

Basic immunology

Lecture 5.

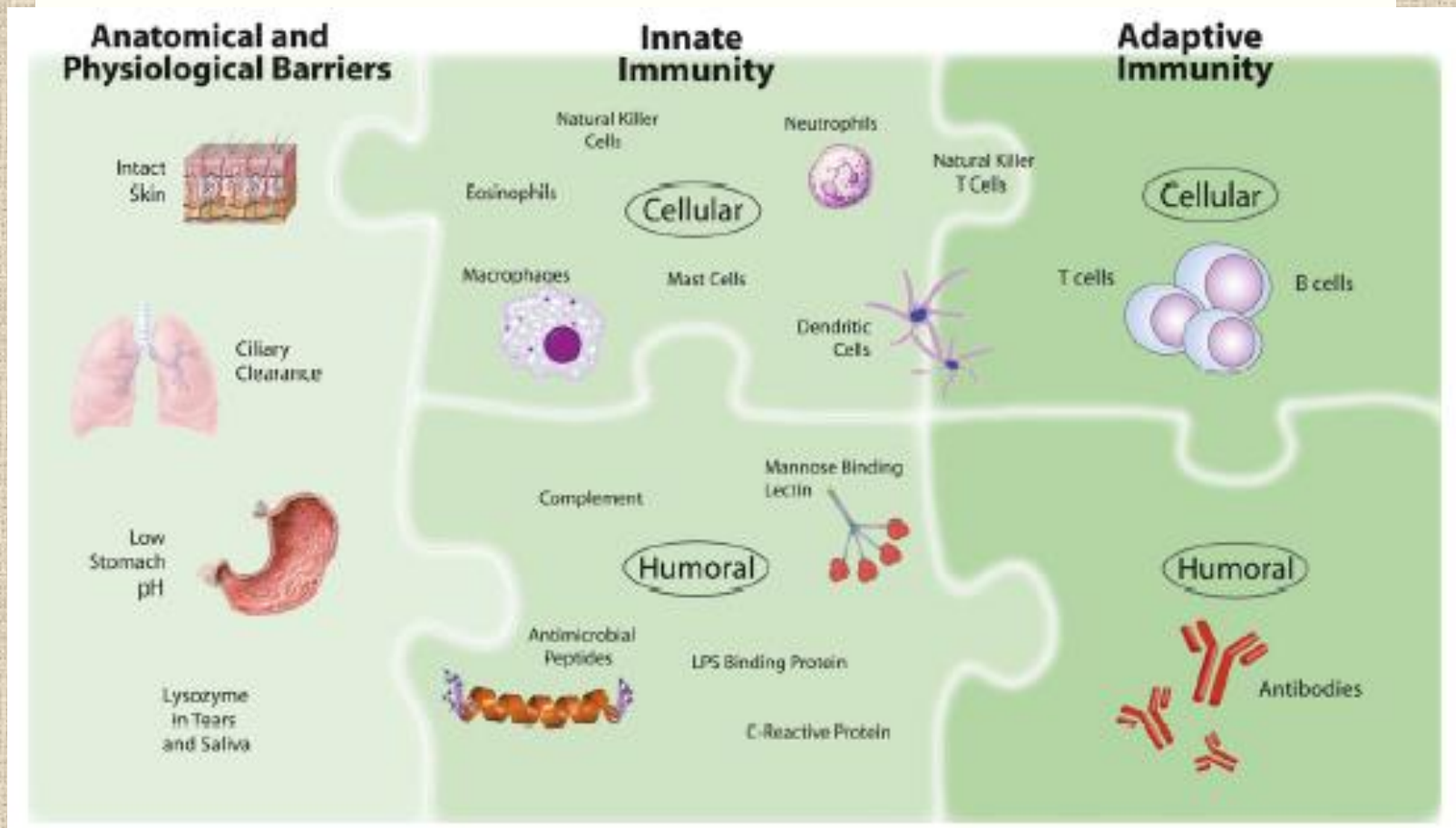
Innate immunity, cell adhesion

Péter Engelmann

- Different levels of the immune response
- Recognition molecules of the innate immunity
- Adhesion molecules, extravasation („homing”)

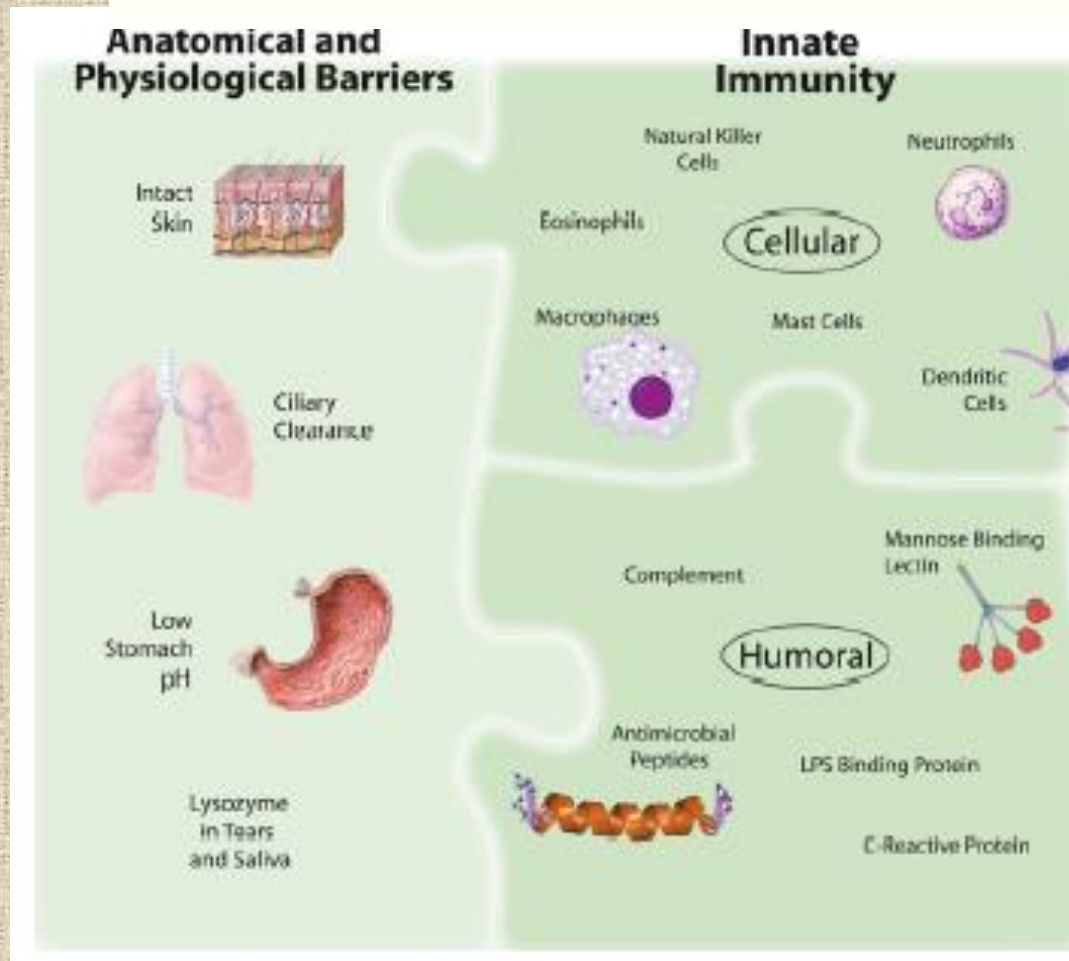
The levels of host defense

- Anatomic „barriers”
- Innate immunity, inflammation
- Adaptive immunity



The levels of host defense

- Anatomic „barriers”
- Innate immunity, inflammation
- Adaptive immunity



I. First line of defense: anatomic „barriers”

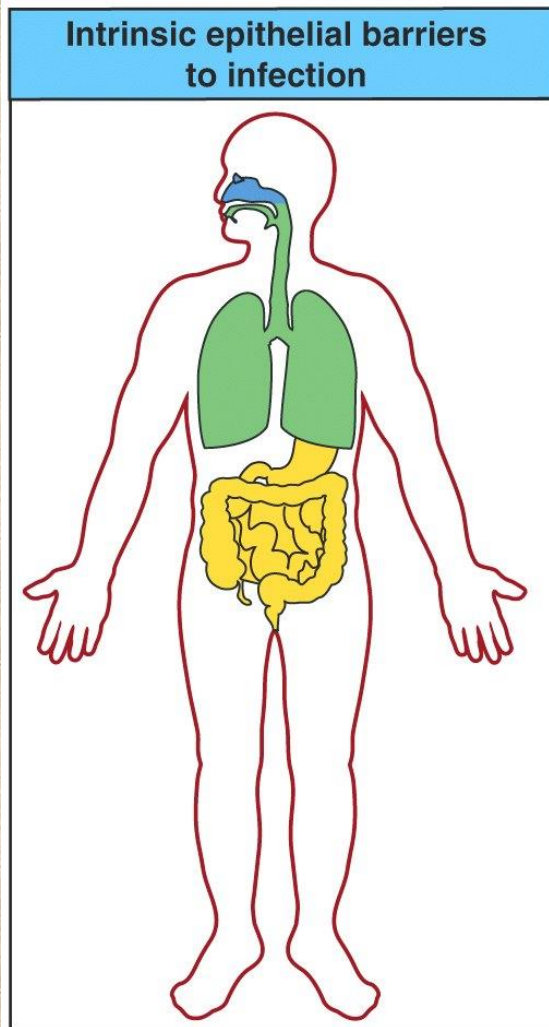
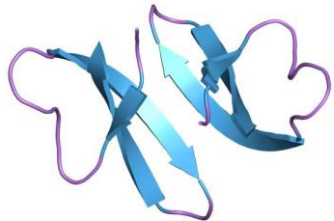


Figure 2-4 Immunobiology, 6/e. (© Garland Science 2005)

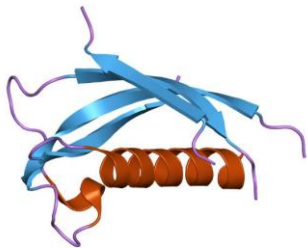
	Skin	Gut	Lungs	Eyes/nose/oral cavity
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH Enzymes (pepsin)	Pulmonary surfactant	Enzymes in tears and saliva (lysozyme)
	β -defensins Lamellar bodies Cathelicidin	α -defensins (cryptdins) RegIII (lecticidins) Cathelicidin	α -defensins Cathelicidin	Histatins β -defensins
	Normal microbiota			
Microbiological				

1. Mechanical defense
2. Slightly acidic environment
3. Normal (commensal) microorganisms
4. Antimicrobial factors in the body fluids, on the skin.
5. Cilia

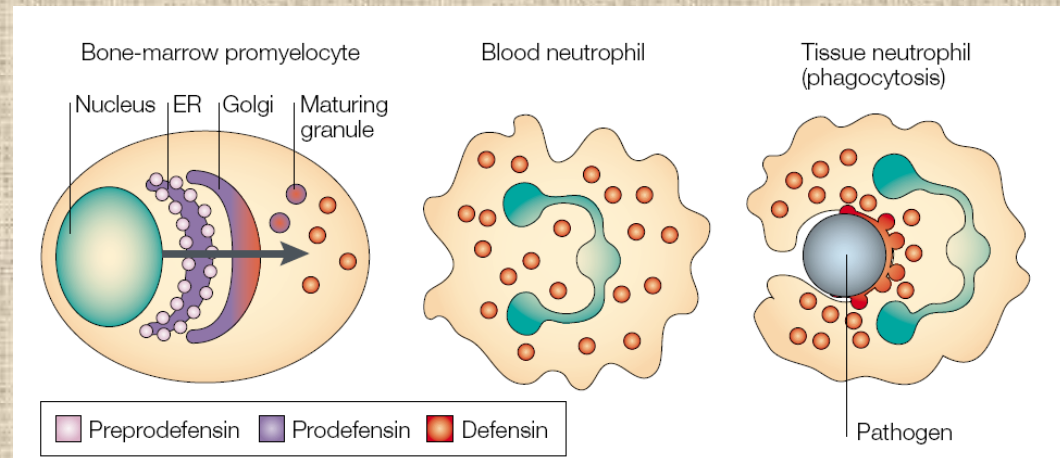
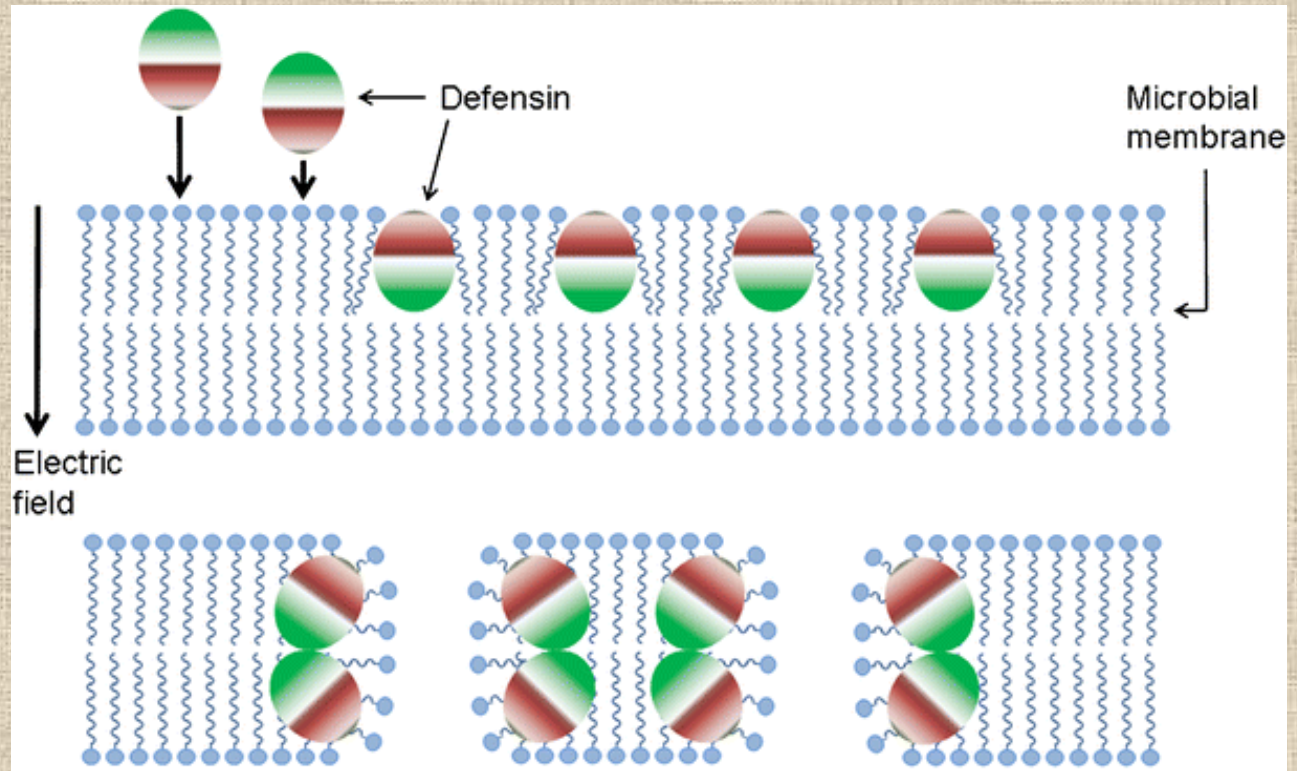
Antimicrobial peptides



Defensin



Cathelicidin

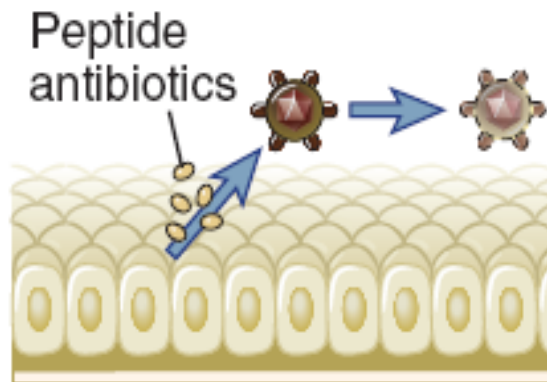


The role of epithelial barriers

Physical barrier
to infection

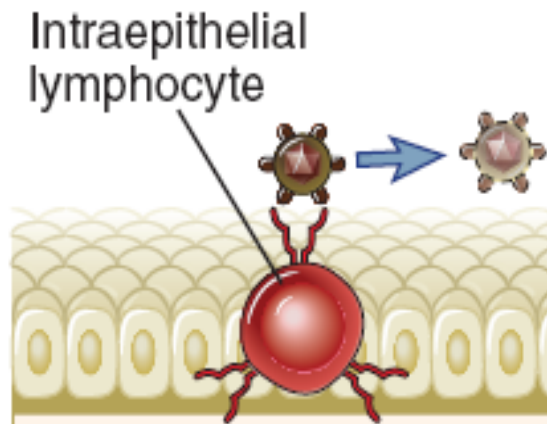


Killing of microbes
by locally produced
antibiotics,
defensins,
cathelicidins



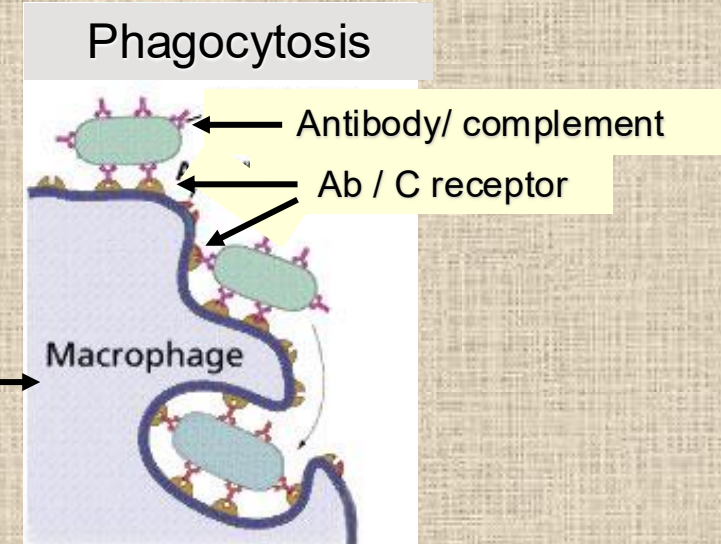
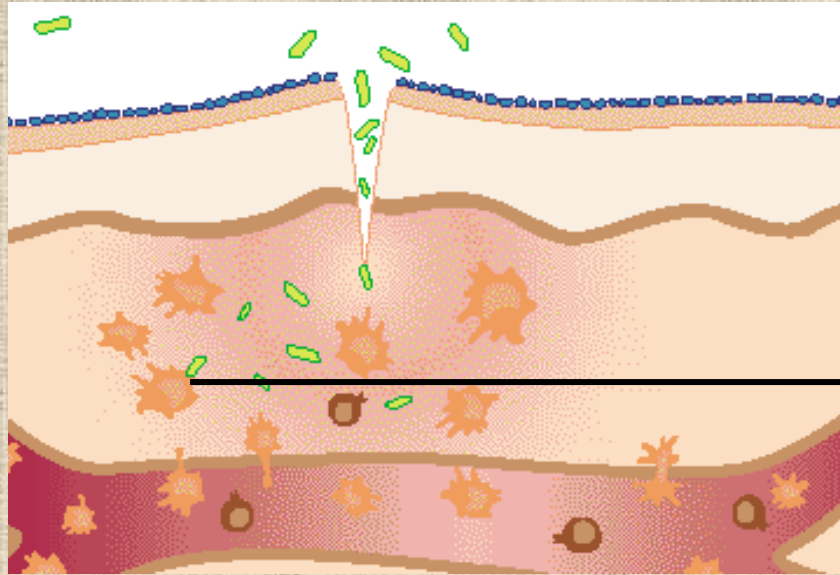
Defensins,
cathelicidins

Killing of microbes
and infected cells
by intraepithelial
lymphocytes

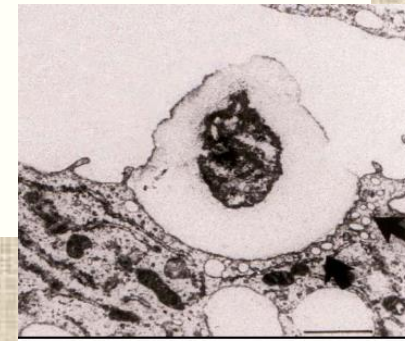


Mast cells, IEL:
 $\gamma\delta$ T cells

II. Second line of defense: innate immunity, phagocytes, inflammation



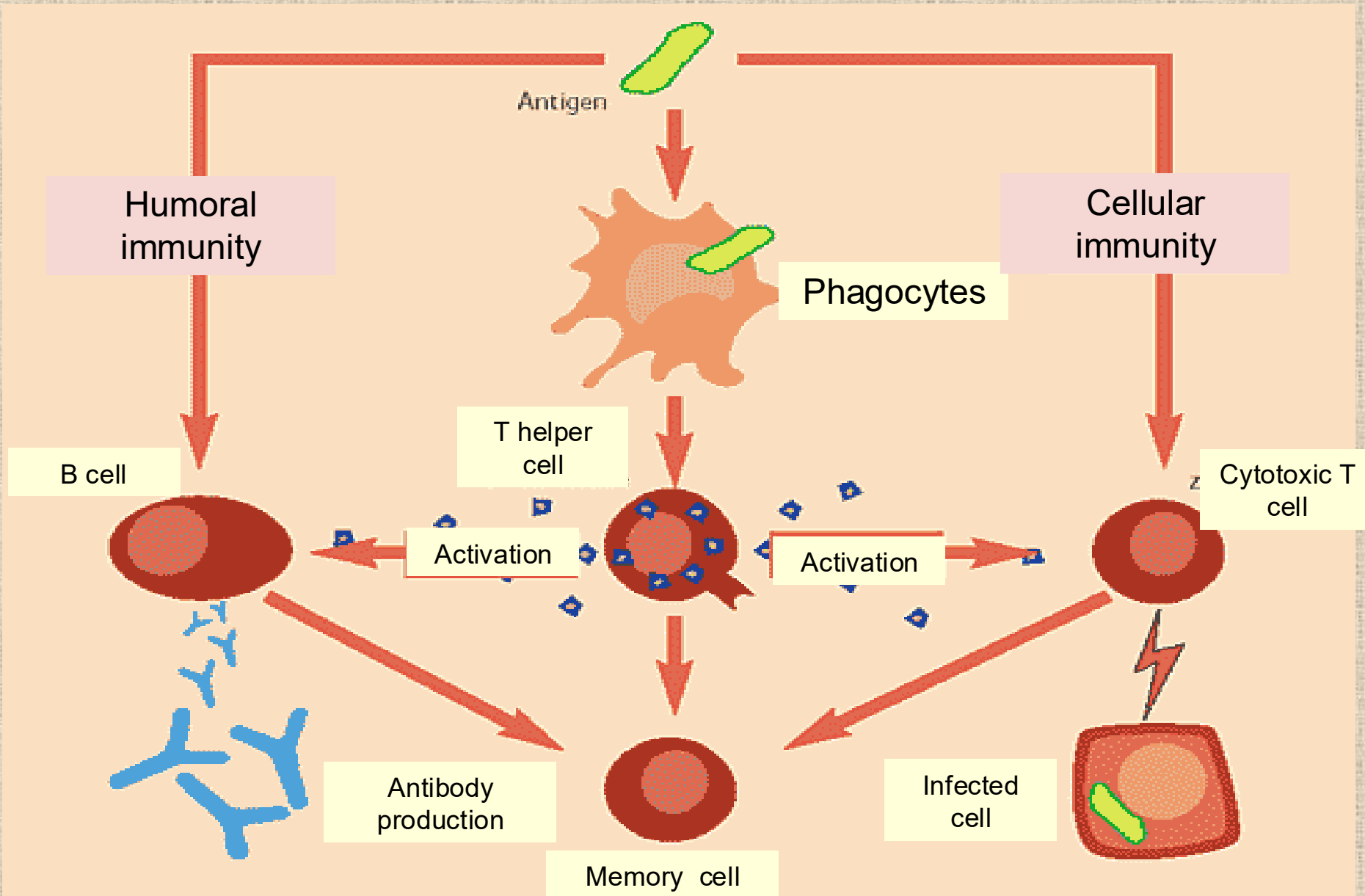
1. **Phagocytes** in the blood and tissues.
2. Soluble **proteins** (immunoglobulin and complement, C-reactive protein), bind to microbe surface (**opsonisation**) to enhance the phagocytosis.



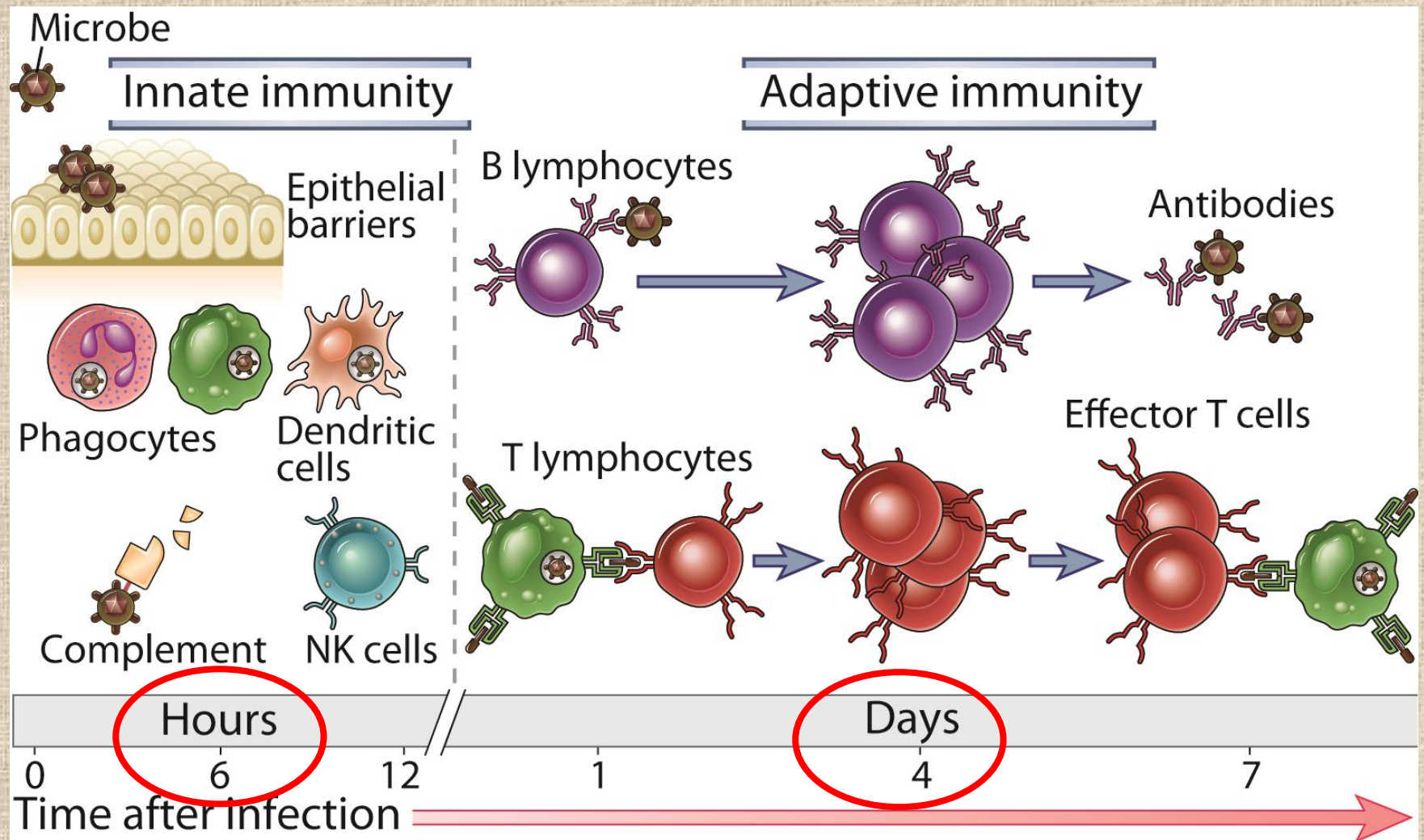
Functions of innate immunity

- 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
- Activate and influence the adaptive immunity

III. The third line of defense: adaptive immunity



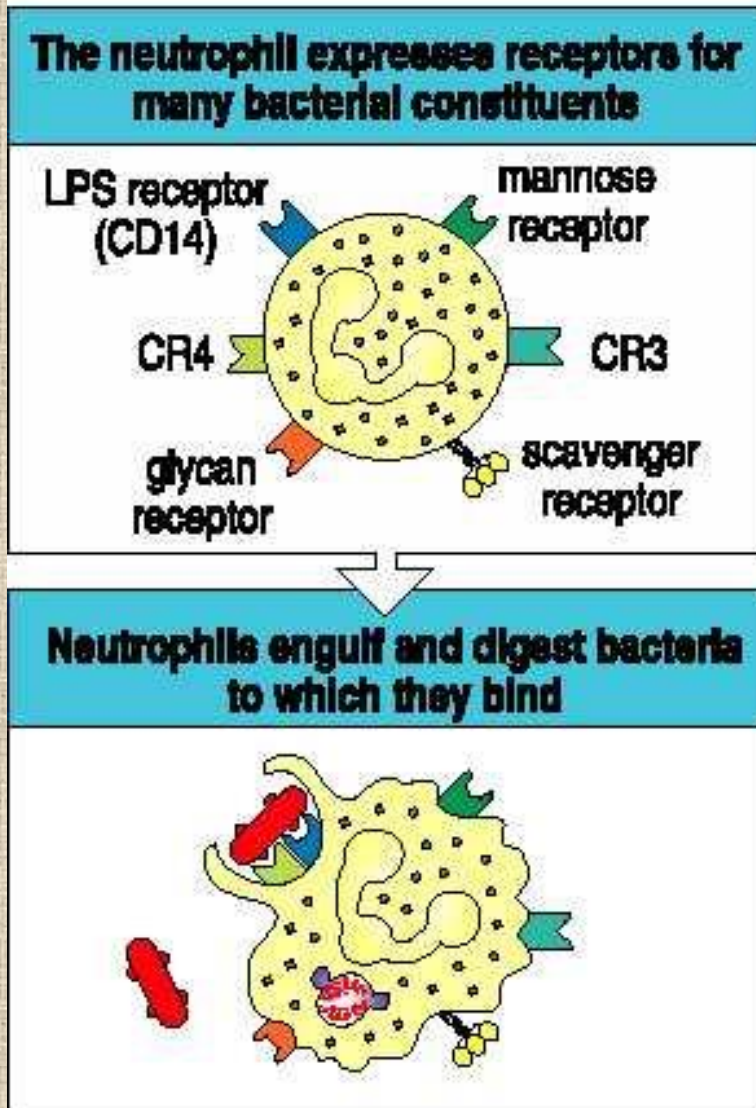
The kinetics of innate and adaptive immune response



- Different levels of the immune response
- Recognition molecules of innate immunity
- Adhesion molecules, extravasation („homing”)

Recognition of pathogens, damaged cells, phagocytosis

Figure 8.8



PRR= „Pattern Recognition Receptors”

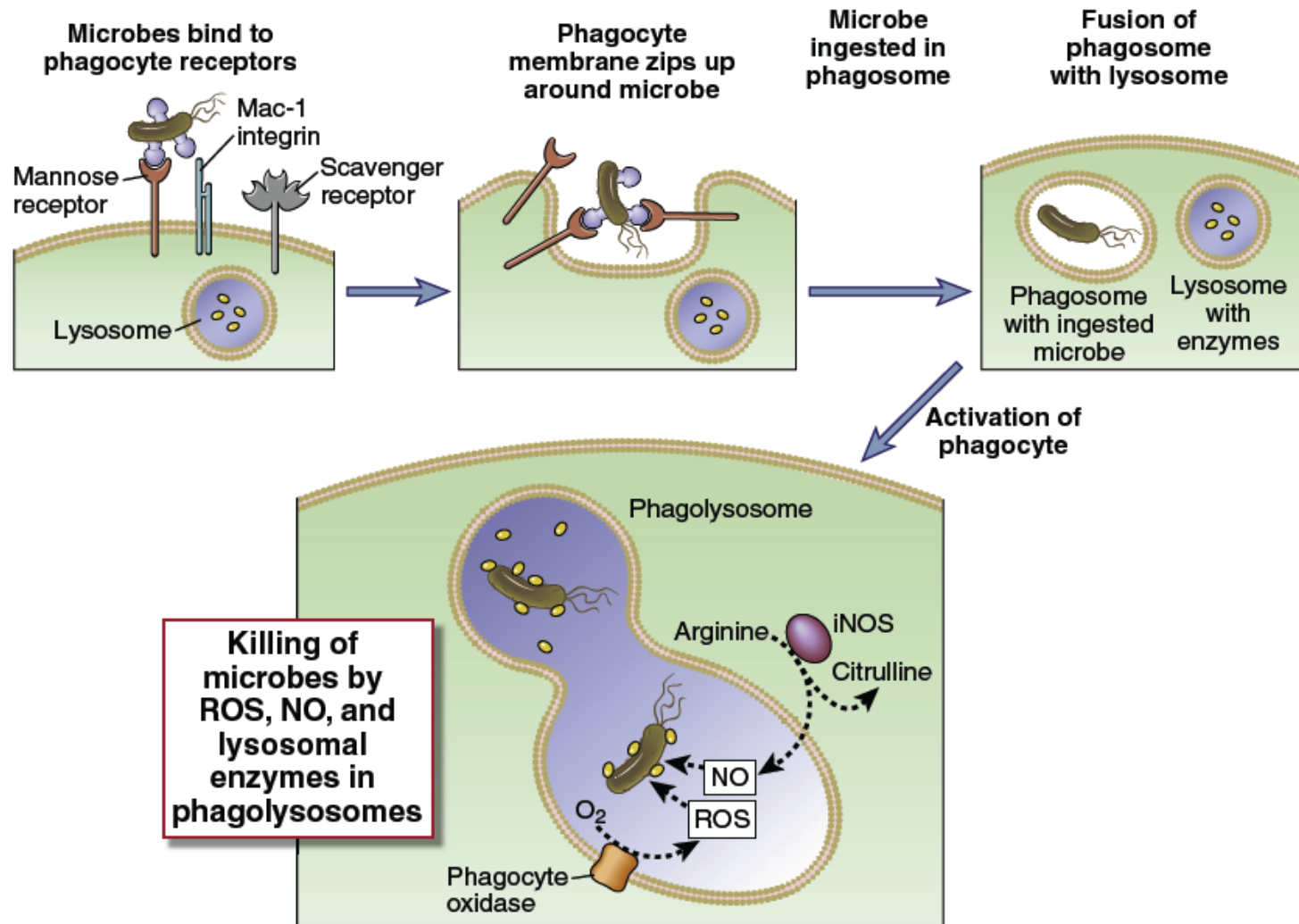
→ Binding to the PAMPS of microbes

PAMP=„Pathogen Associated Molecular Patterns

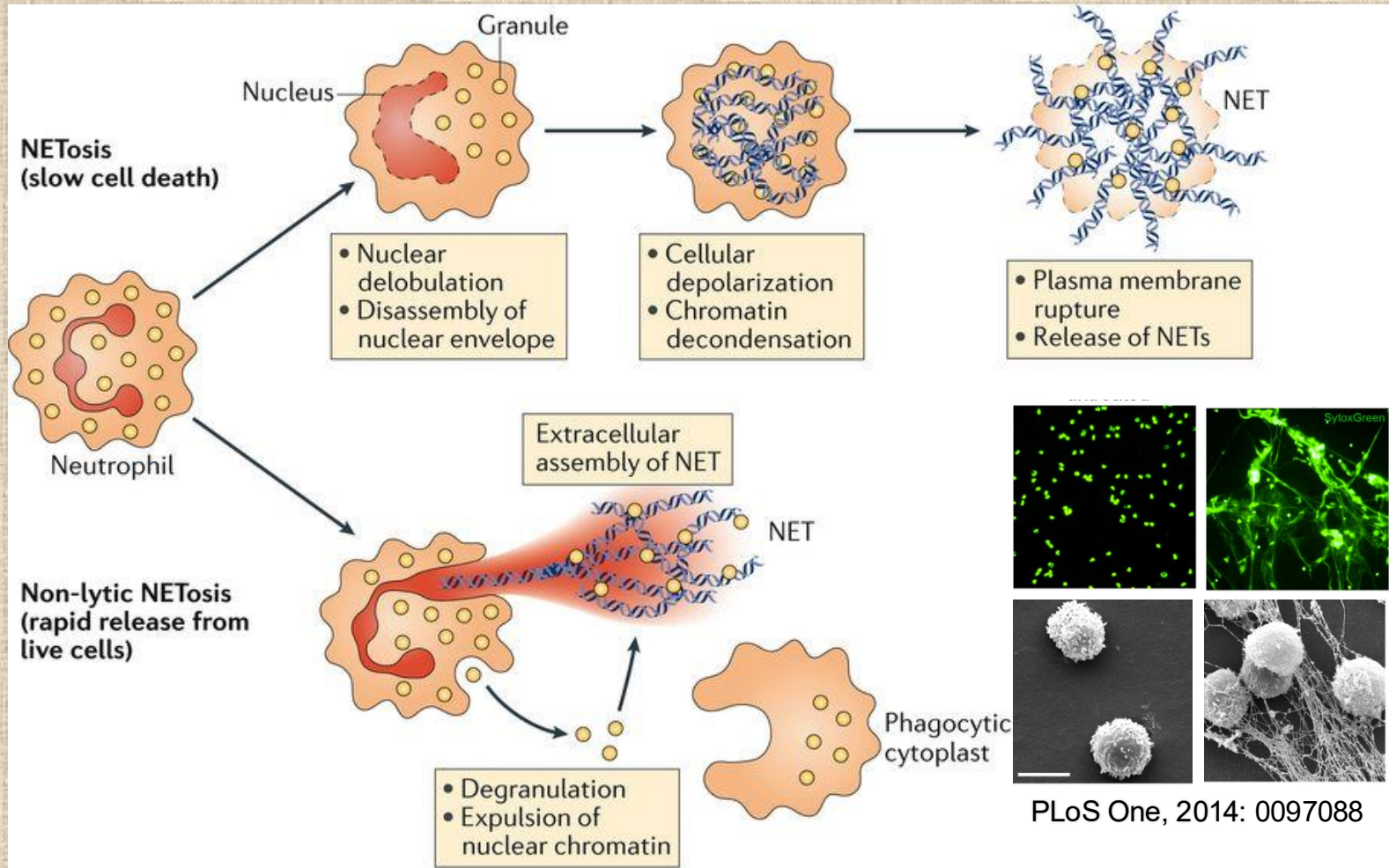
→ Binding to the DAMPs of damaged cells

DAMPs=„Danger Associated Molecular Patterns”, danger signals

The process of phagocytosis



The process of NETs

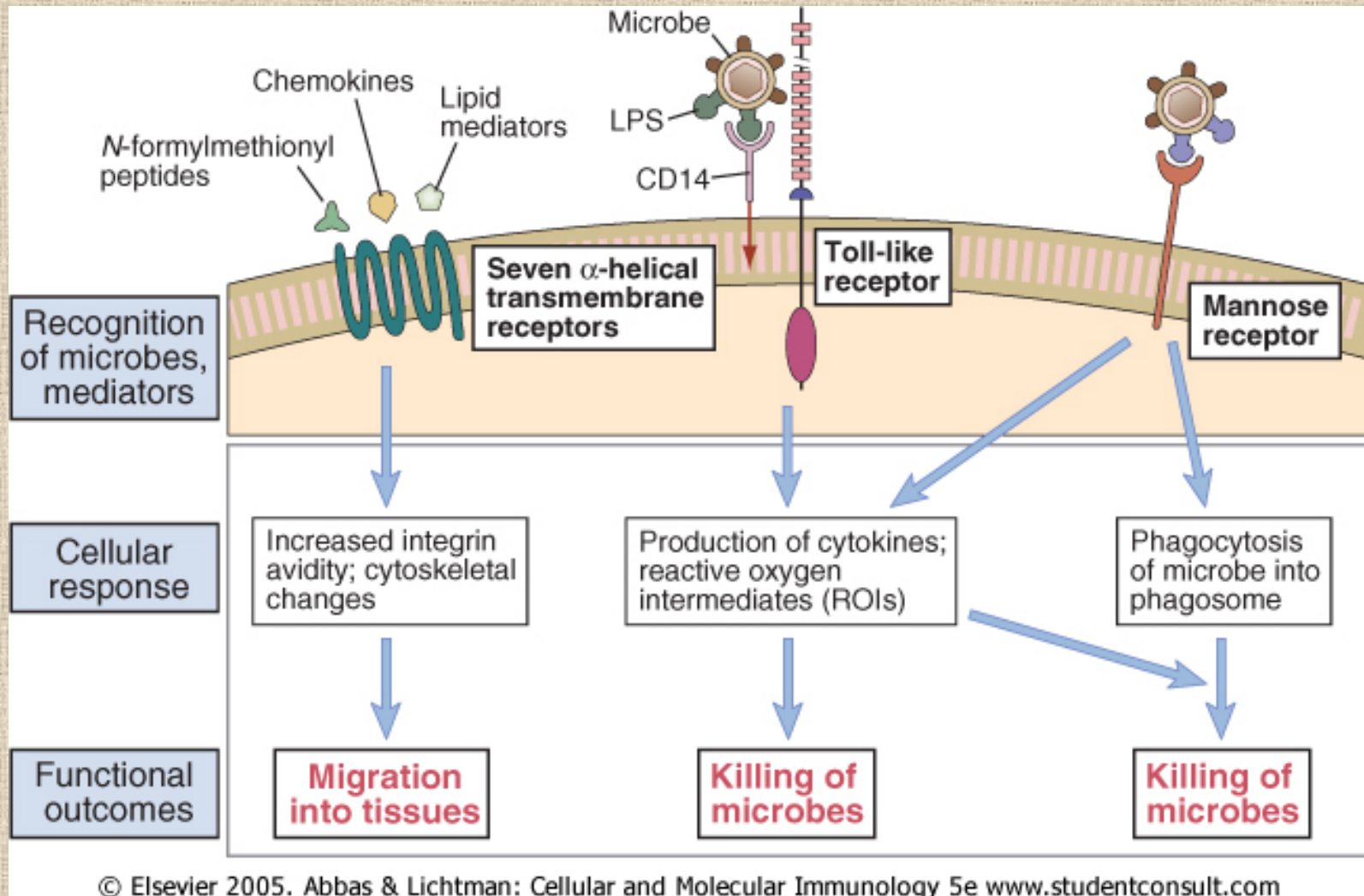


PLoS One, 2014: 0097088

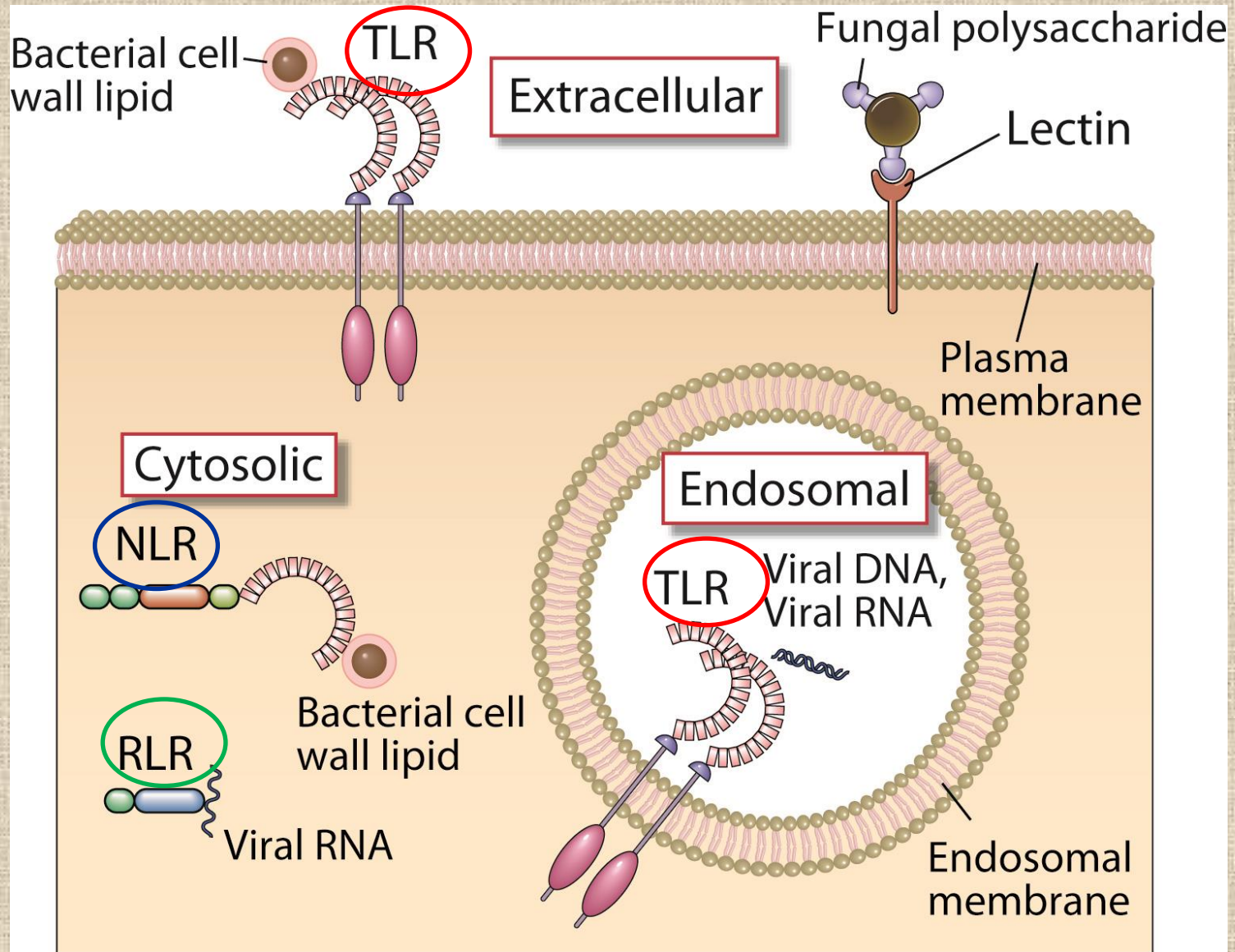
Nature Reviews | Immunology

NET: neutrophil extracellular traps

Phagocyte receptors



Pattern recognition receptors

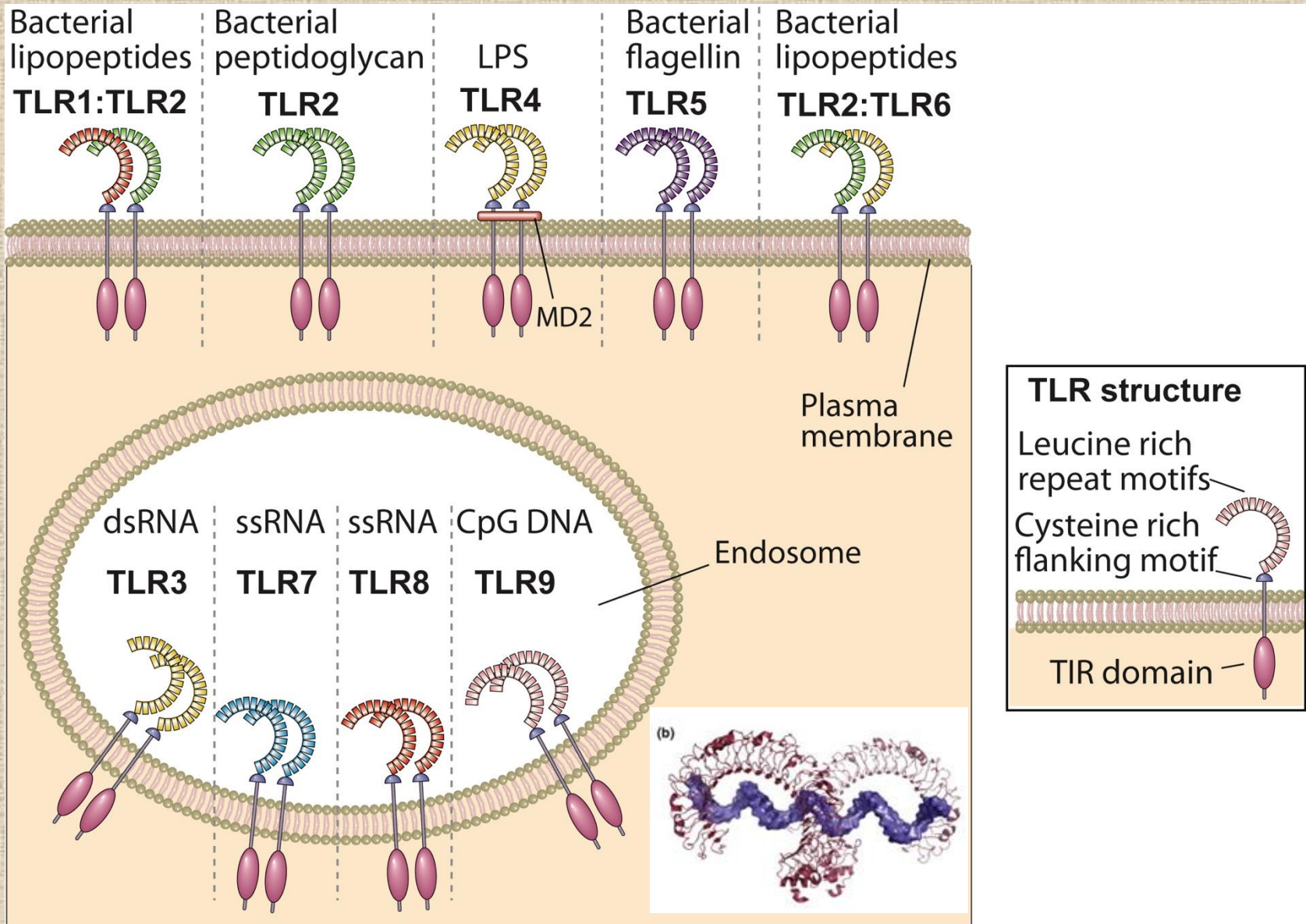


Toll-like receptors (TLR)

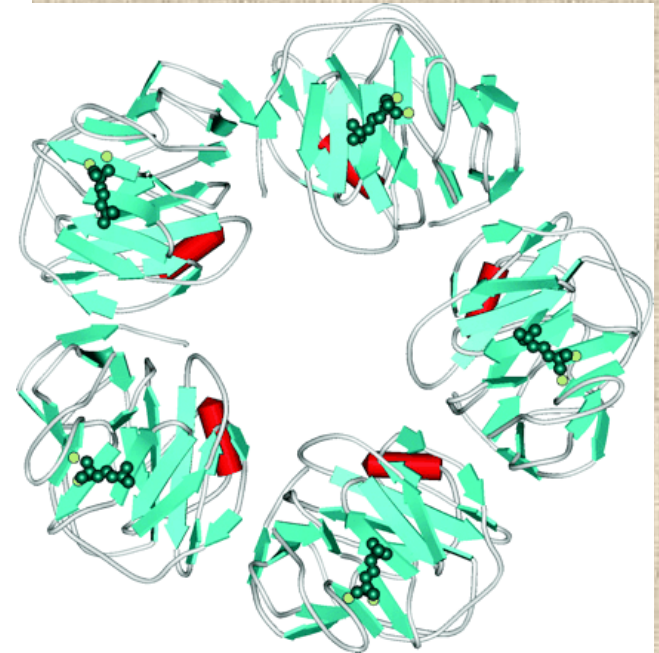
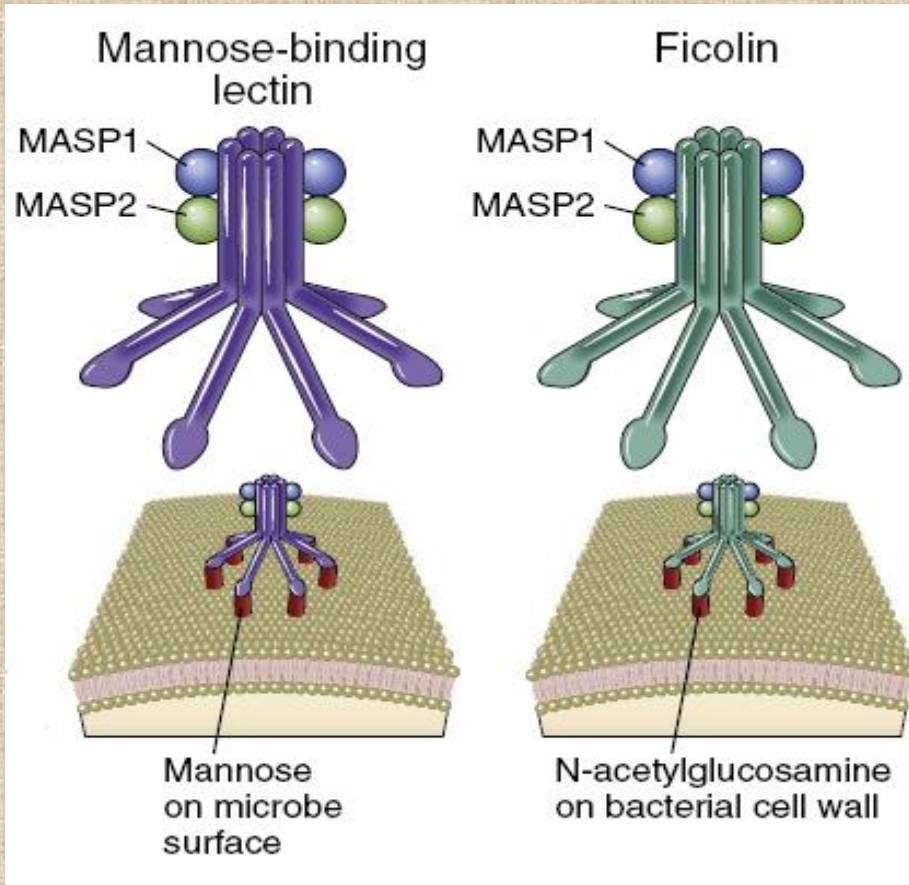
NOD-like receptors (NLR)

RIG-like receptors (RLR)

Pattern recognition receptors: Toll-like receptors (TLR)



Soluble pattern recognition molecules

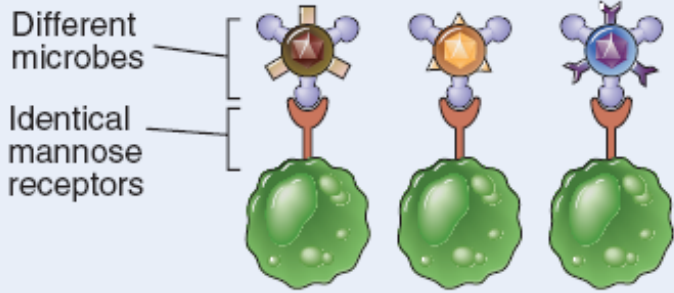
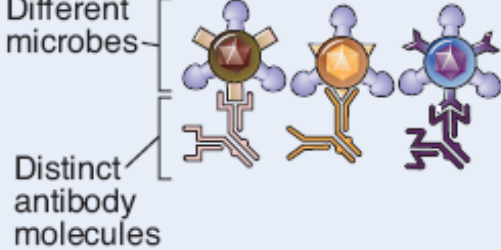
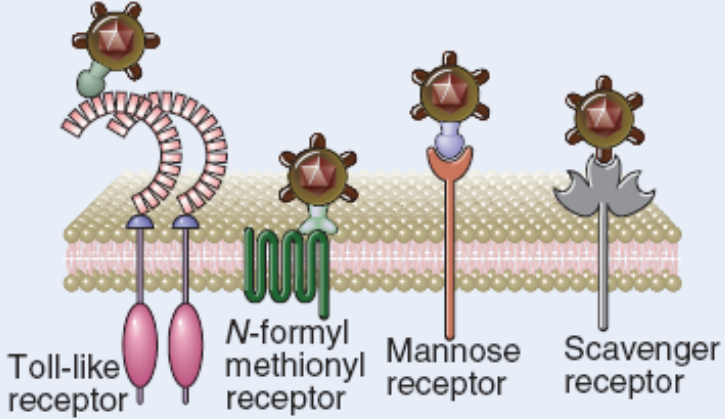
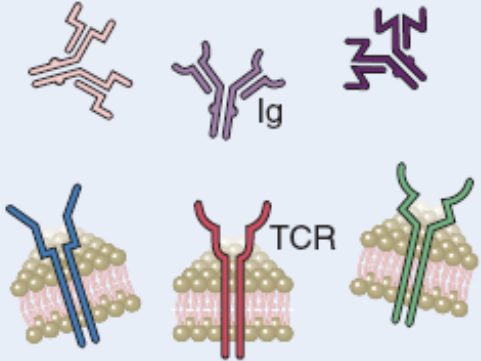


Collectins (MBL, SP-A, SP-D): C-type lectin domain

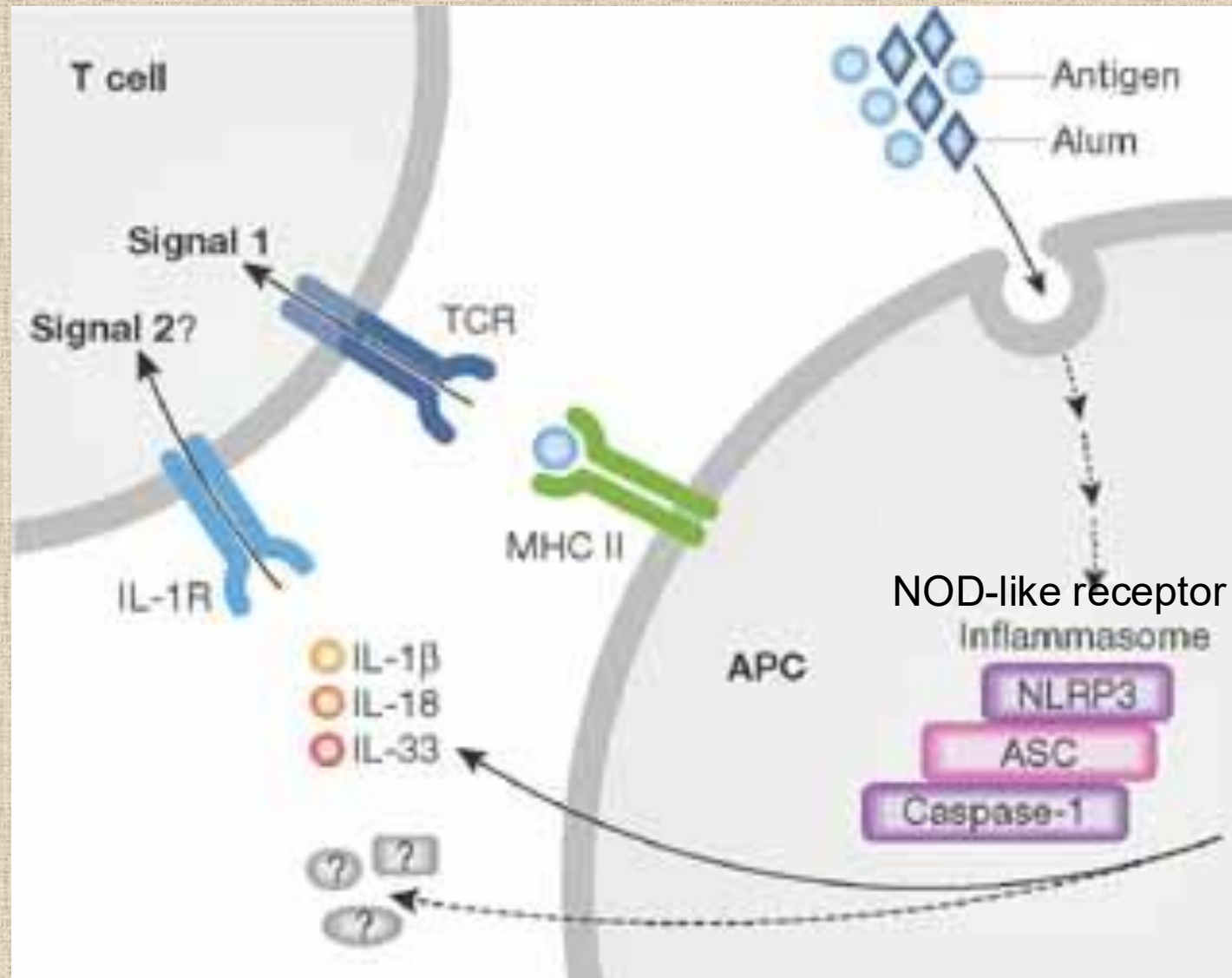
Ficolin: Fibrinogen domain

Pentraxins: C-reactive protein (CRP), Serum amyloid P

Specificity of innate and adaptive immunity

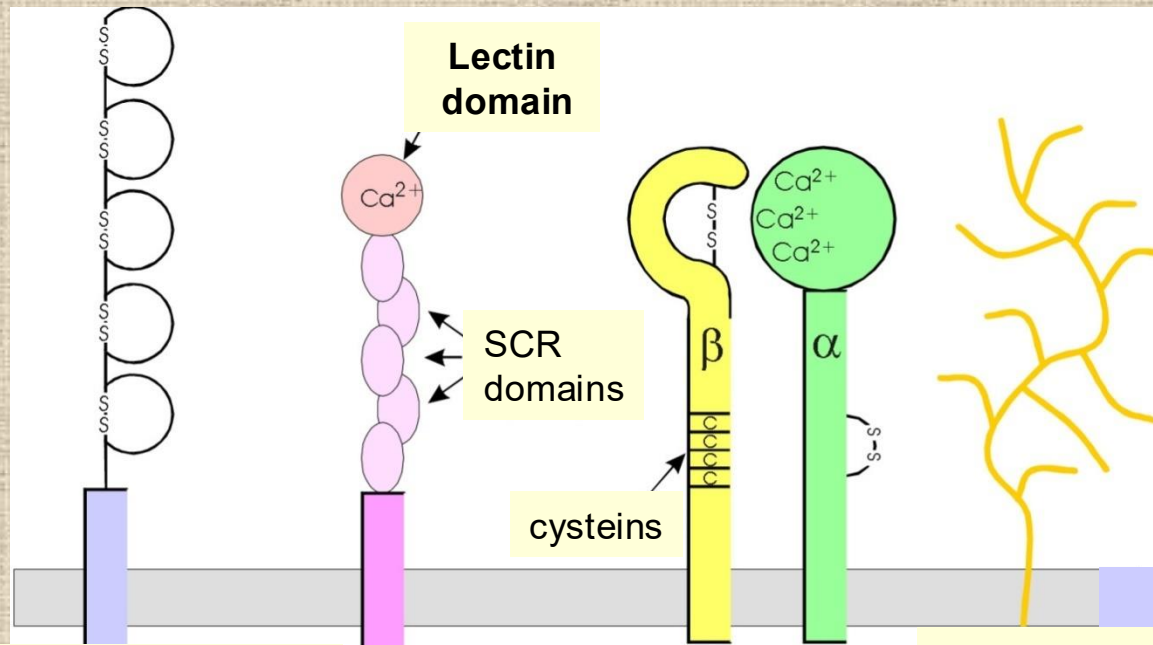
	Innate Immunity	Adaptive Immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns) Different microbes Identical mannose receptors 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens Different microbes Distinct antibody molecules 
Receptors	Encoded in germline limited diversity (pattern recognition receptors)  Toll-like receptor N-formyl methionyl receptor Mannose receptor Scavenger receptor	Encoded by genes produced by somatic recombination of gene segments; greater diversity  Ig TCR
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of self and non-self	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

Vaccination and the role of adjuvants



- Different levels of the immune system
- Recognition molecules of the innate immunity
- Adhesion molecules, extravasation („homing”)

Families of adhesion molecules



**Ig-superfamily
members**

Selectins

Integrins

**Mucin-like
molecules**

**„other”
accessory
molecules**

CD2

CD4

CD8

B7

CD28

CTLA 4

ICAM

L selectin

E selectin

P selectin

VLA

LFA

Mac1

„vascular
addressins”

CD45

CD44

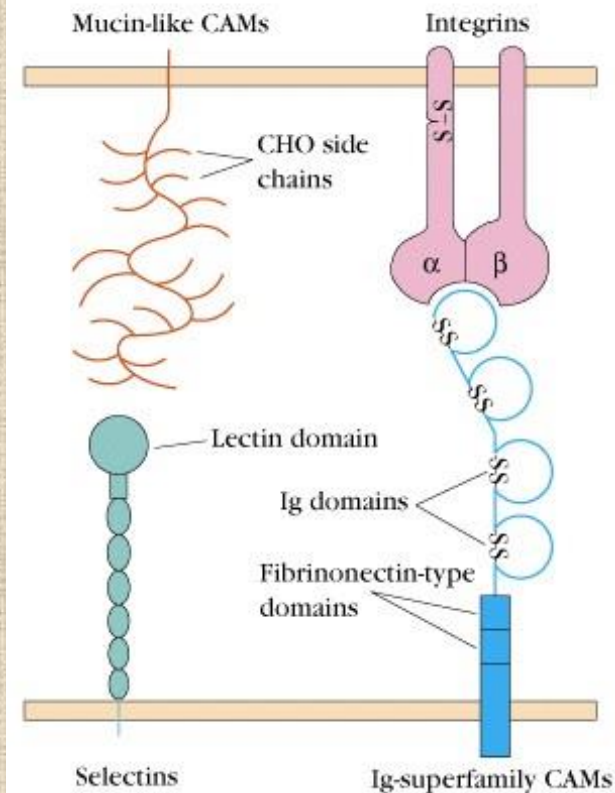
CD40, CD40L

CD19/CD21/CD81

CD22

Adhesion molecules build receptor – ligand interactions

(a) General structure of CAM families



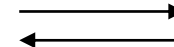
(b) Selected CAMs belonging to each family

Mucin-like CAMs:

GlyCAM-1
CD34
PSGL-1
MAdCAM-1

Selectins:

L-selectin
P-selectin
E-selectin

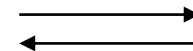


Ig-superfamily CAMs:

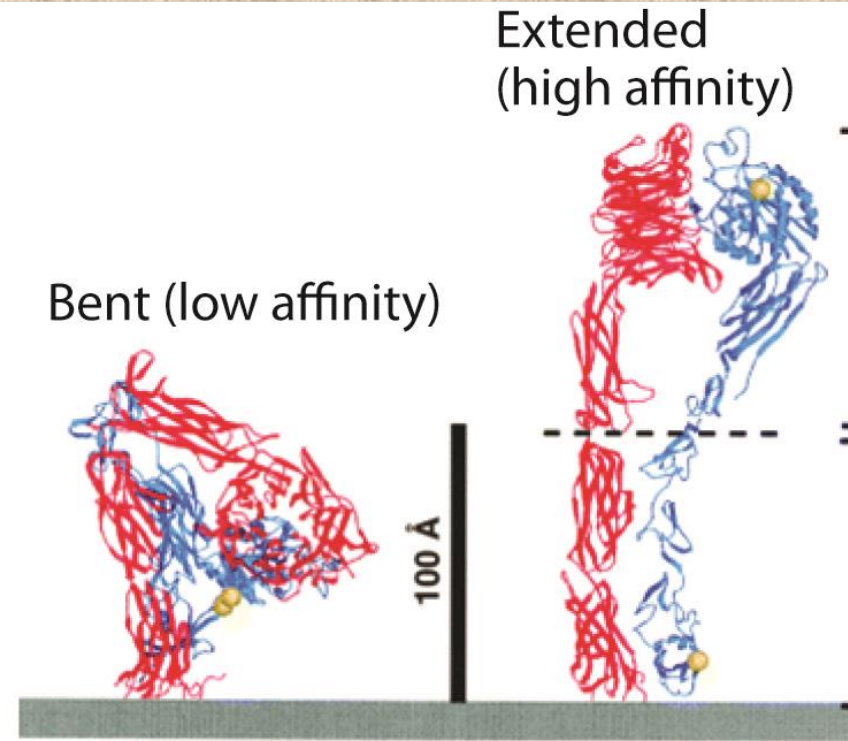
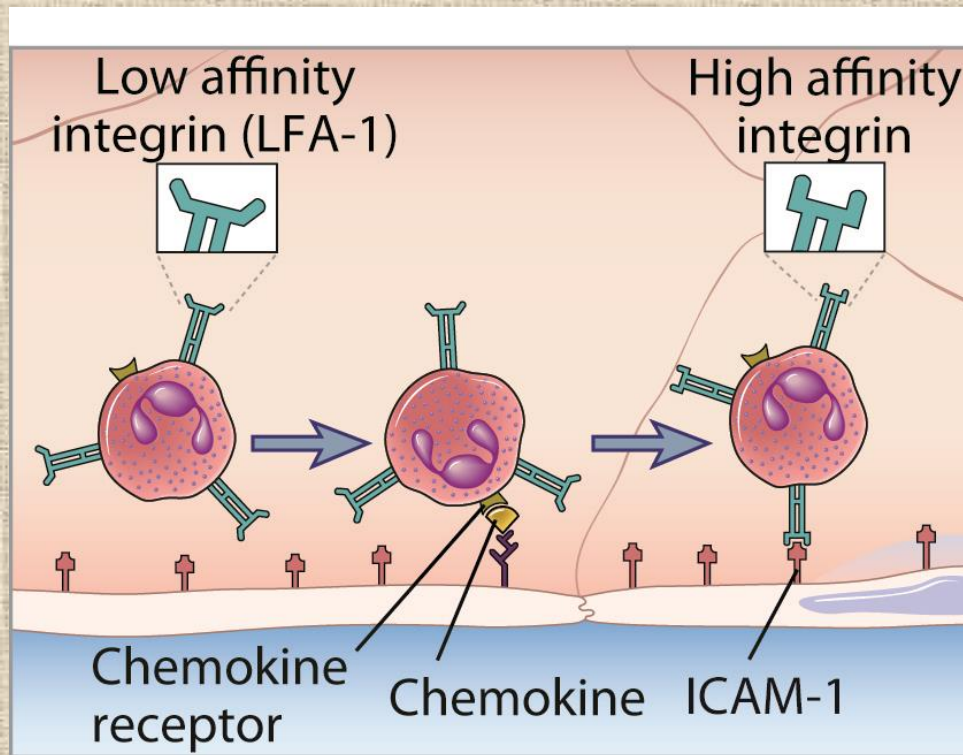
ICAM-1, -2, -3
VCAM-1
LFA-2 (CD2)
LFA-3 (CD58)
MAdCAM-1

Integrins:

$\alpha 4 \beta 1$ (VLA-4, LPAM-2)
 $\alpha 4 \beta 7$ (LPAM-1)
 $\alpha 6 \beta 1$ (VLA-6)
 $\alpha L \beta 2$ (LFA-1)
 $\alpha M \beta 2$ (Mac-1)
 $\alpha X \beta 2$ (CR4, p150/95)



Chemokines accelerate conformational changes in integrins

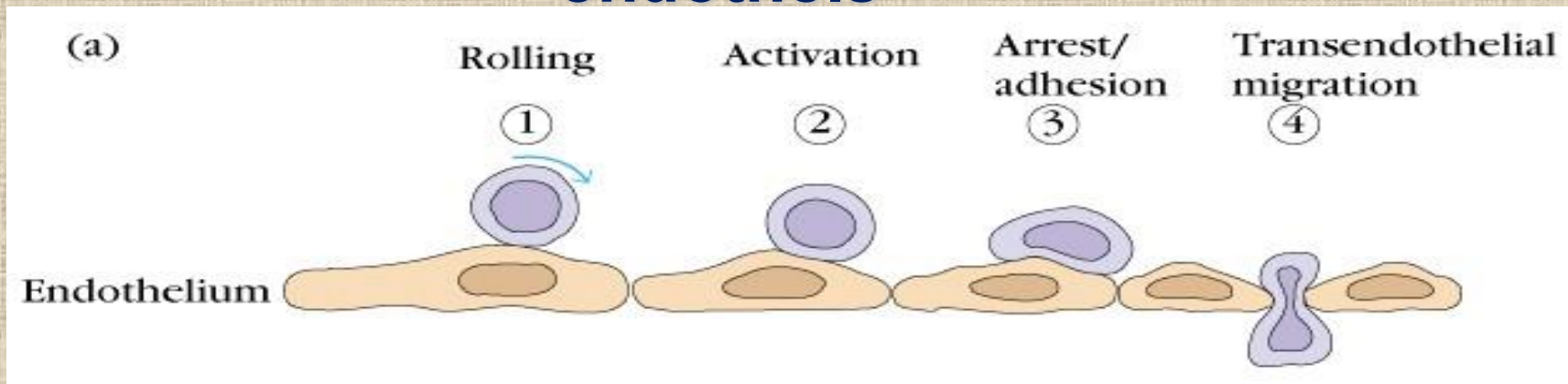


Leukocyte functional antigen 1 (LFA-1)



Intercellular adhesion molecule 1 (ICAM-1)

Neutrophils extravasation through the inflamed endothels

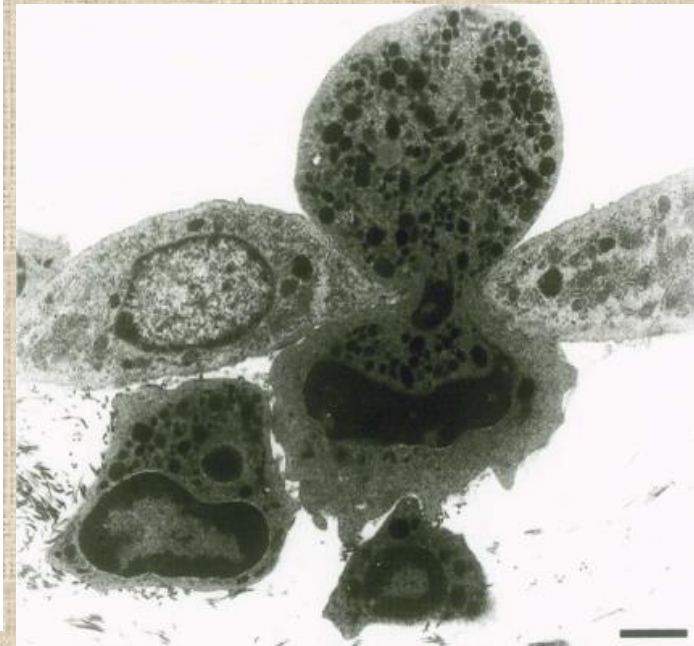
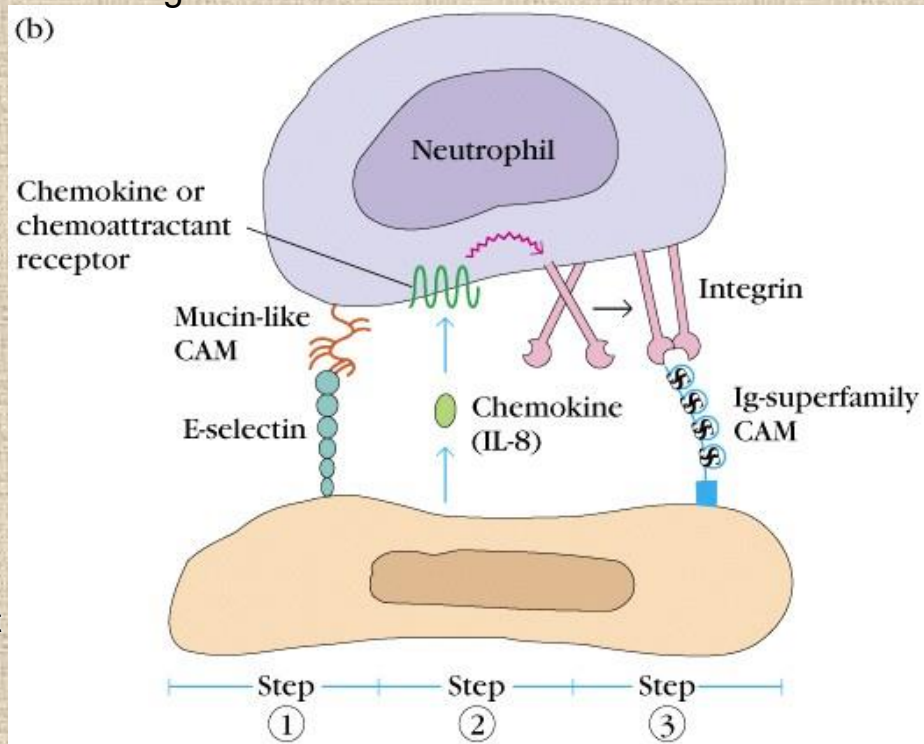


1. Selectin-mediated rolling

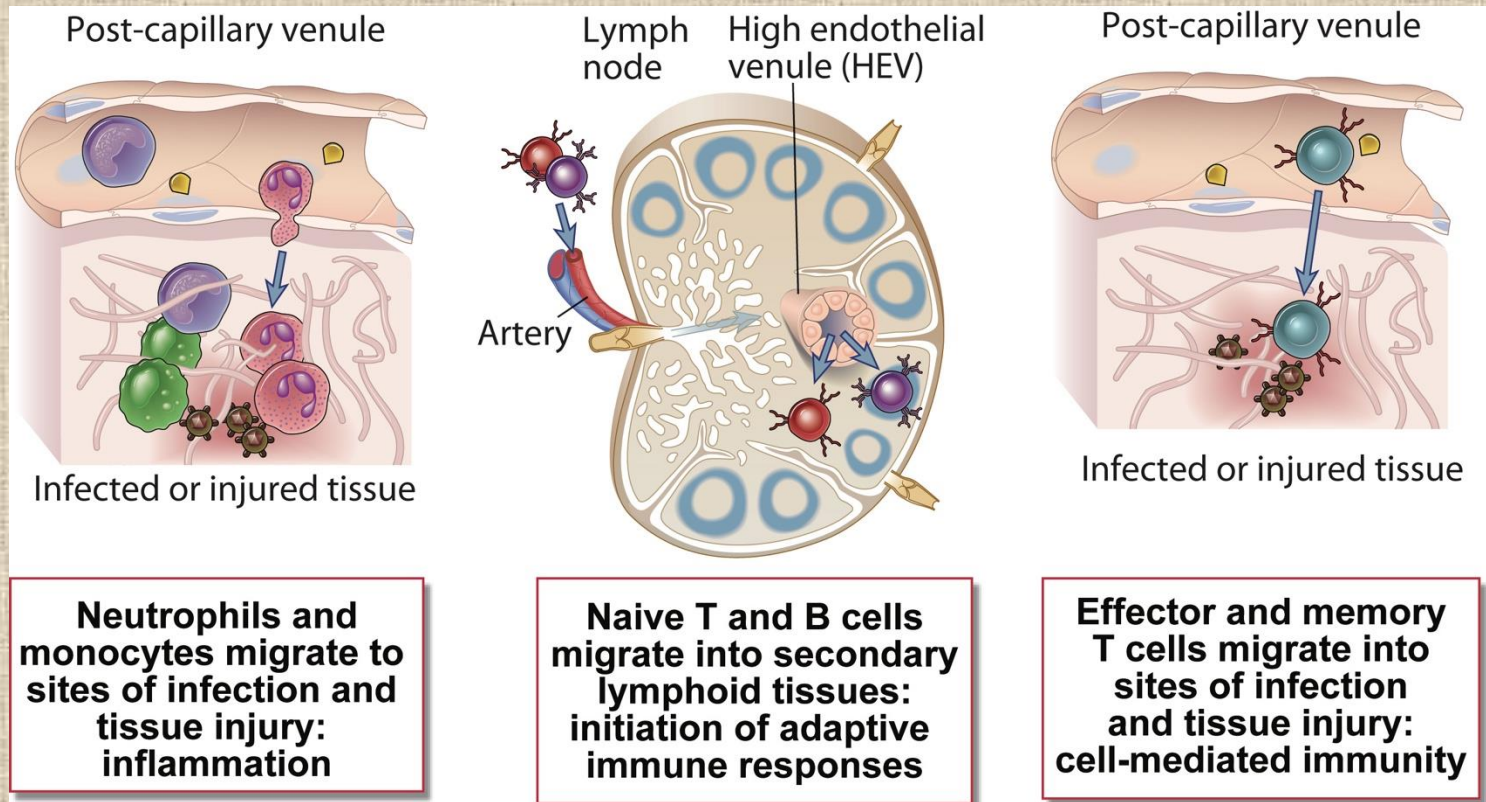
2. Chemoattractant mediated activation

3. Integrin-mediated adhesion

4. Transendothelial migration



Lymphocyte recirculation: continuous migration of cells from the blood and lymph into the lymphoid and inflamed tissues = HOMING



Role:

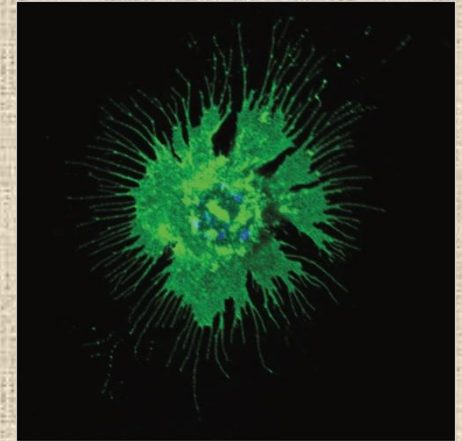
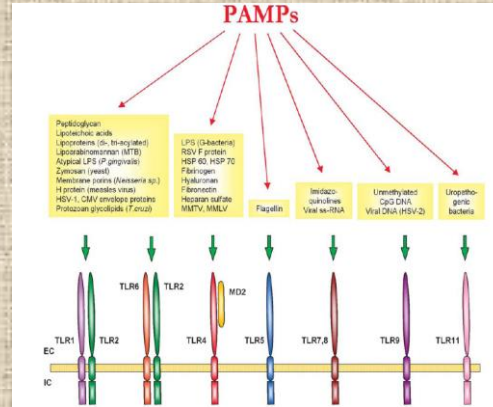
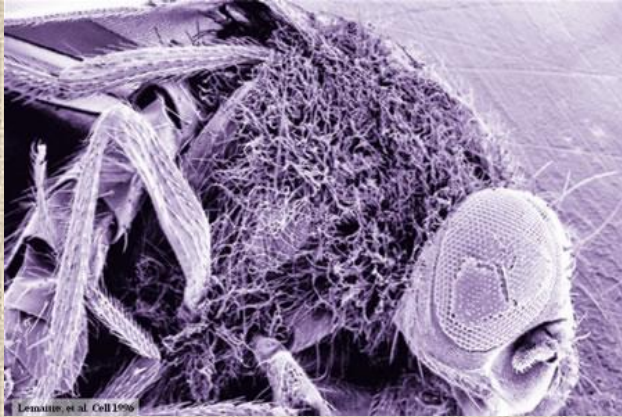
- Promotes the encounter with antigen
- Promotes the initiation of inflammatory response

Mechanisms:

- Extravasation: adhesion then transmigration of leukocytes through the endothel from the bloodflow into the tissue.

All lymphocyte circulates approx. 1-2 times per day.

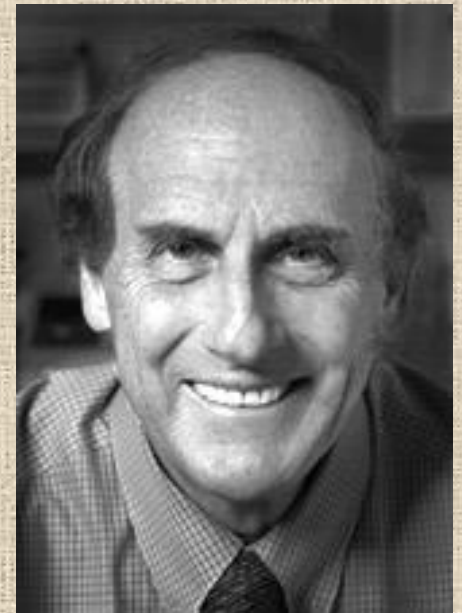
Nobel Laureates in 2011 for medicine and physiology



Jules A. Hoffmann



Bruce A. Beutler



Ralph M. Steinmann