

# Basic immunology

*Lecture 3.*

**Innate immunity, pattern recognition**

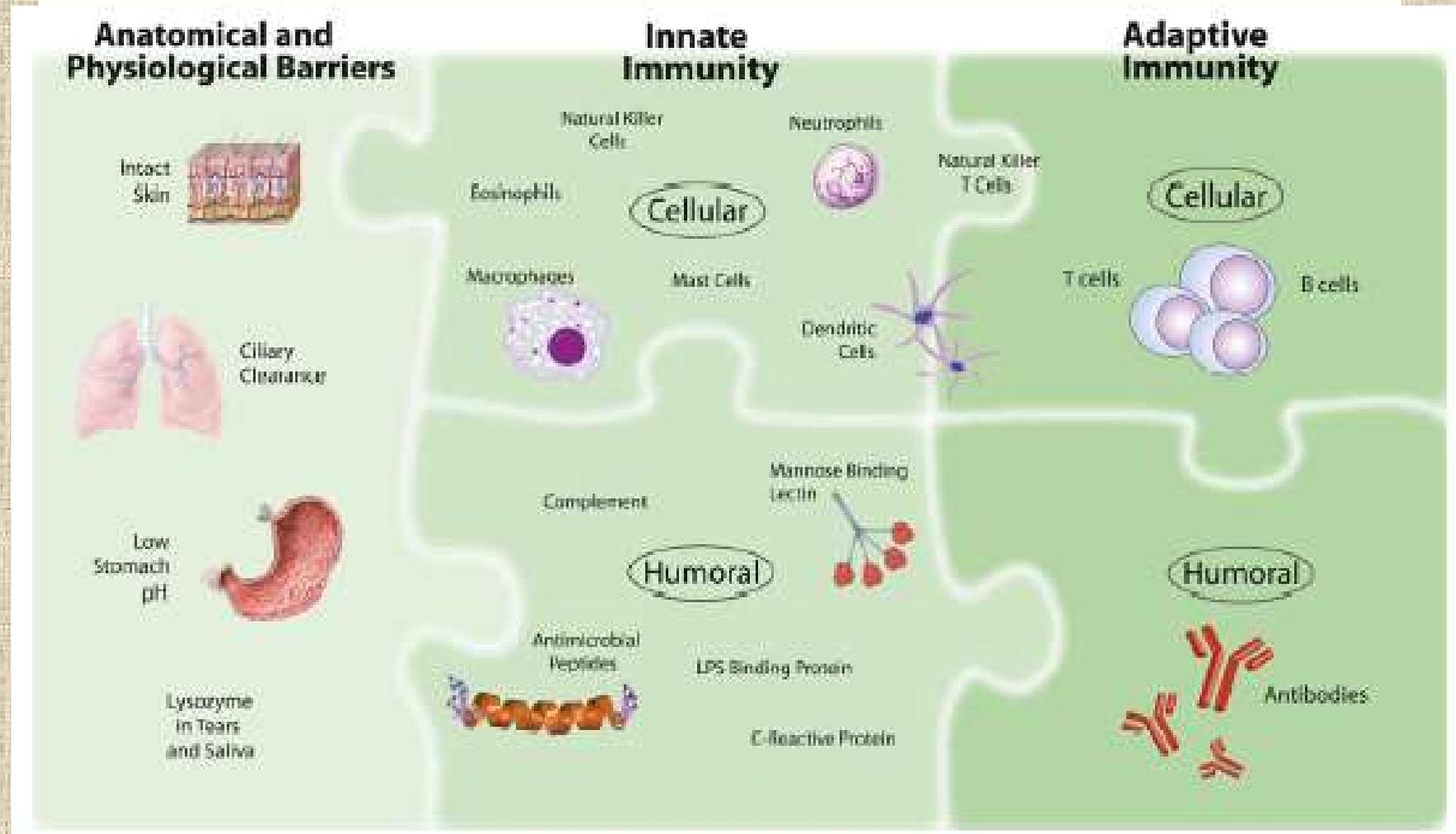


**Péter Engelmann**

- Different levels of the immune response
- Recognition molecules of the innate immunity

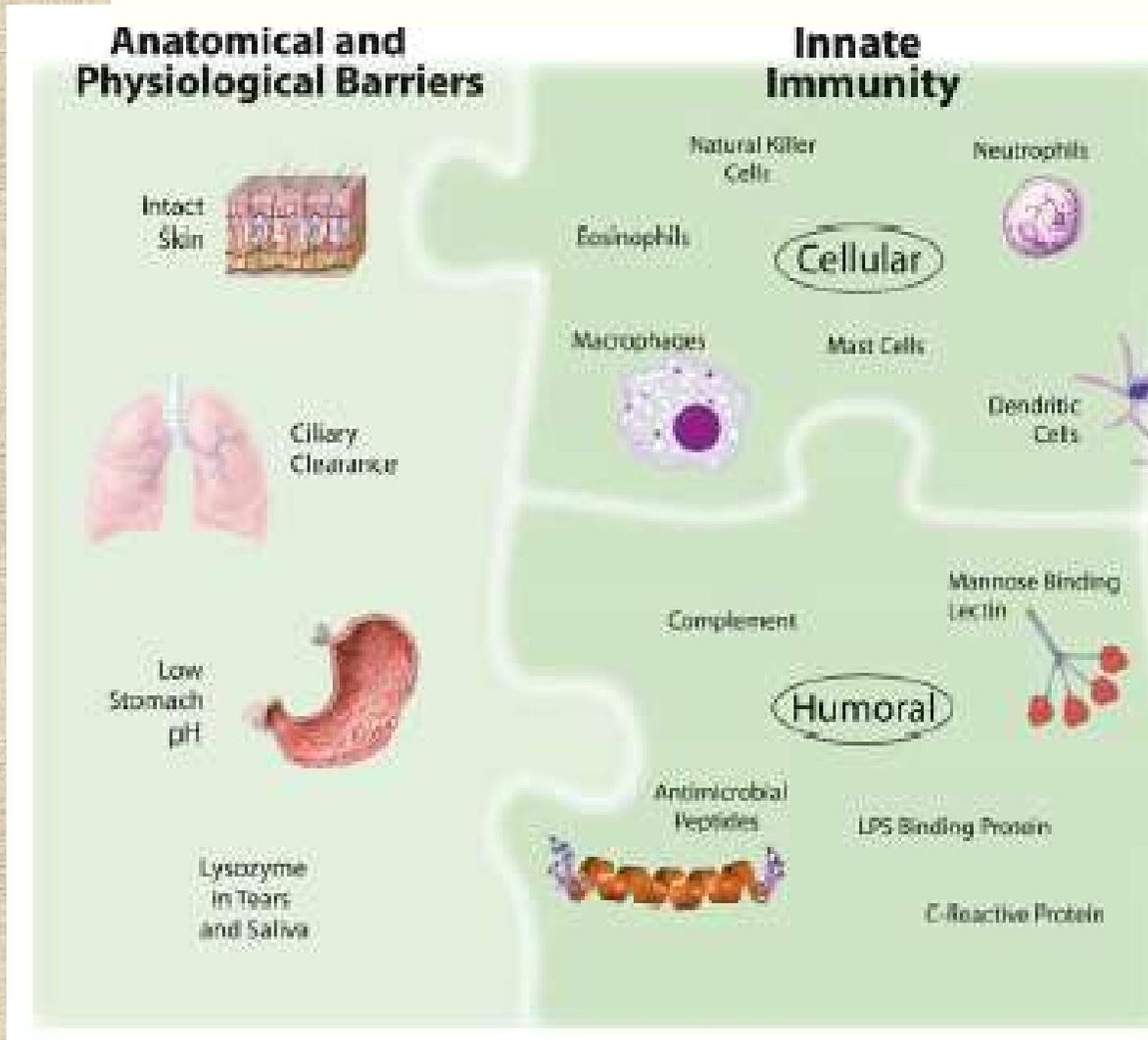
# The levels of host defense

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



# The levels of host defense

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



# I. First line of defense: anatomic „barriers”

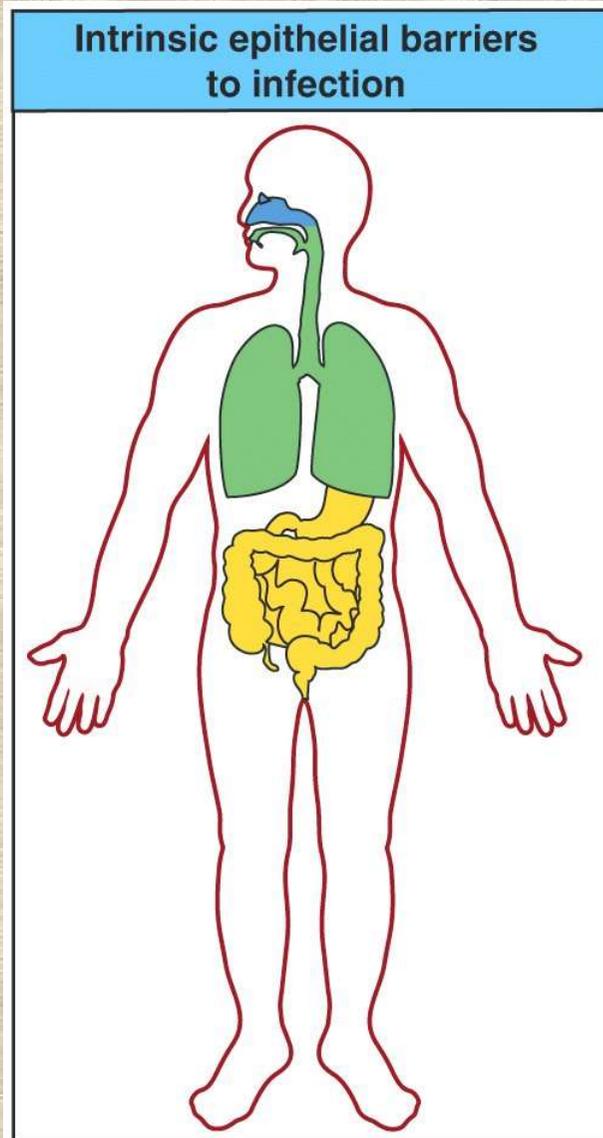
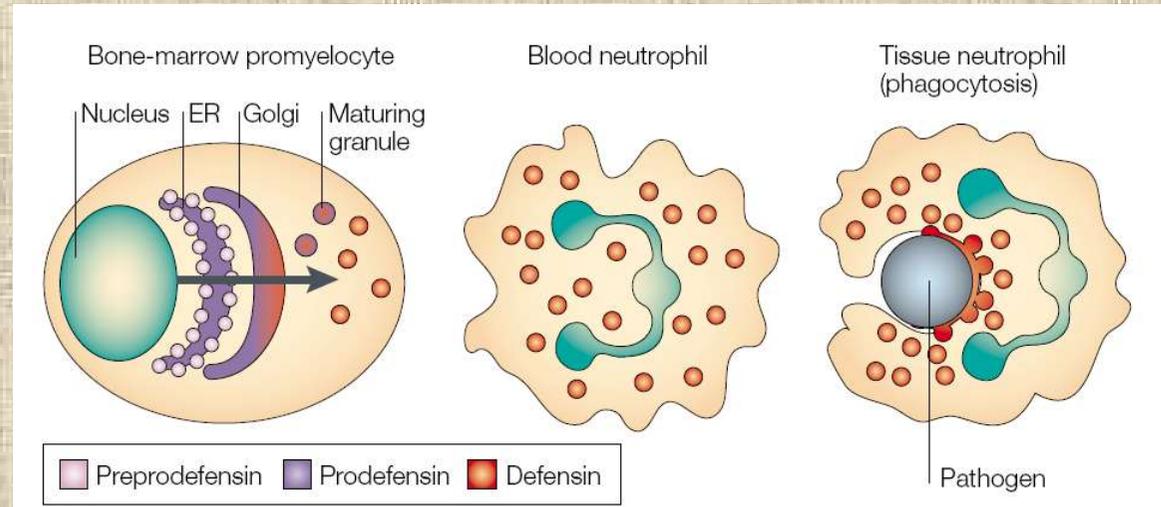
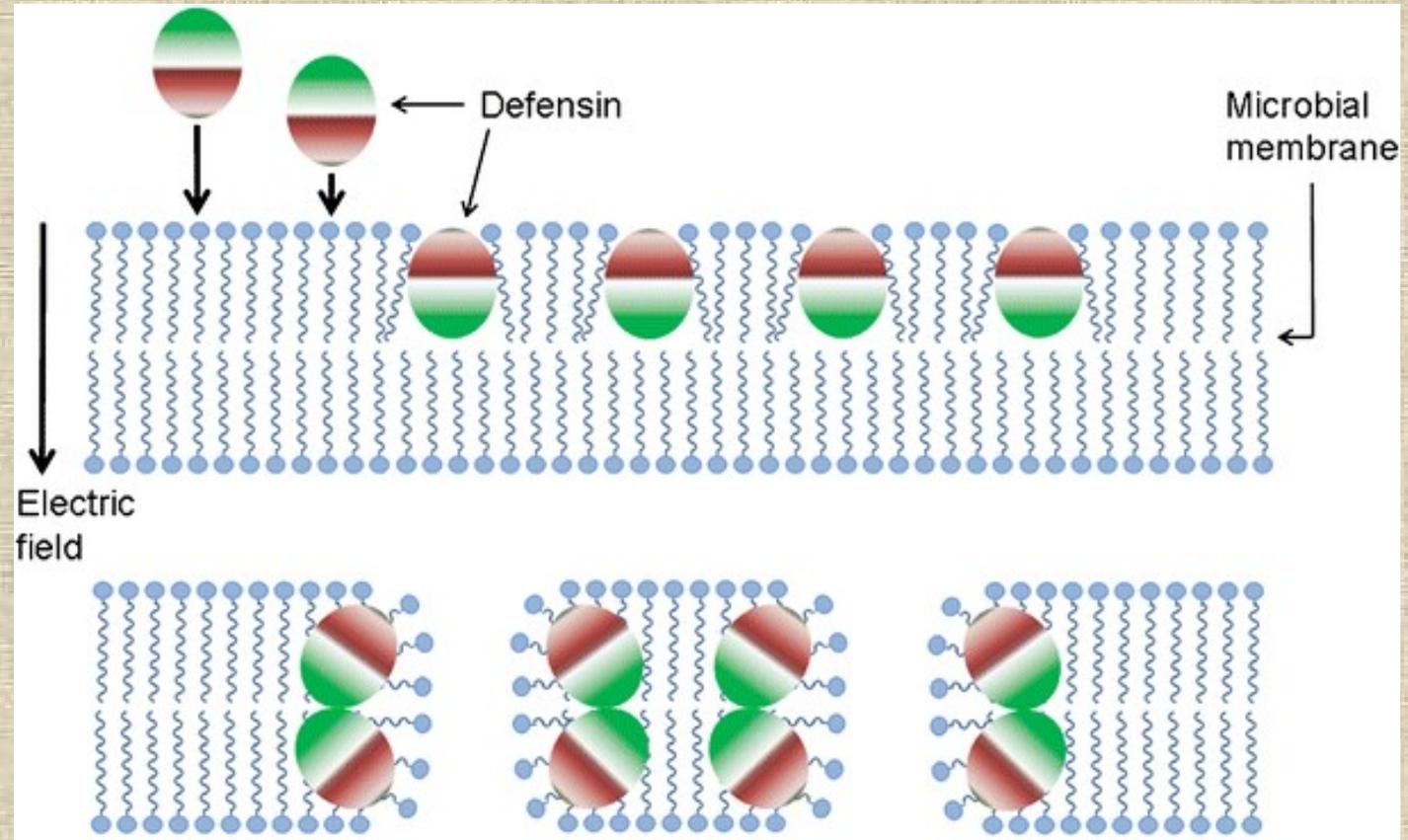
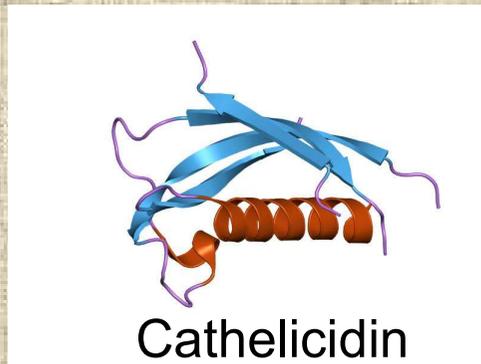
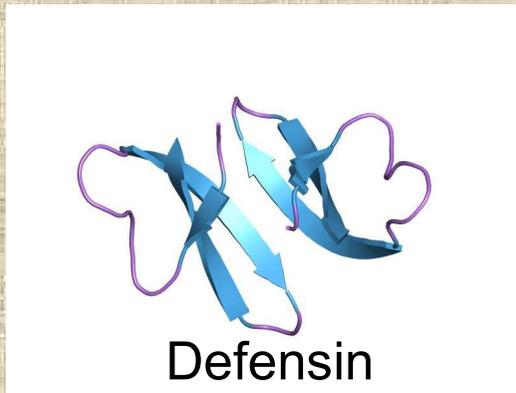


Figure 2-4 Immunobiology, 6/e. (© Garland Science 2005)

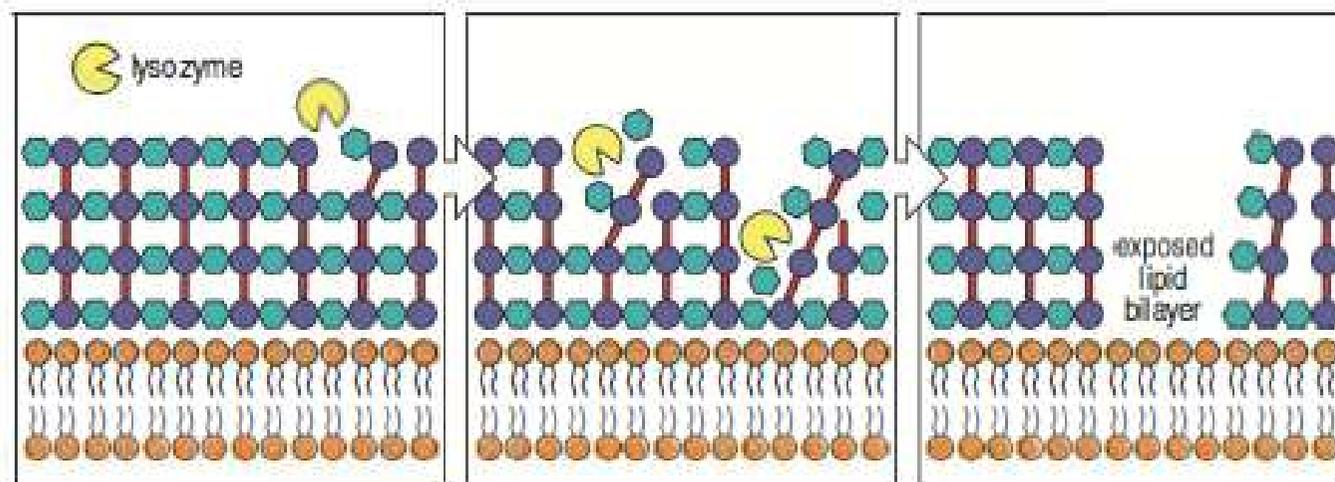
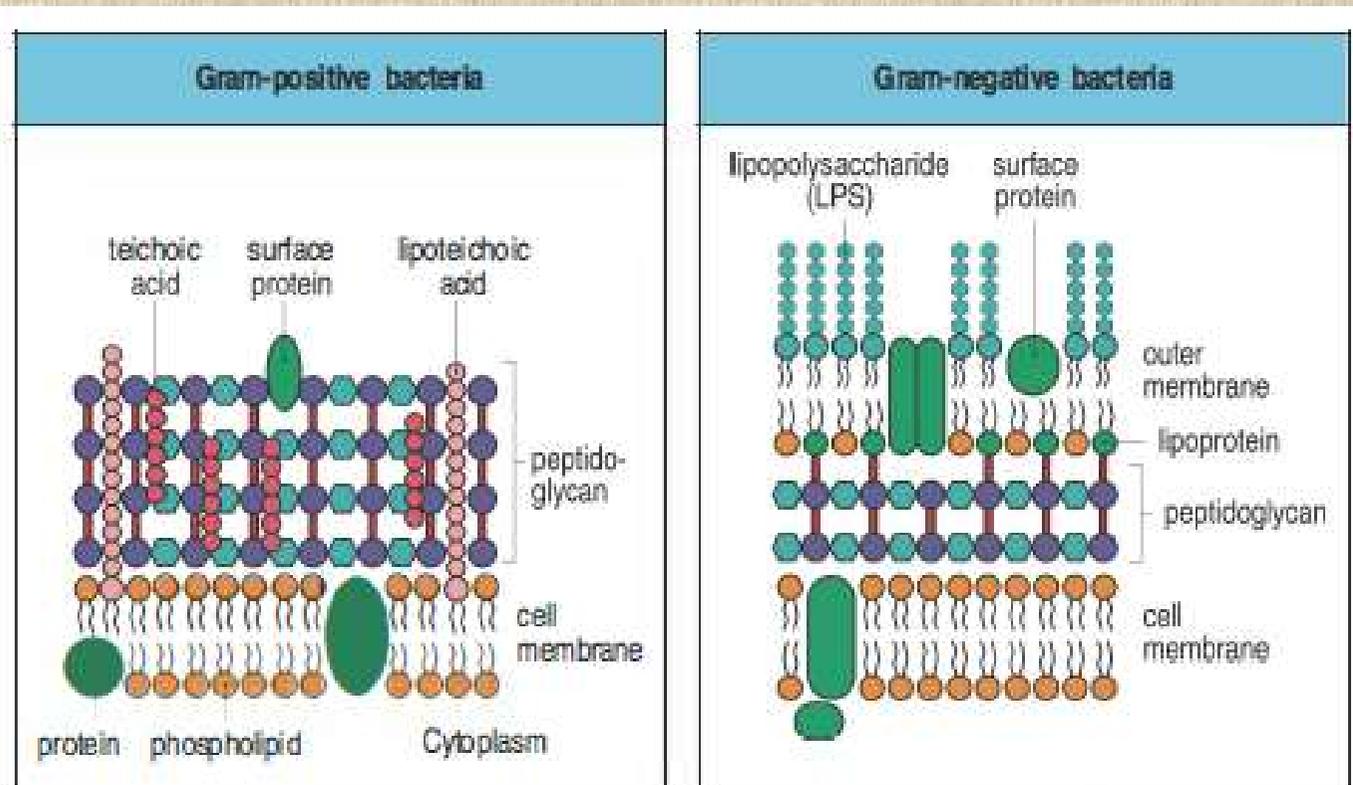
	Skin	Gut	Lungs	Eyes/nose/oral cavity
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH	Pulmonary surfactant	Enzymes in tears and saliva (lysozyme)
		Enzymes (pepsin)		
	$\beta$ -defensins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

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

# Antimicrobial peptides I

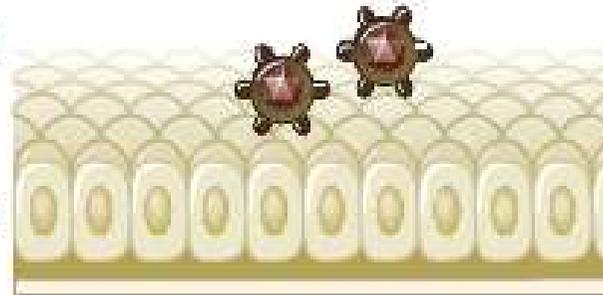


# Antimicrobial peptides II

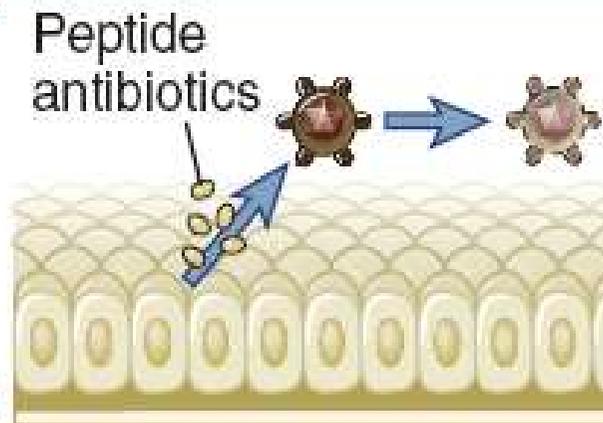


# The role of epithelial barriers

Physical barrier  
to infection

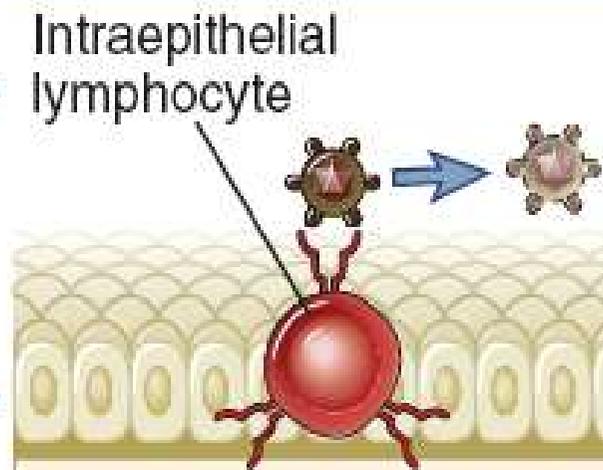


Killing of microbes  
by locally produced  
antibiotics,  
defensins,  
cathelicidins



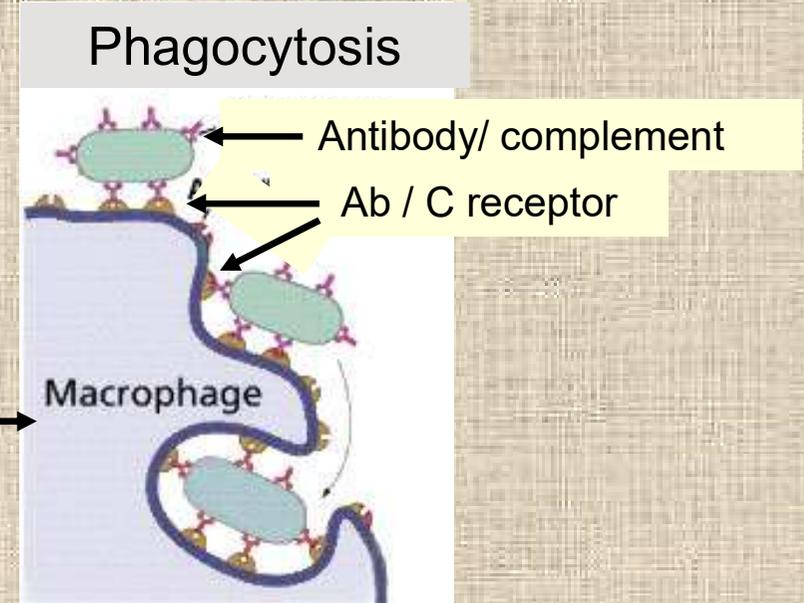
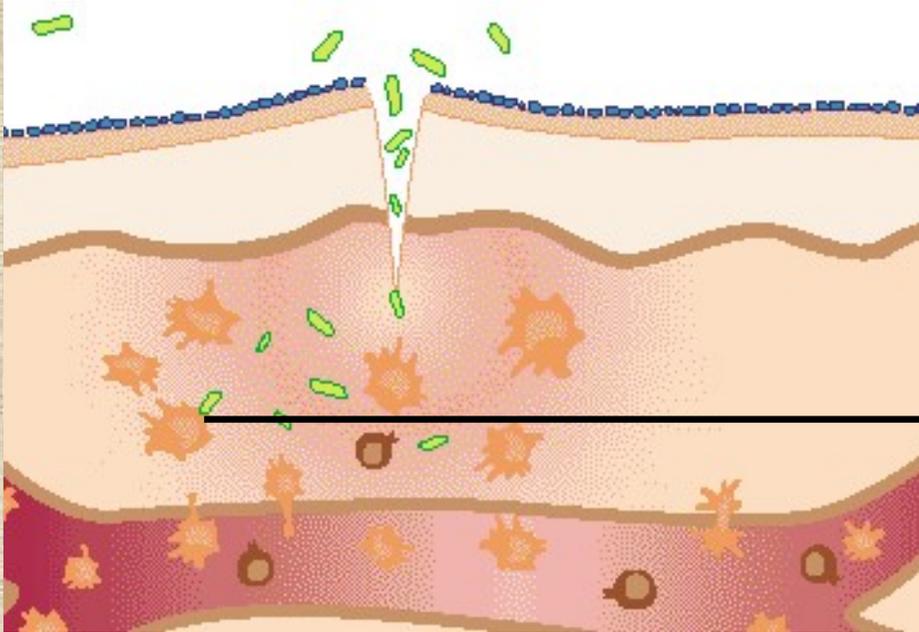
Defensins,  
cathelicidins

Killing of microbes  
and infected cells  
by intraepithelial  
lymphocytes

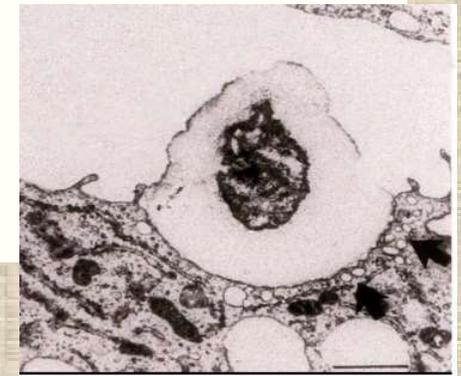


Mast cells, IEL:  
 $\gamma\delta$  T cells

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



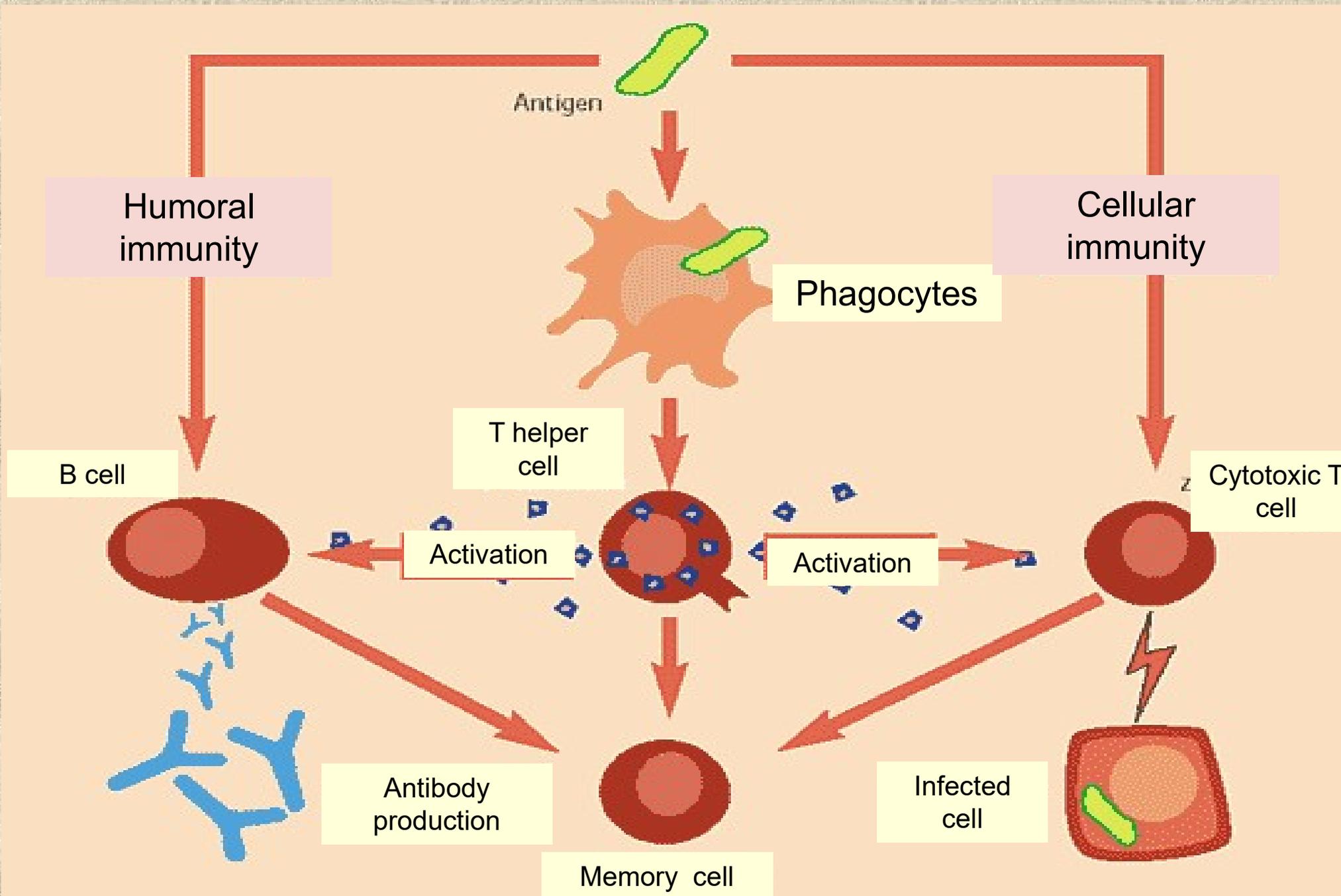
1. Phagocytes in the blood and tissues.
2. Soluble proteins (immunoglobulin and complement), bind to microbe surface (opsonisation) to enhance the phagocytosis.



# 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

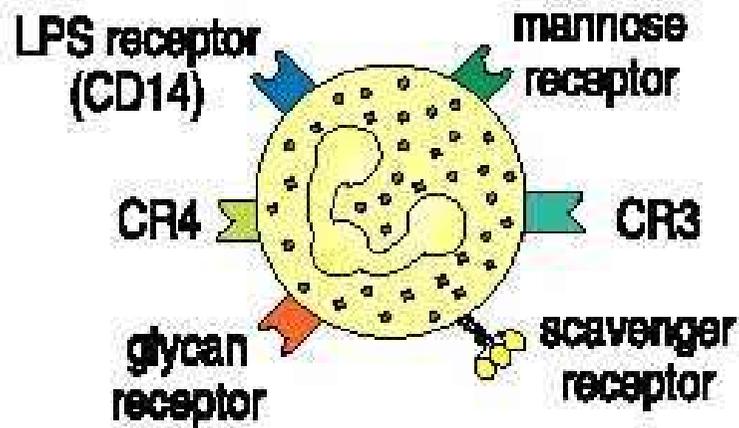


- Different levels of the immune response
- Recognition molecules of innate immunity

# Recognition of pathogens, phagocytosis

Figure 8.8

**The neutrophil expresses receptors for many bacterial constituents**



**Neutrophils engulf and digest bacteria to which they bind**



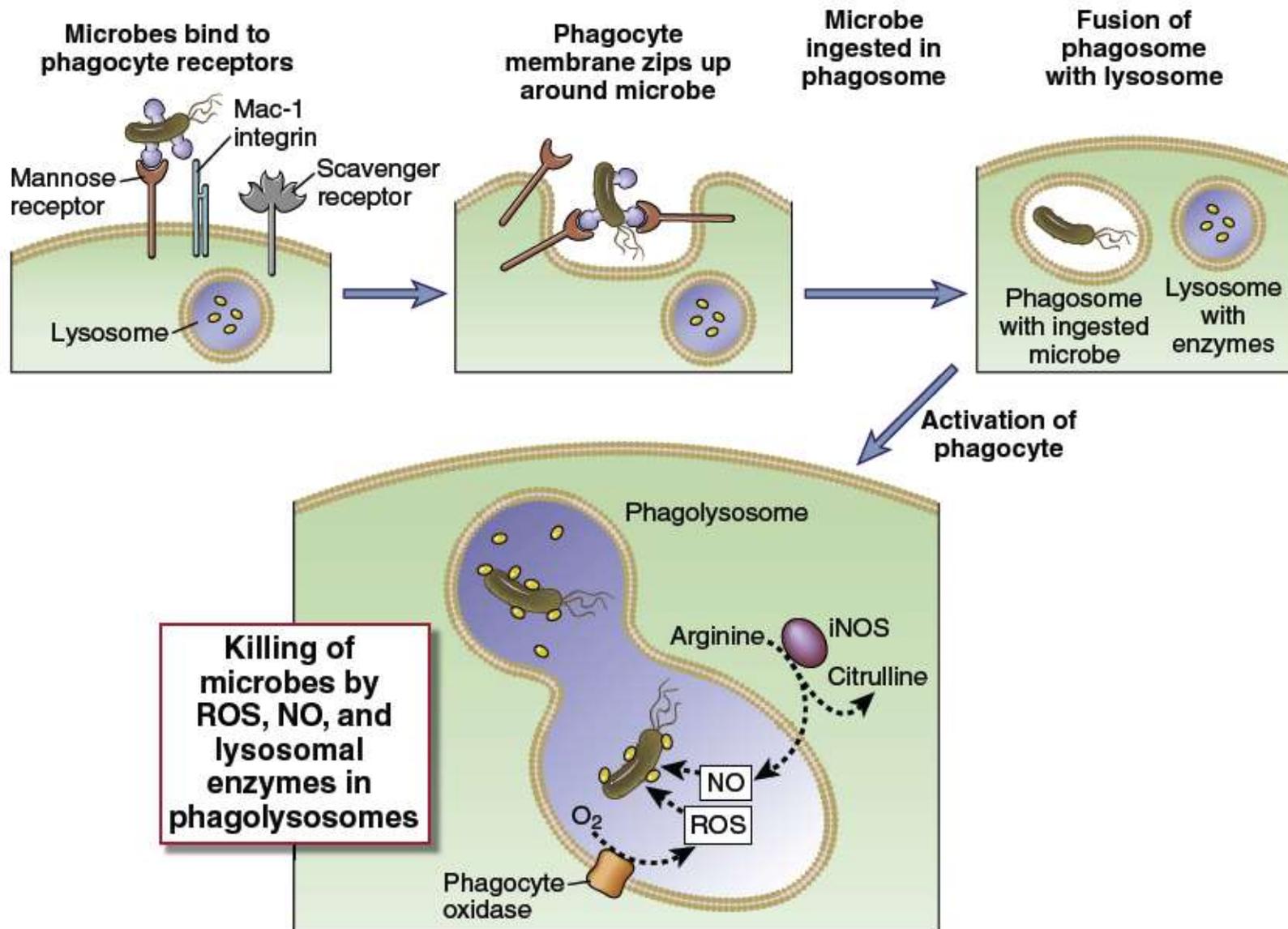
PRR= „Pattern Recognition Receptors”

→Binding to the PAMPS of microbes

PAMP=„Pathogen Associated Molecular Patterns

DAMPs = „Danger/Damage Associated Molecular Patterns”

# Process of phagocytosis

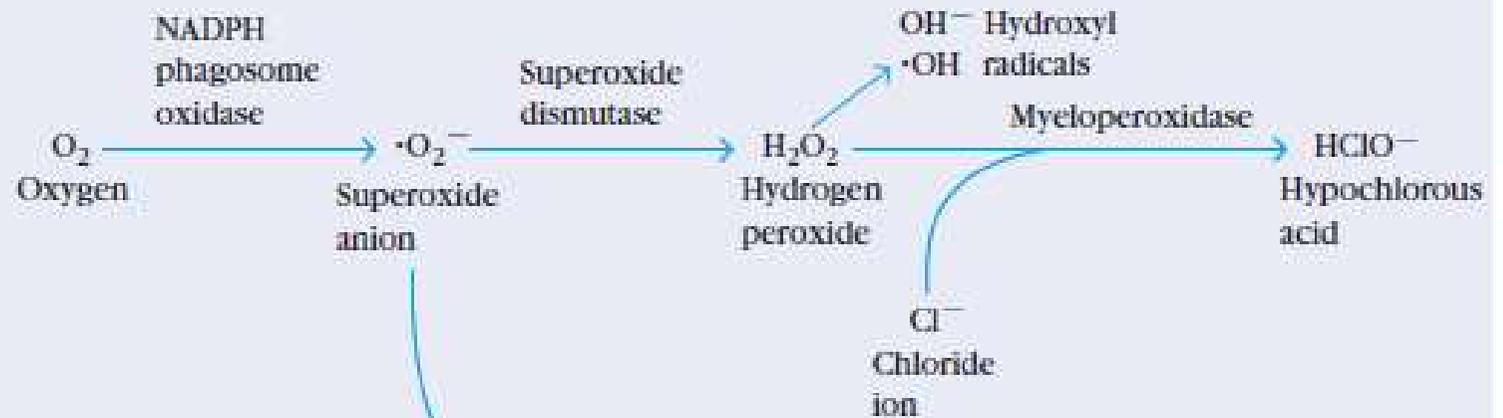


# Reactive oxygen/nitrogen intermediers

## Antimicrobial species generated from oxygen and nitrogen

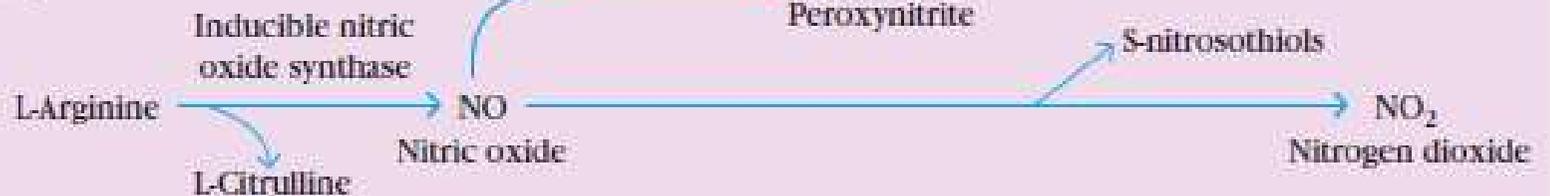
### Reactive oxygen species (ROS)

$\cdot\text{O}_2^-$  (superoxide anion)  
 $\text{OH}\cdot$  (hydroxyl radical)  
 $\text{H}_2\text{O}_2$  (hydrogen peroxide)  
 $\text{HClO}$  (hypochlorous acid)

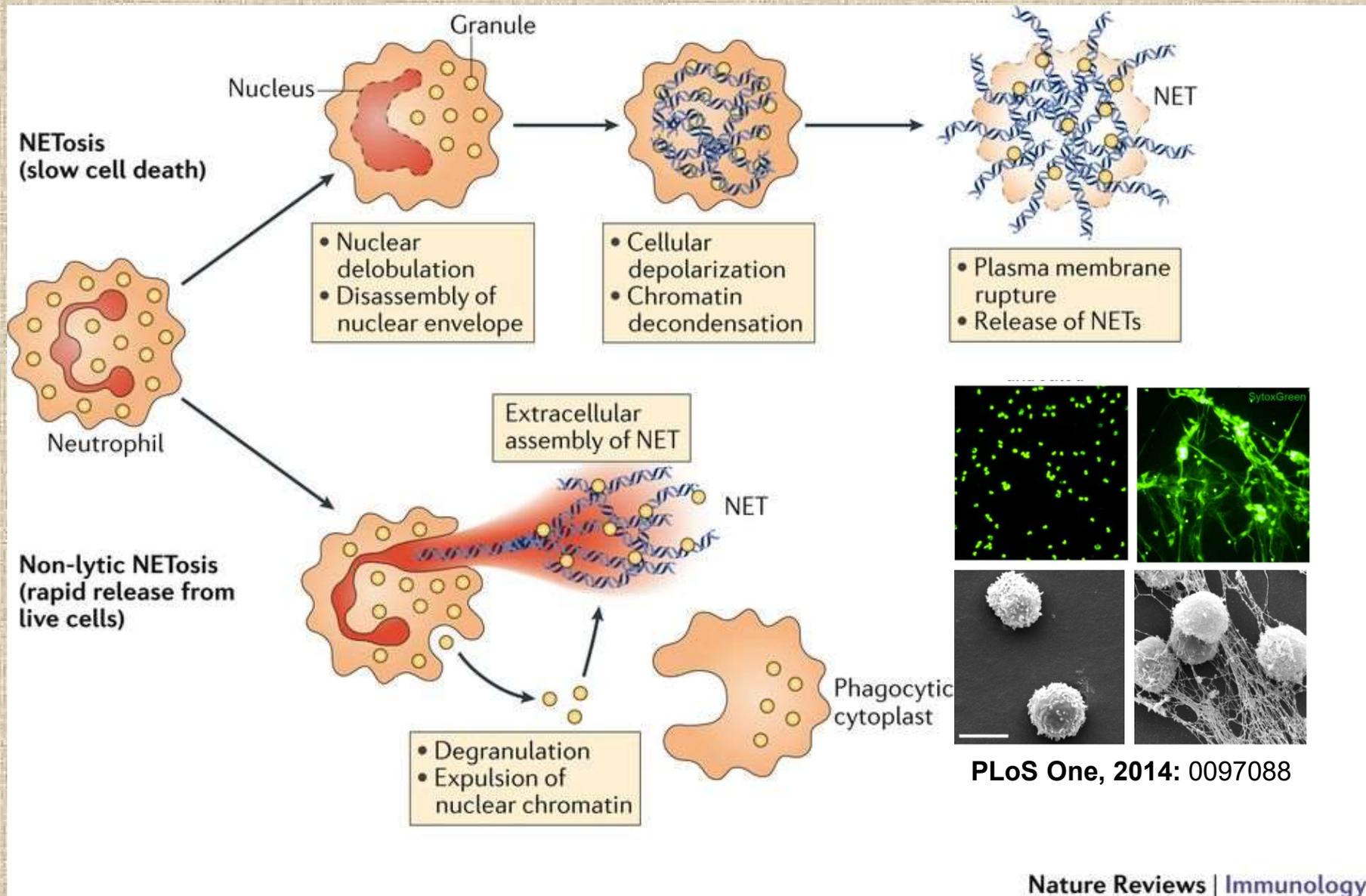


### Reactive nitrogen species (RNS)

$\text{NO}$  (nitric oxide)  
 $\text{NO}_2$  (nitrogen dioxide)  
 $\text{ONOO}^-$  (peroxynitrite)

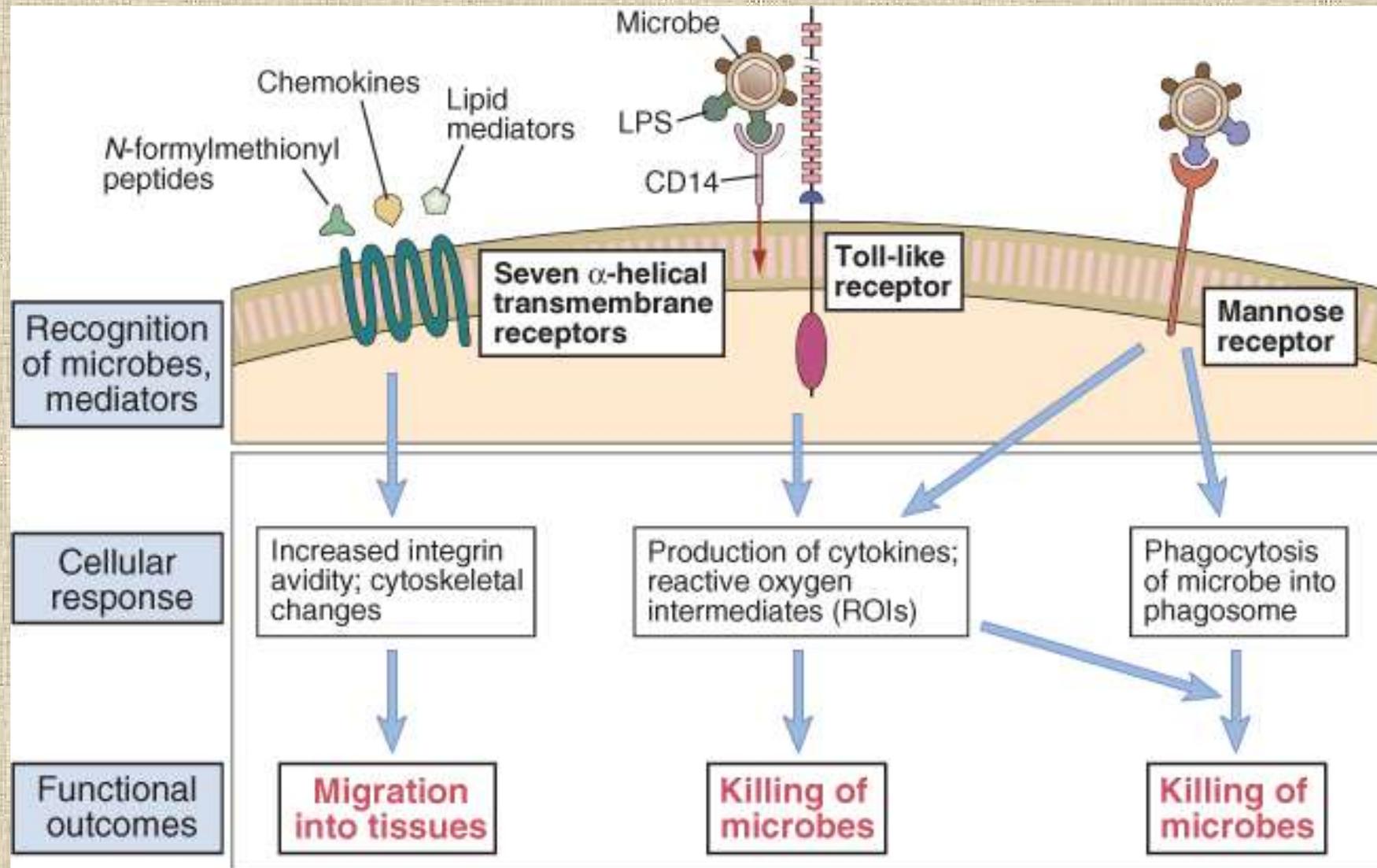


# Process of NETosis



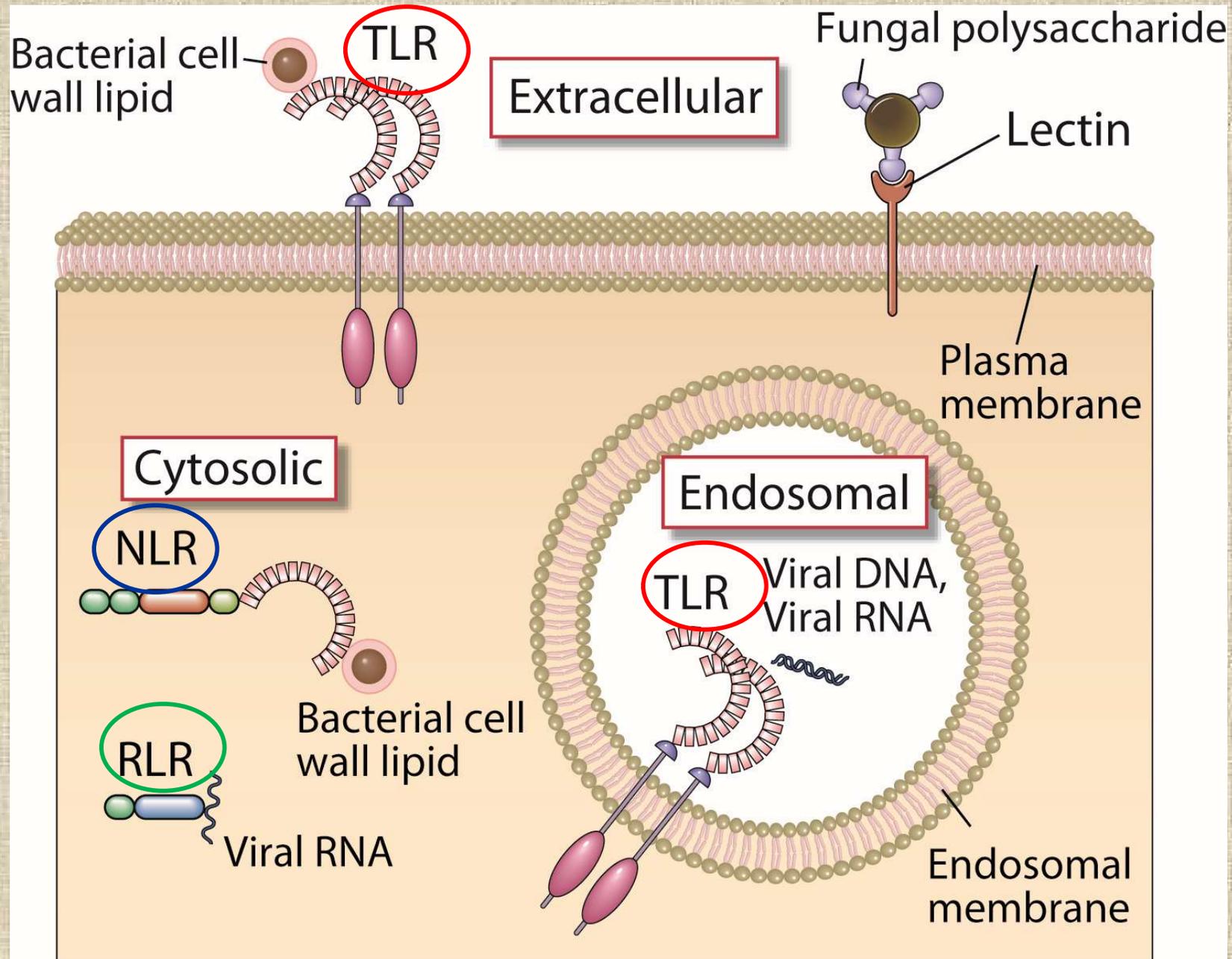
**NET: neutrophyl extracellular trap**

# Phagocyte receptors



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# Pattern recognition receptors

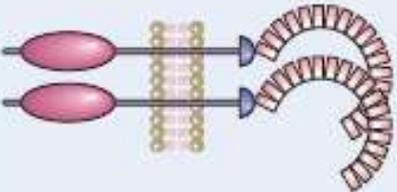
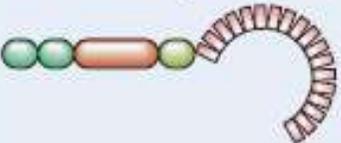
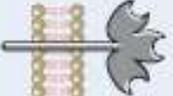


Toll-like receptors (TLR)

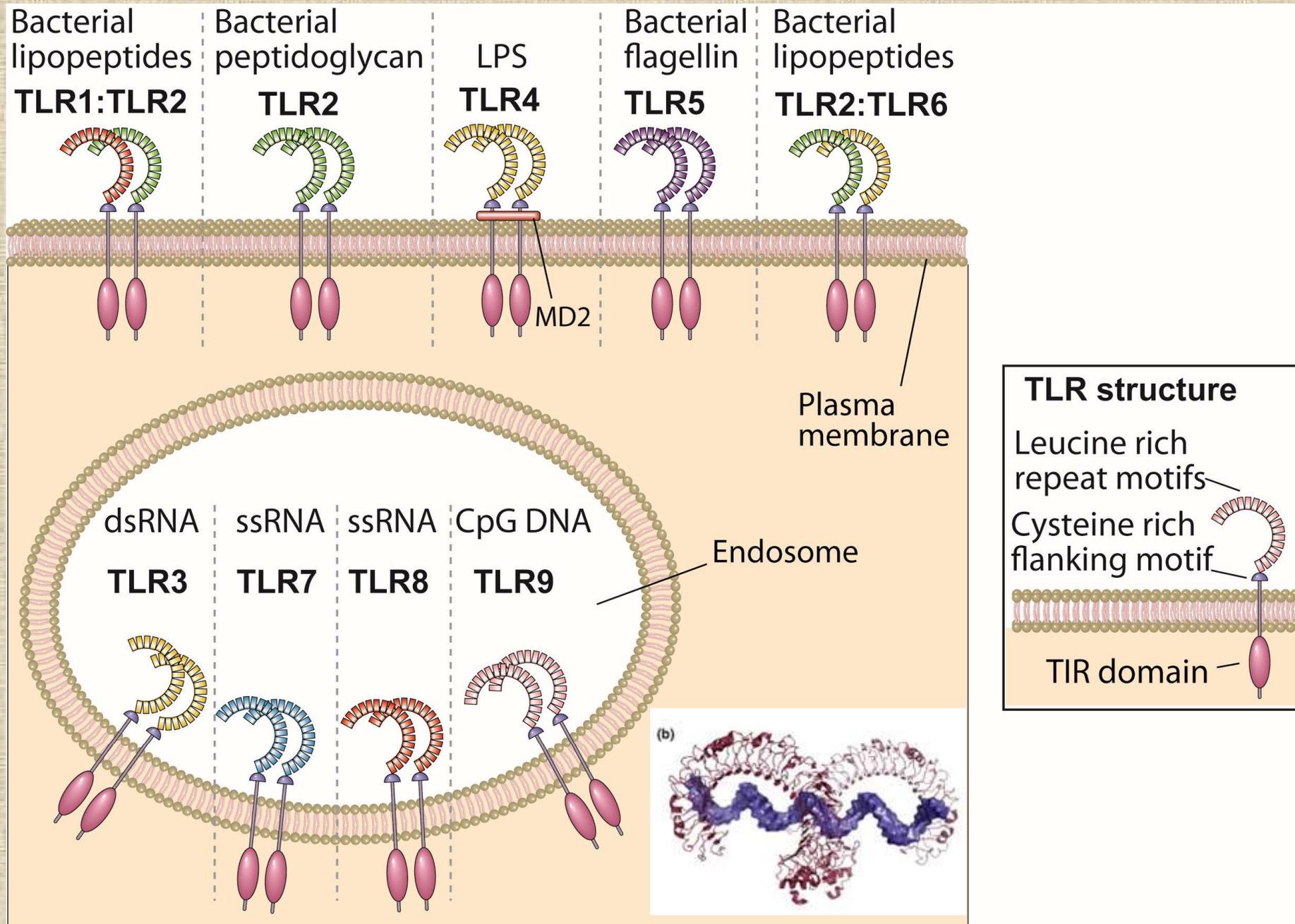
NOD-like receptors (NLR)

RIG-like receptors (RLR)

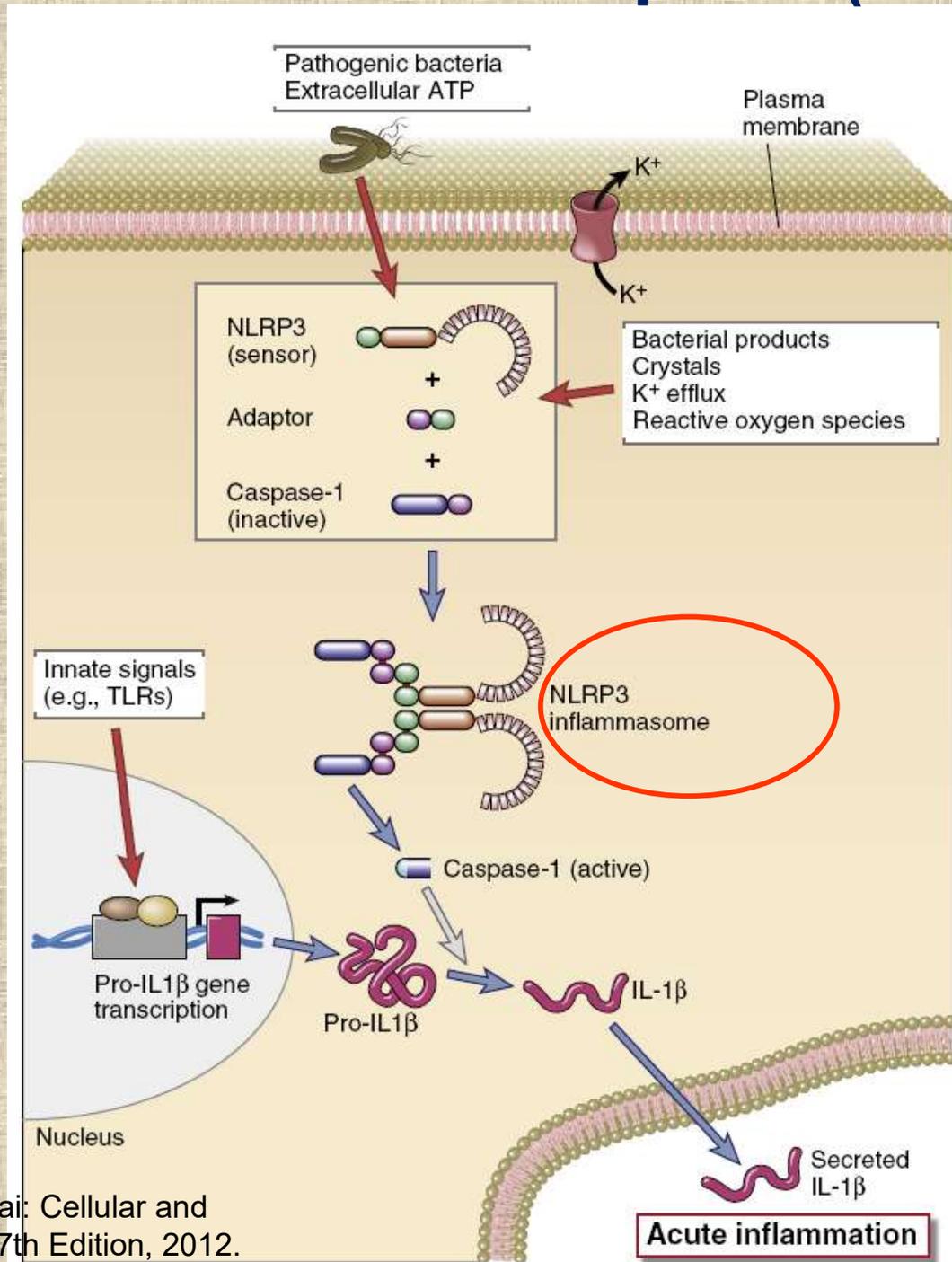
# Main groups of pattern recognition receptors

<p>Toll-like receptors (TLRs)</p> 	<p>Plasma membrane and endosomal membranes of dendritic cells, phagocytes, B cells endothelial cells, and many other cell types</p>	<p>TLRs 1-9</p>	<p>Various microbial molecules including bacterial LPS and peptidoglycans, viral nucleic acids</p>
<p>NOD-like receptors (NLRs)</p> 	<p>Cytoplasm of phagocytes epithelial cells, and other cells</p>	<p>NOD1/2 NALP family (inflammasomes)</p>	<p>Bacterial cell wall peptidoglycans Flagellin, muramyl dipeptide, LPS; urate crystals; products of damaged cells</p>
<p>RIG-like receptors (RLRs)</p> 	<p>Cytoplasm of phagocytes and other cells</p>	<p>RIG-1, MDA-5</p>	<p>Viral RNA</p>
<p>C-type lectin-like receptors</p> 	<p>Plasma membranes of phagocytes</p>	<p>Mannose receptor  Dectin</p>	<p>Microbial surface carbohydrates with terminal mannose and fructose Glucans present in fungal cell walls</p>
<p>Scavenger receptors</p> 	<p>Plasma membranes of phagocytes</p>	<p>CD36</p>	<p>Microbial diacylglycerides</p>
<p><i>N</i>-Formyl met-leu-phe receptors</p> 	<p>Plasma membranes of phagocytes</p>	<p>FPR and FPRL1</p>	<p>Peptides containing <i>N</i>-formylmethionyl residues</p>

# Pattern recognition receptors: Toll-like receptors (TLR)

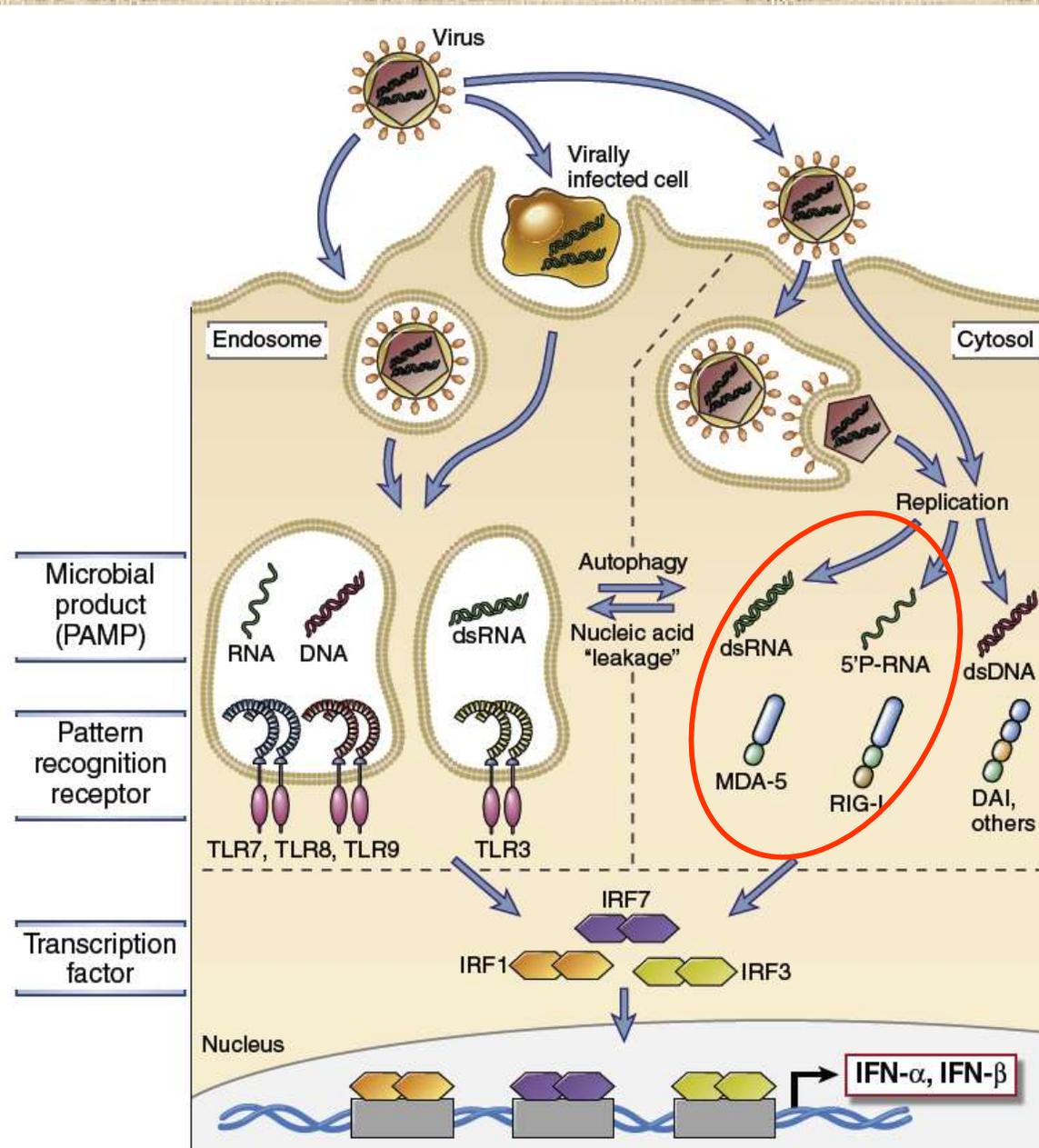


# Pattern recognition receptors: NOD-like receptors (NLR)

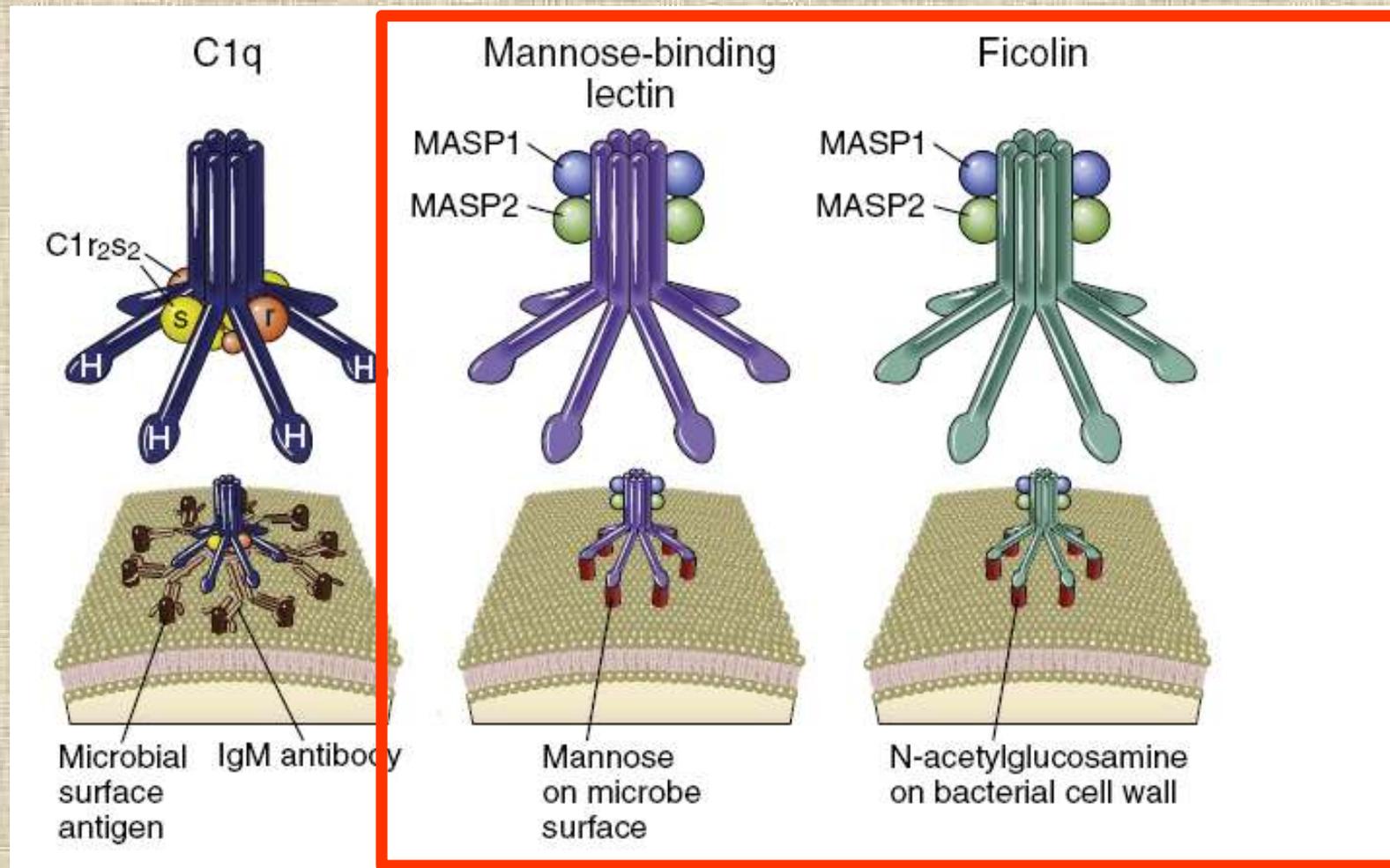


NOD: Nucleotide oligomerization domain

# Pattern recognition receptors: RIG-like receptors (RLR)



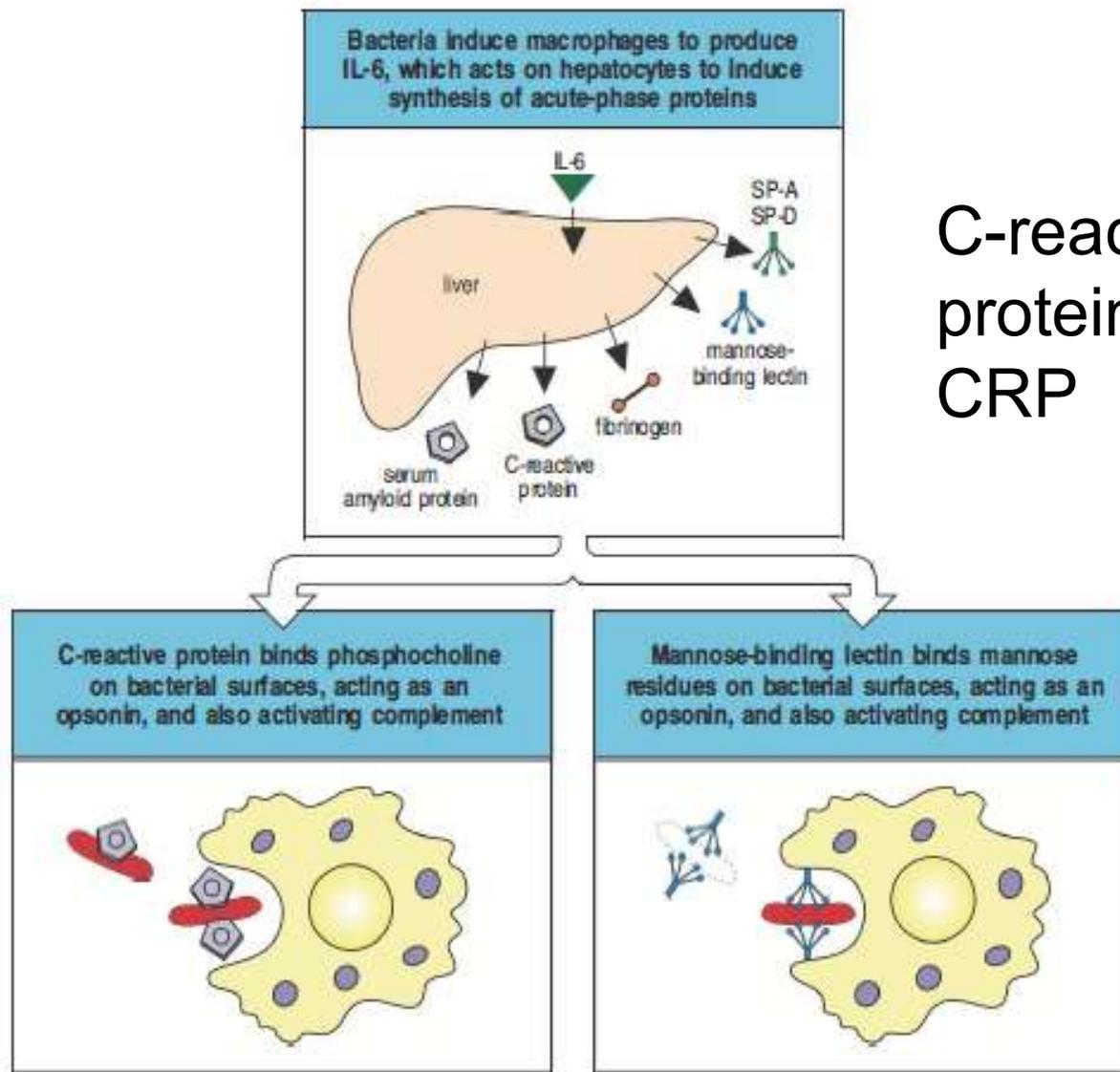
# Soluble pattern recognition molecules I



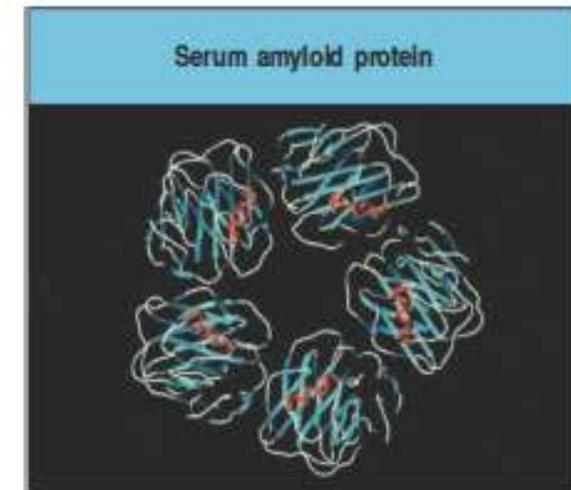
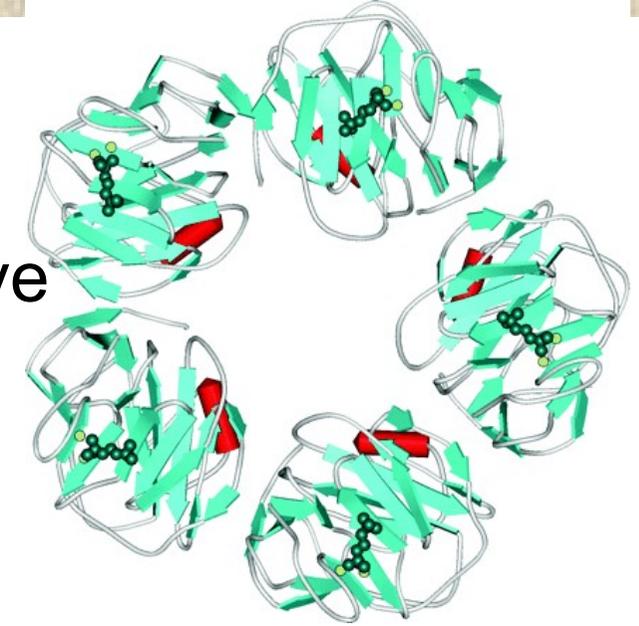
**Collectin (MBL, SP-A, SP-D):** C-type lectin domain

**Ficolin:** Fibrinogen domain

# Soluble pattern recognition molecules II: pentraxins



C-reactive protein-  
CRP



# Clinical significance of C-reactive protein level

Risk of infection, sepsis



CRP test, complete blood count, blood culture  
Then start Antibiotics treatment



CRP 48 hr



CRP <10 mg/L & blood culture negative



Discontinue antibiotic treatment

CRP >10 mg/L,  
Continue antibiotics therapy

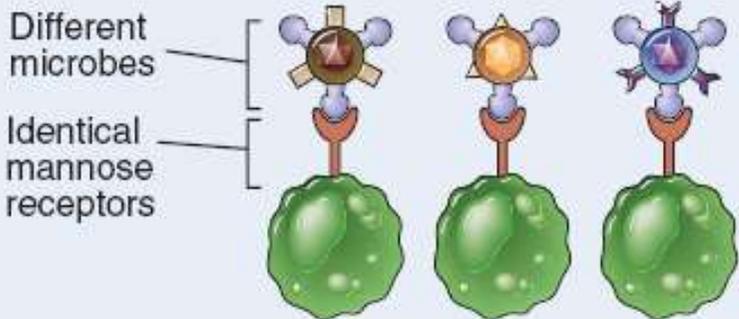
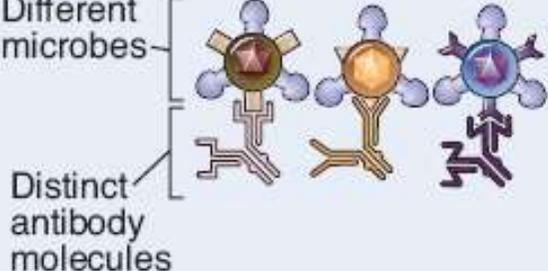
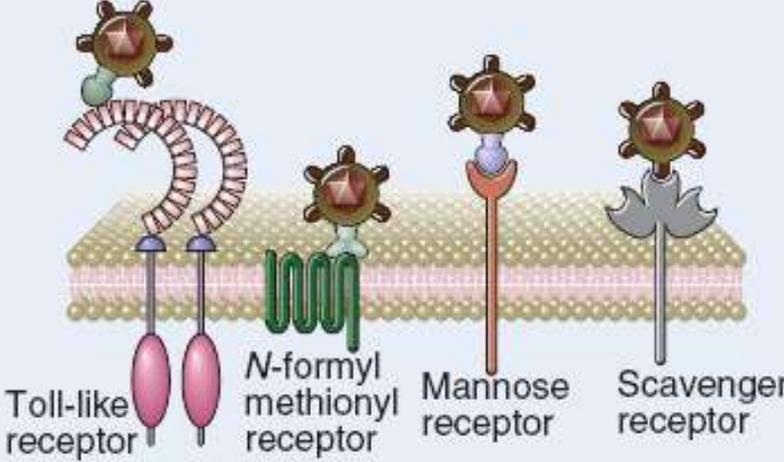
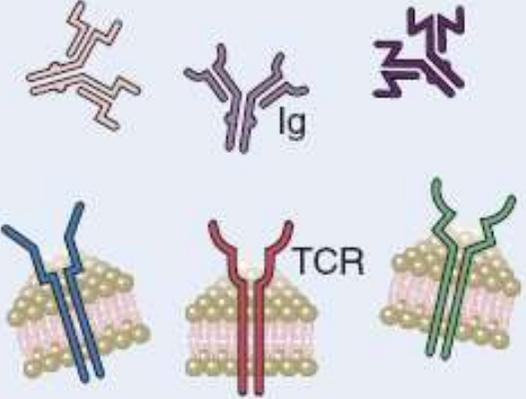


CRP at 7 days

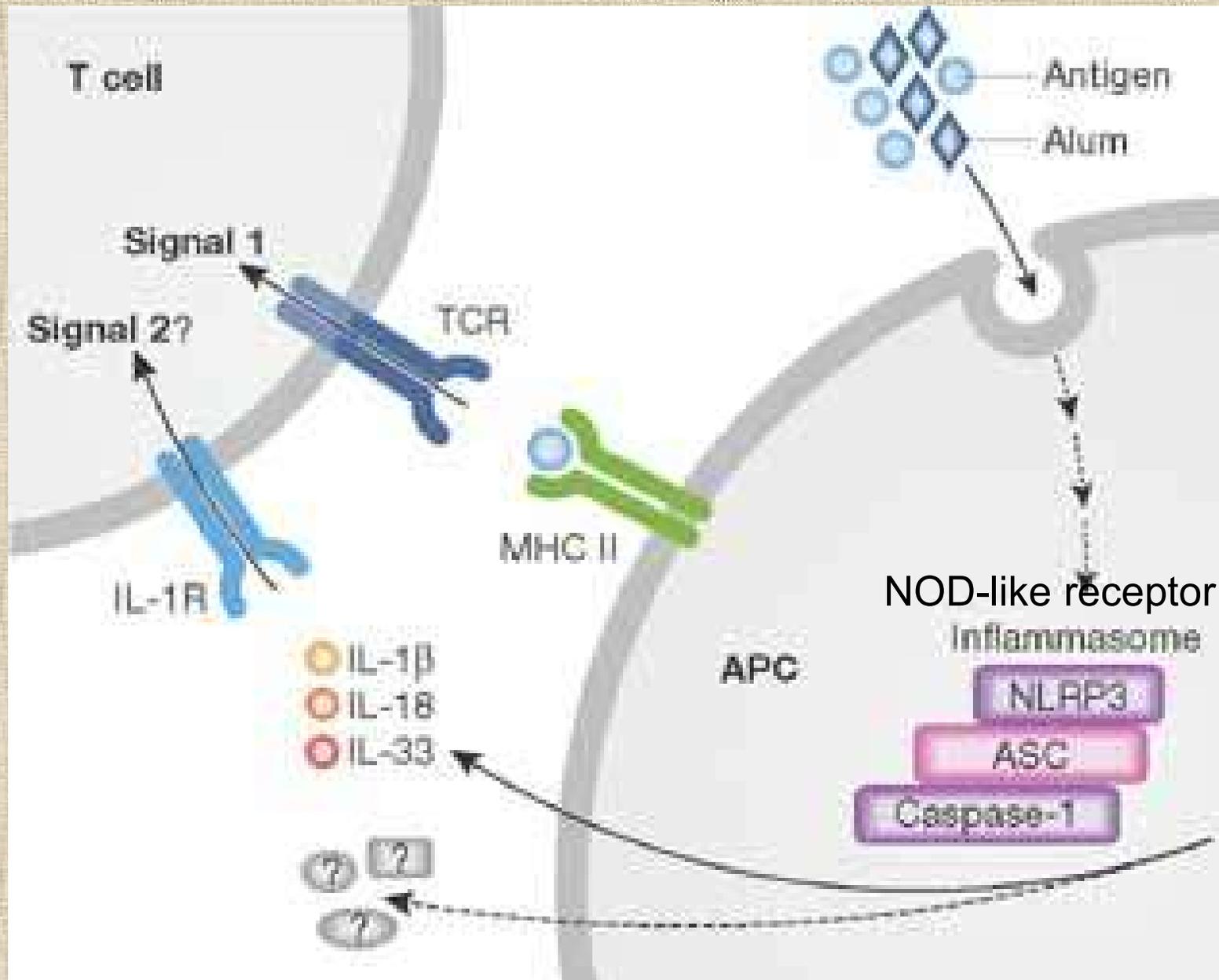
CRP <10 mg/L: discontinue antibiotic treatment

CRP >10 mg/L: reevaluate (new blood count, change antibiotics)

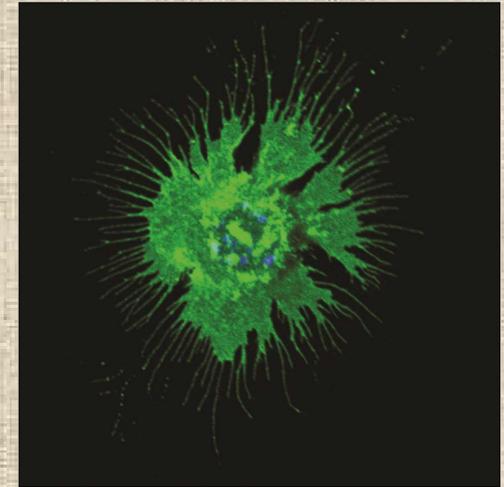
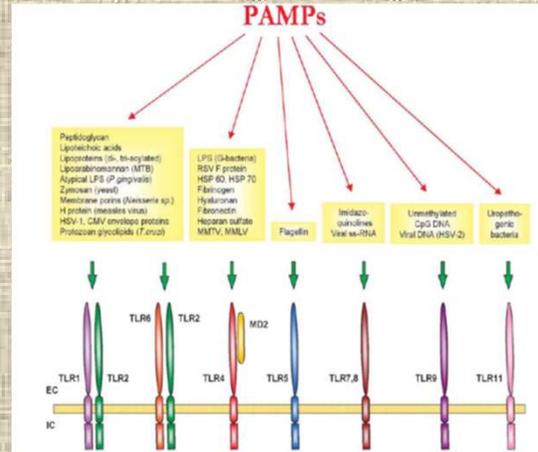
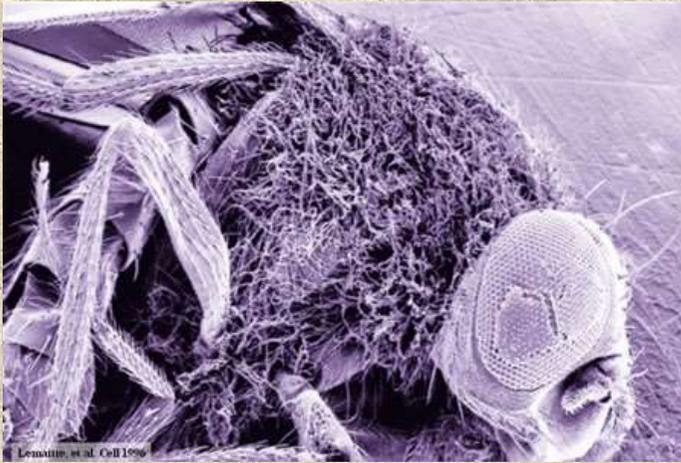
# Specificity of innate and adaptive immunity

	Innate Immunity	Adaptive Immunity
Specificity	For structures shared by <b>classes of microbes</b> (pathogen-associated molecular patterns)	For structural detail of microbial molecules ( <b>antigens</b> ); may recognize nonmicrobial antigens
	<p>Different microbes</p> <p>Identical mannose receptors</p> 	<p>Different microbes</p> <p>Distinct antibody molecules</p> 
Receptors	<b>Encoded in germline</b> limited diversity (pattern recognition receptors)	Encoded by genes produced by <b>somatic recombination of gene segments</b> ; greater diversity
	 <p>Toll-like receptor</p> <p>N-formyl methionyl receptor</p> <p>Mannose receptor</p> <p>Scavenger receptor</p>	 <p>Ig</p> <p>TCR</p>
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	<b>Yes; healthy host cells are not recognized</b> 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)

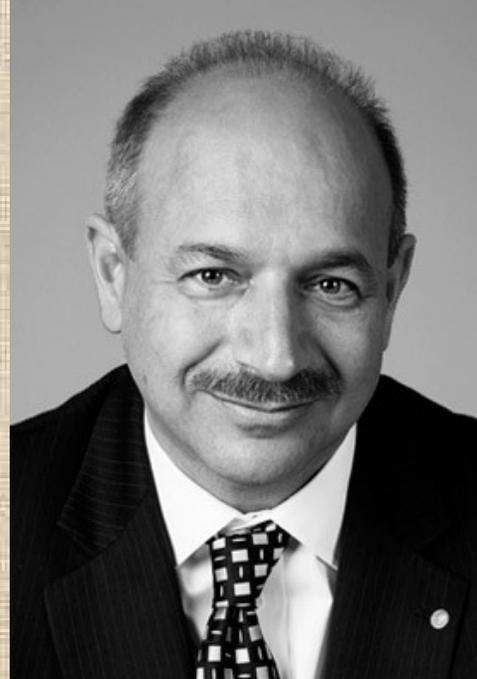
# Vaccination and the role of adjuvants



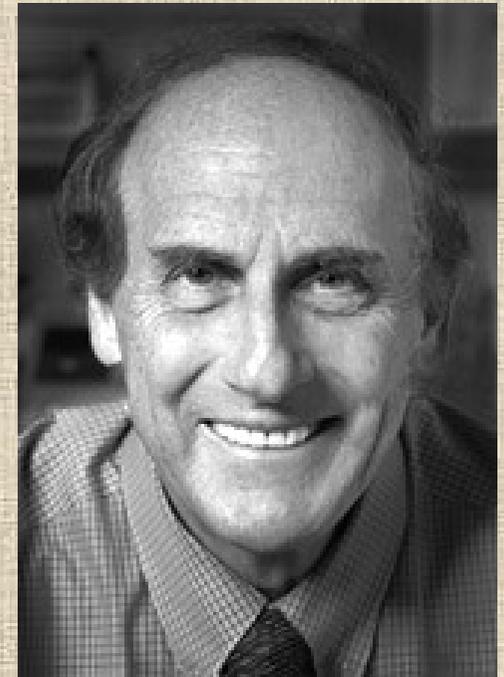
# Nobel Laureates in 2011 for medicine and physiology



Jules A. Hoffmann



Bruce A. Beutler



Ralph M. Steinmann