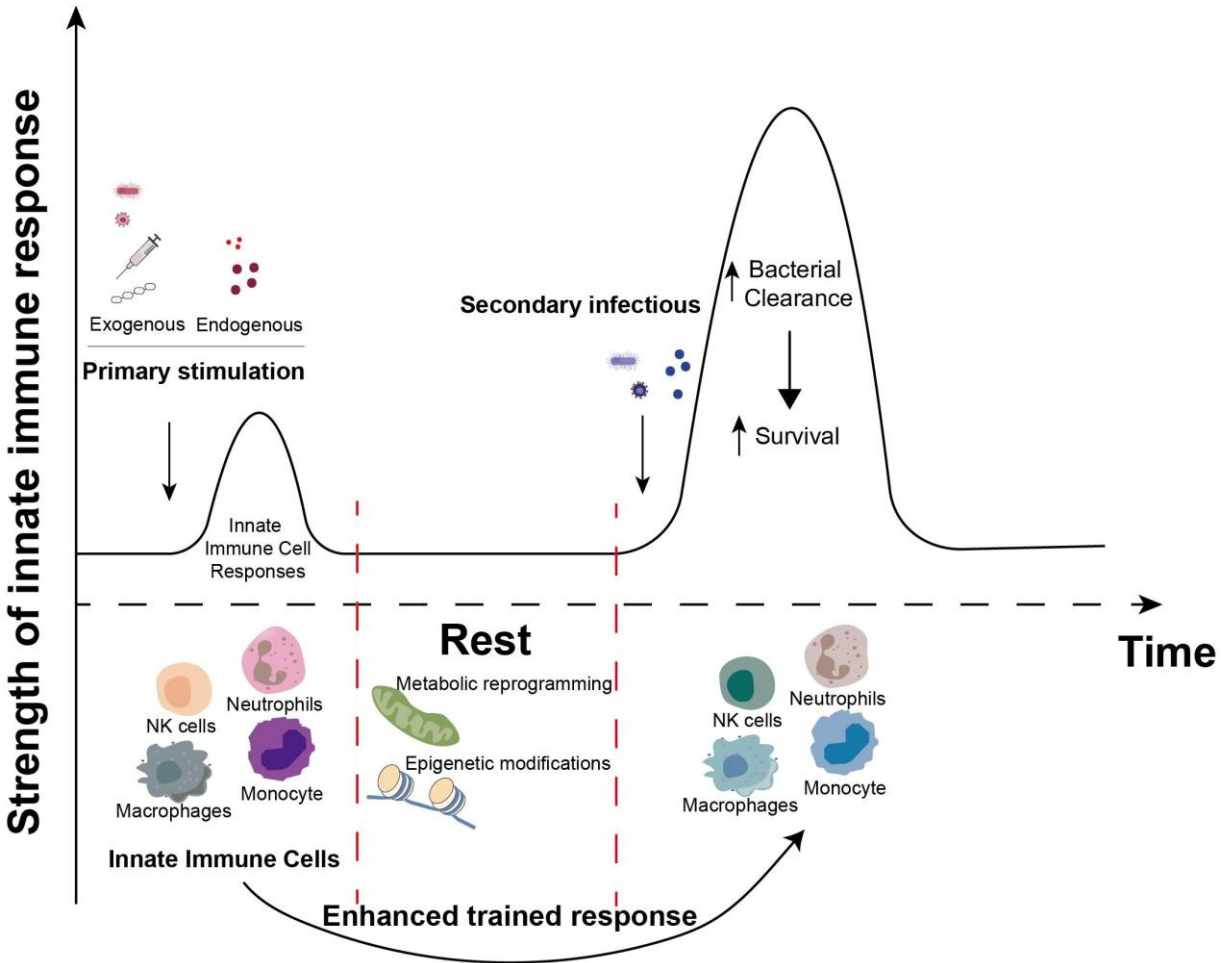
Class I HLA molecules :

- Expressed by all nucleated cells

Class II HLA molecules

- Expressed by **professional antigen-presenting cells** (DCs, B cells, mono/macrophages)

Trained innate immunity



wang et al Front Immunol 2024

- ‘Trained innate immunity’ ability of innate immune system to have an **enhanced inflammatory or antimicrobial response** upon re-exposure to pathogens or danger signals.
- Observed even with heterologous stimulation.
- Based on the epigenetic and metabolic reprogramming of innate cell precursors (bone marrow or tissues)
- BCG and beta-glucans are canonical inducers.
- Several innate cells have been shown to be trainable (e.g. monocytes, neutrophils, ILC3, NK cells).
- It is distinct from priming, differentiation/polarization, maturation.
- Different from ‘innate immune memory’: ability of the innate immune system to retain a "memory-like" response after encountering certain stimuli (pathogens). It is recallable. (NK cells)

Thank you for your attention