

Basic immunology

Lecture 3.

Innate immunity, pattern recognition

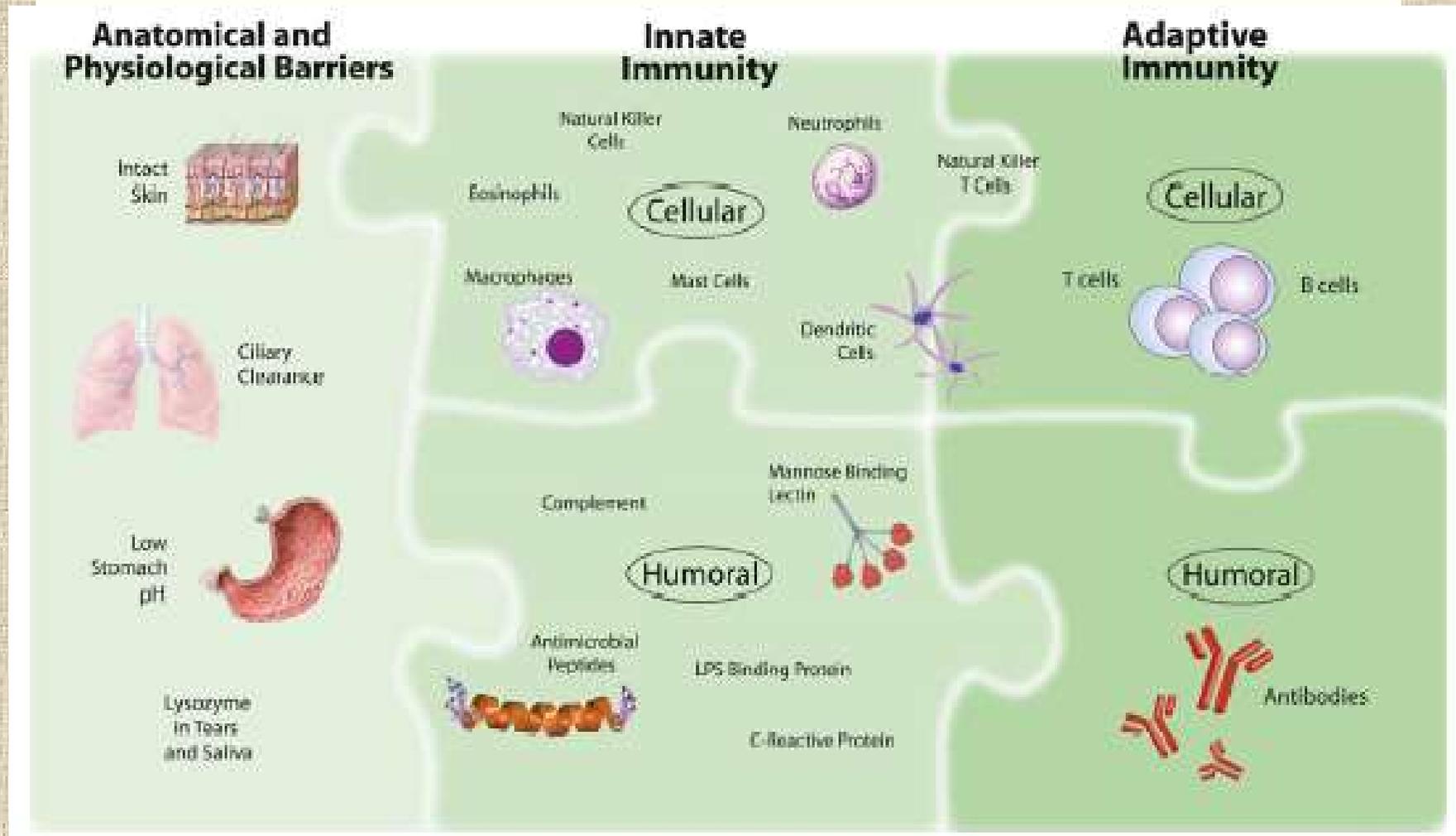


Péter Engelmann

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

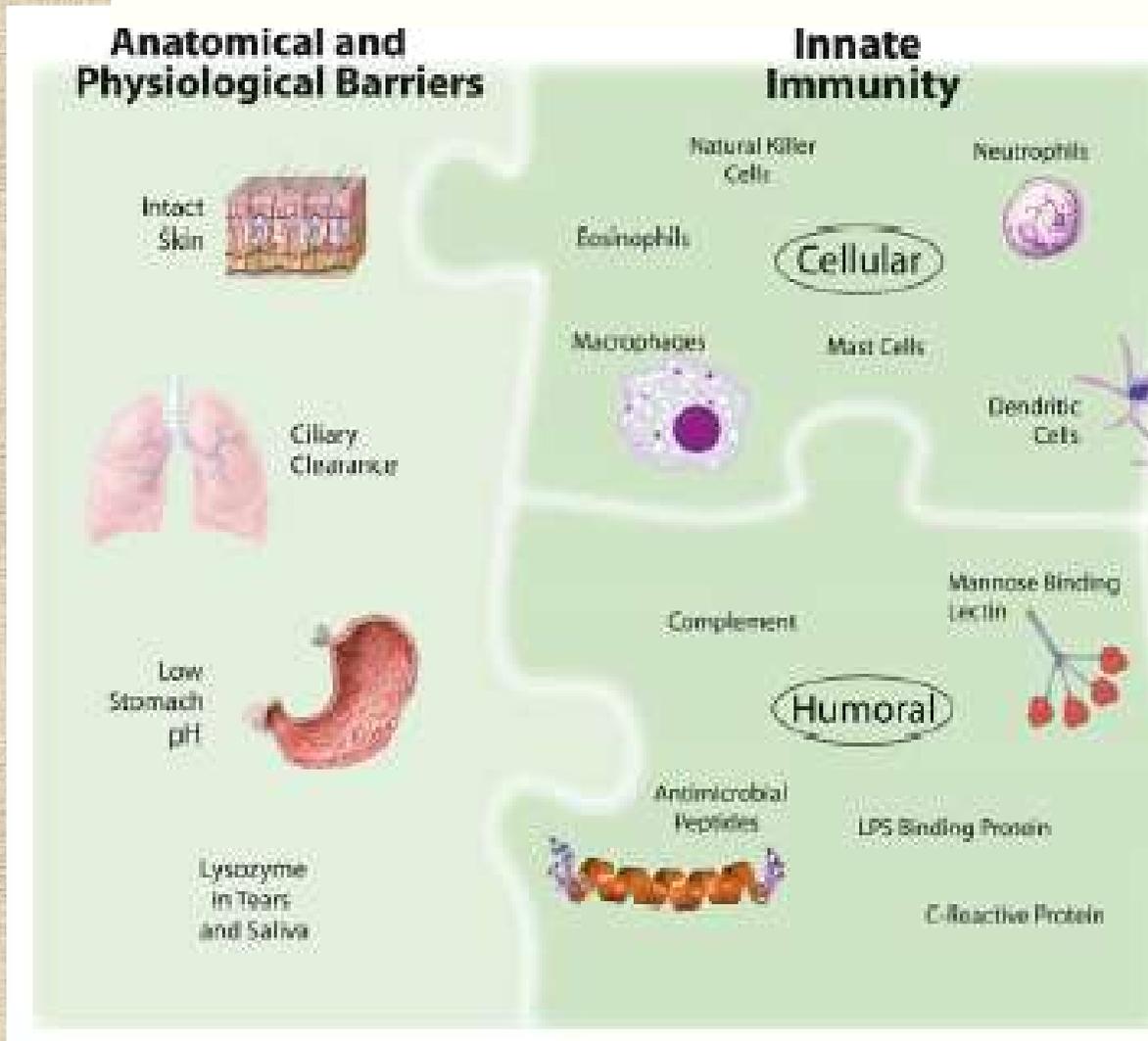
The levels of host defense

- 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”

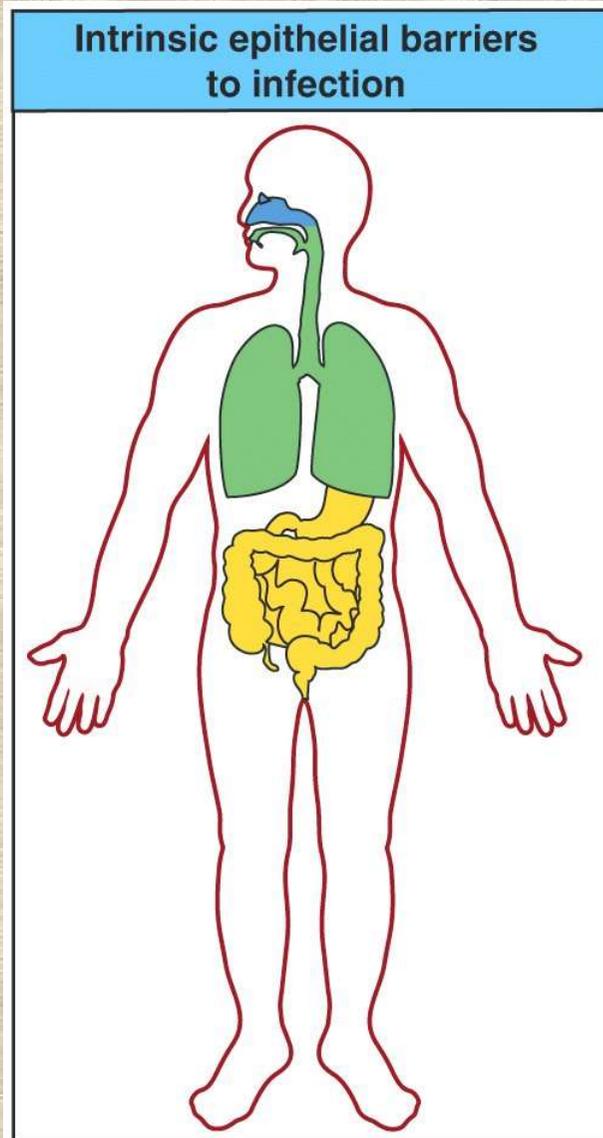
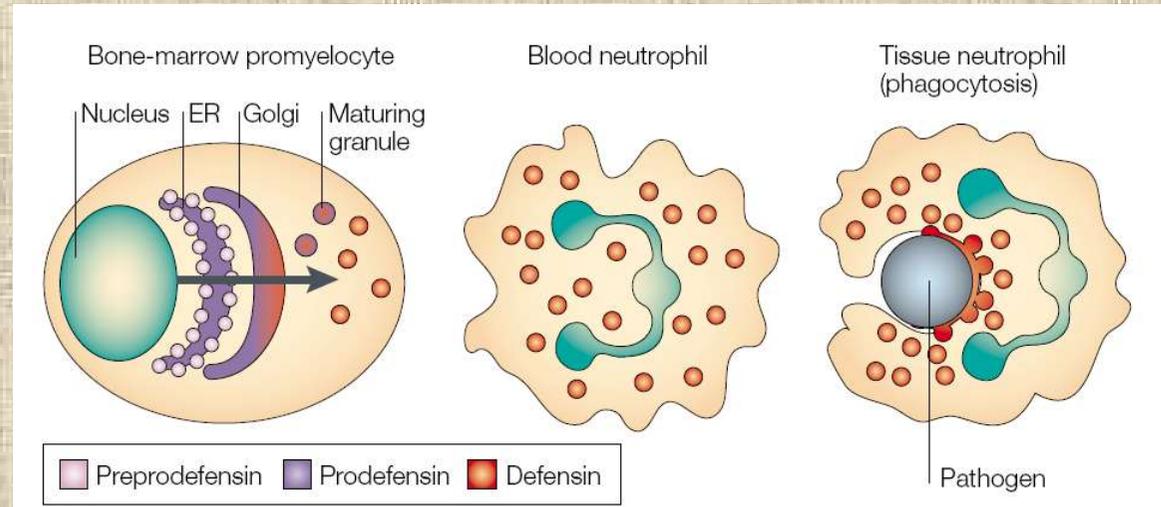
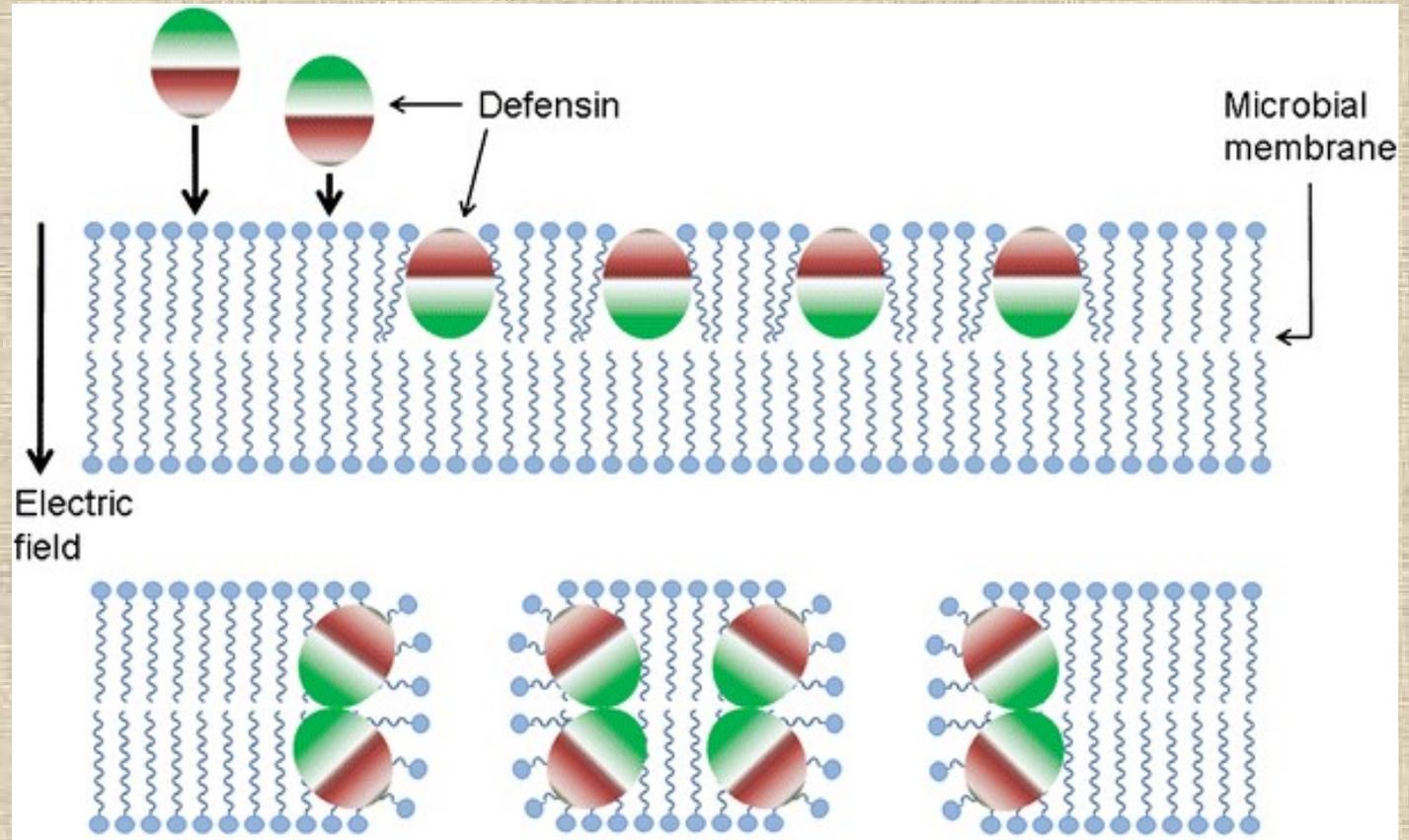
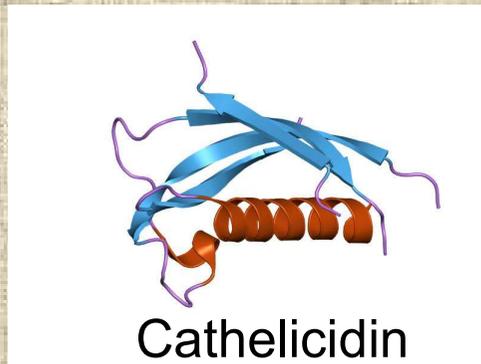
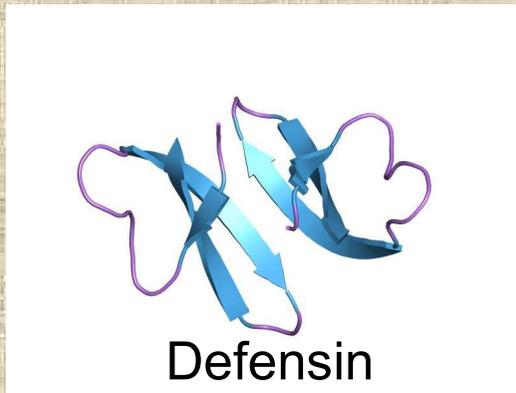


Figure 2-4 Immunobiology, 6/e. (© Garland Science 2005)

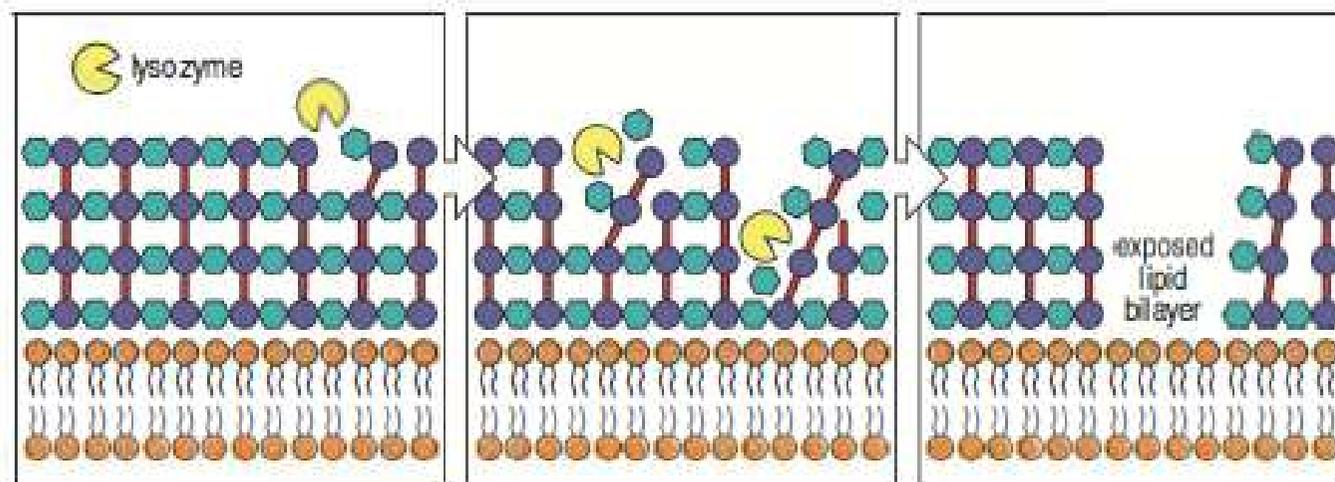
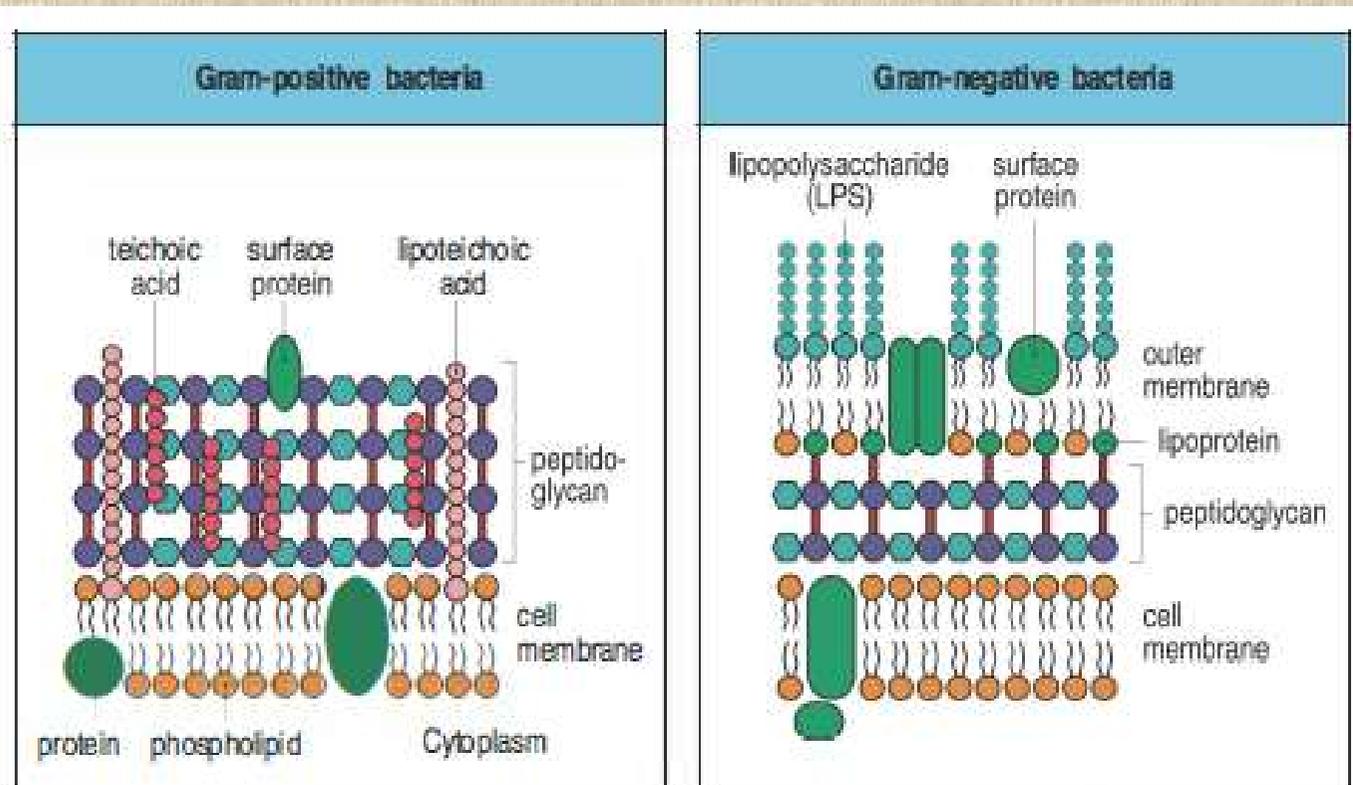
	Skin	Gut	Lungs	Eyes/nose/oral cavity
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH Enzymes (pepsin)	Pulmonary surfactant	Enzymes in tears and saliva (lysozyme)
	β -defensins Lamellar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

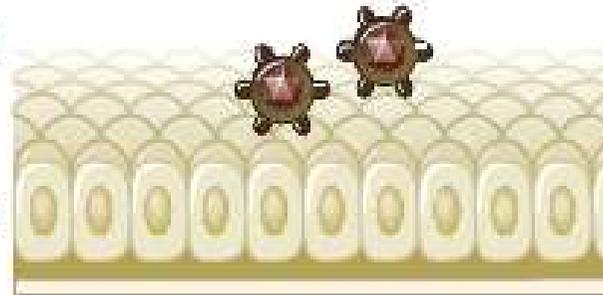


Antimicrobial peptides II

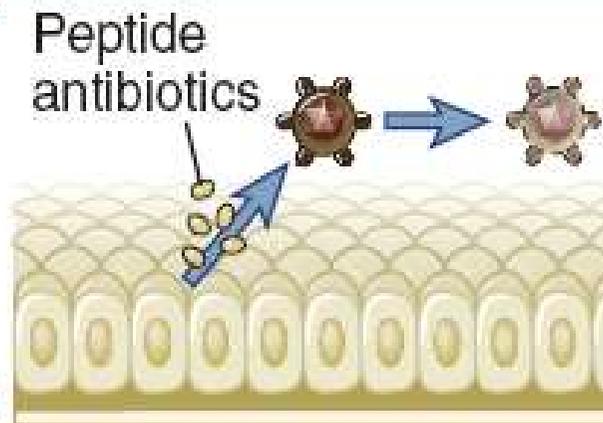


The role of epithelial barriers

Physical barrier
to infection

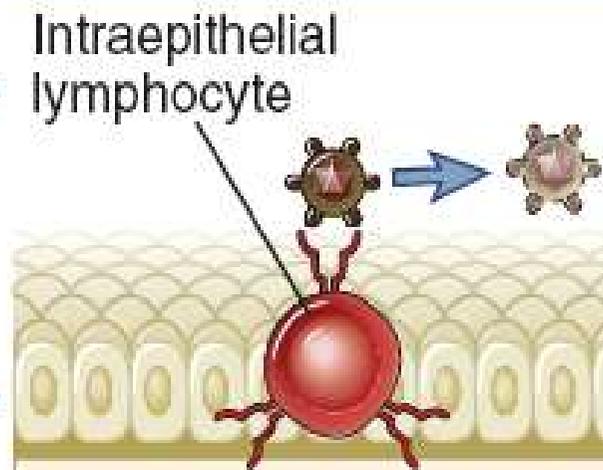


Killing of microbes
by locally produced
antibiotics,
defensins,
cathelicidins



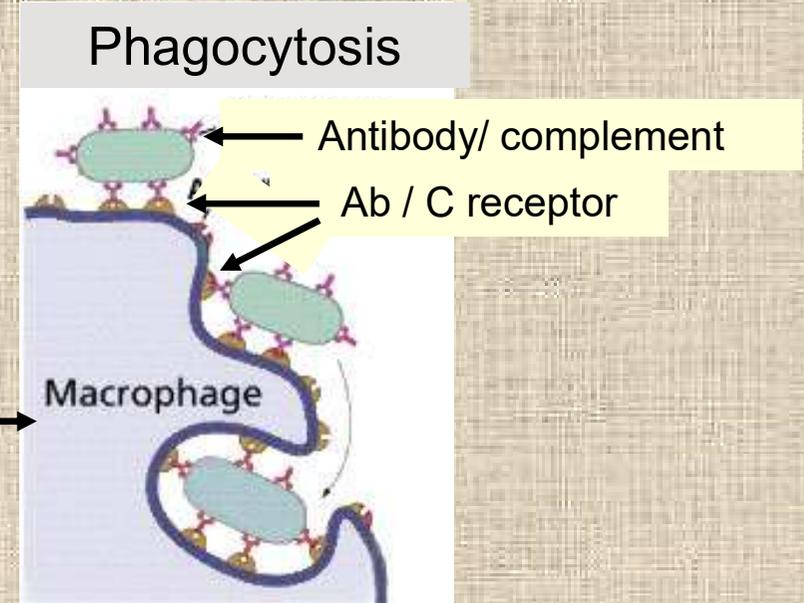
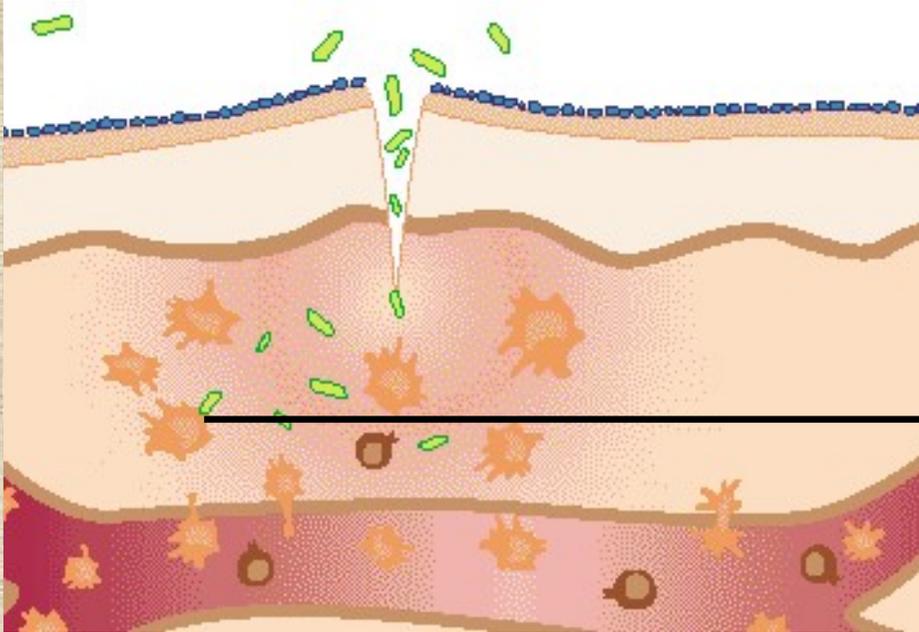
Defensins,
cathelicidins

Killing of microbes
and infected cells
by intraepithelial
lymphocytes

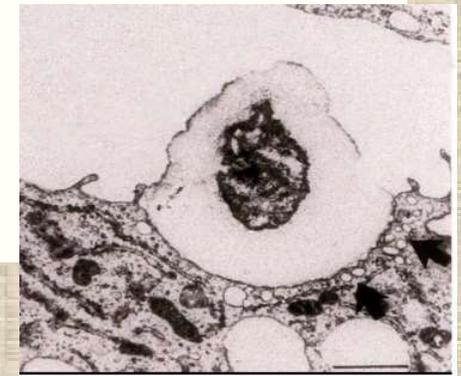


Mast cells, IEL:
 $\gamma\delta$ T cells

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



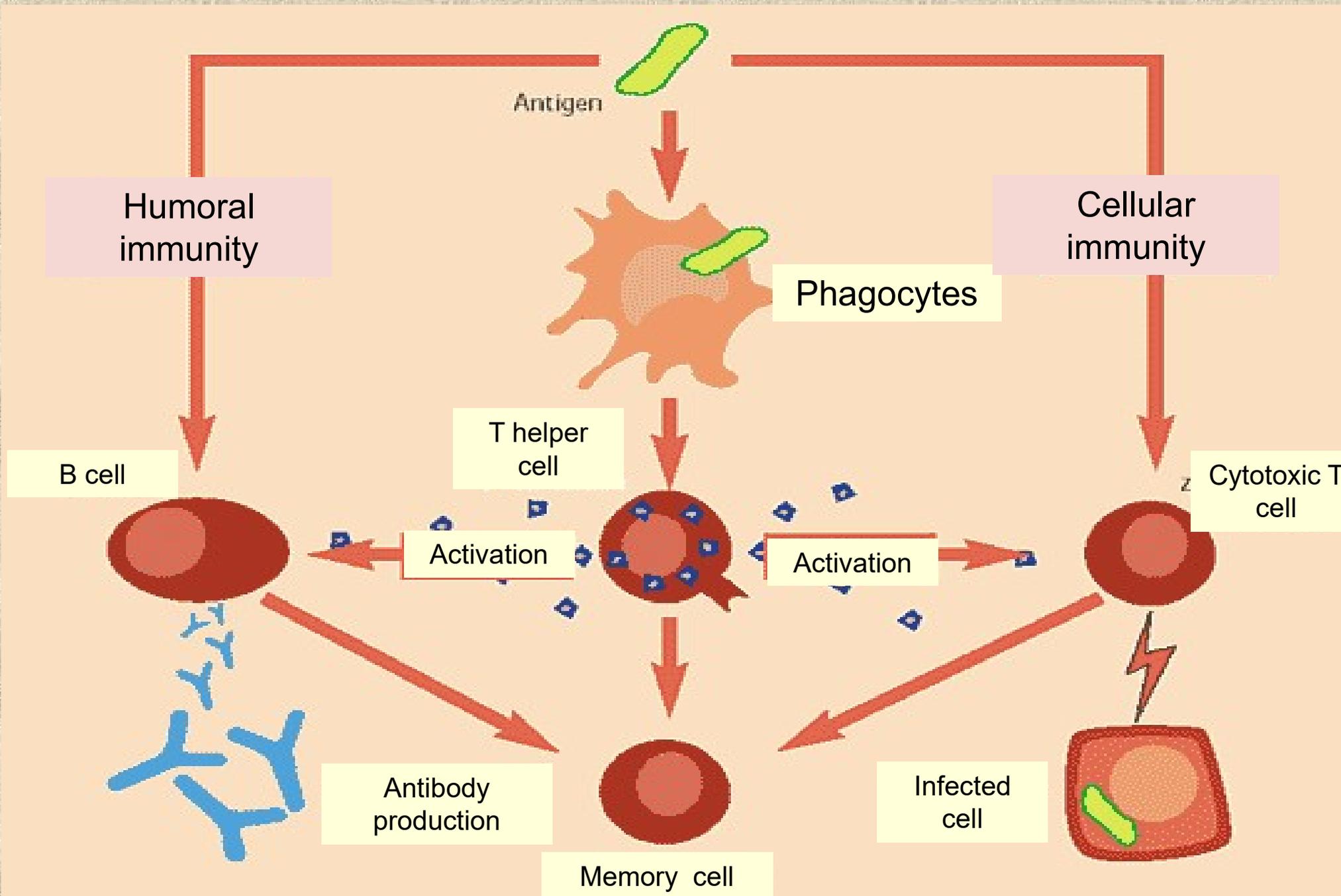
1. **Phagocytes** in the blood and tissues.
2. Soluble **proteins (immunoglobulin and complement)**, bind to microbe surface (**opsonisation**) to enhance the phagocytosis.



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

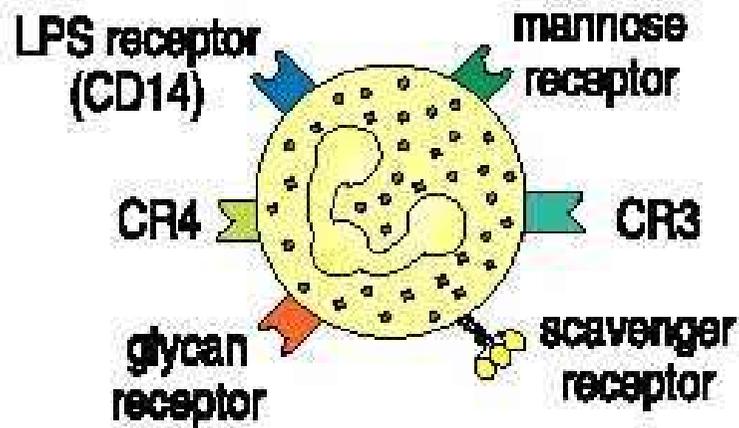


- Different levels of the immune response
- Recognition molecules of innate immunity

Recognition of pathogens, phagocytosis

Figure 8.8

The neutrophil expresses receptors for many bacterial constituents



Neutrophils engulf and digest bacteria to which they bind



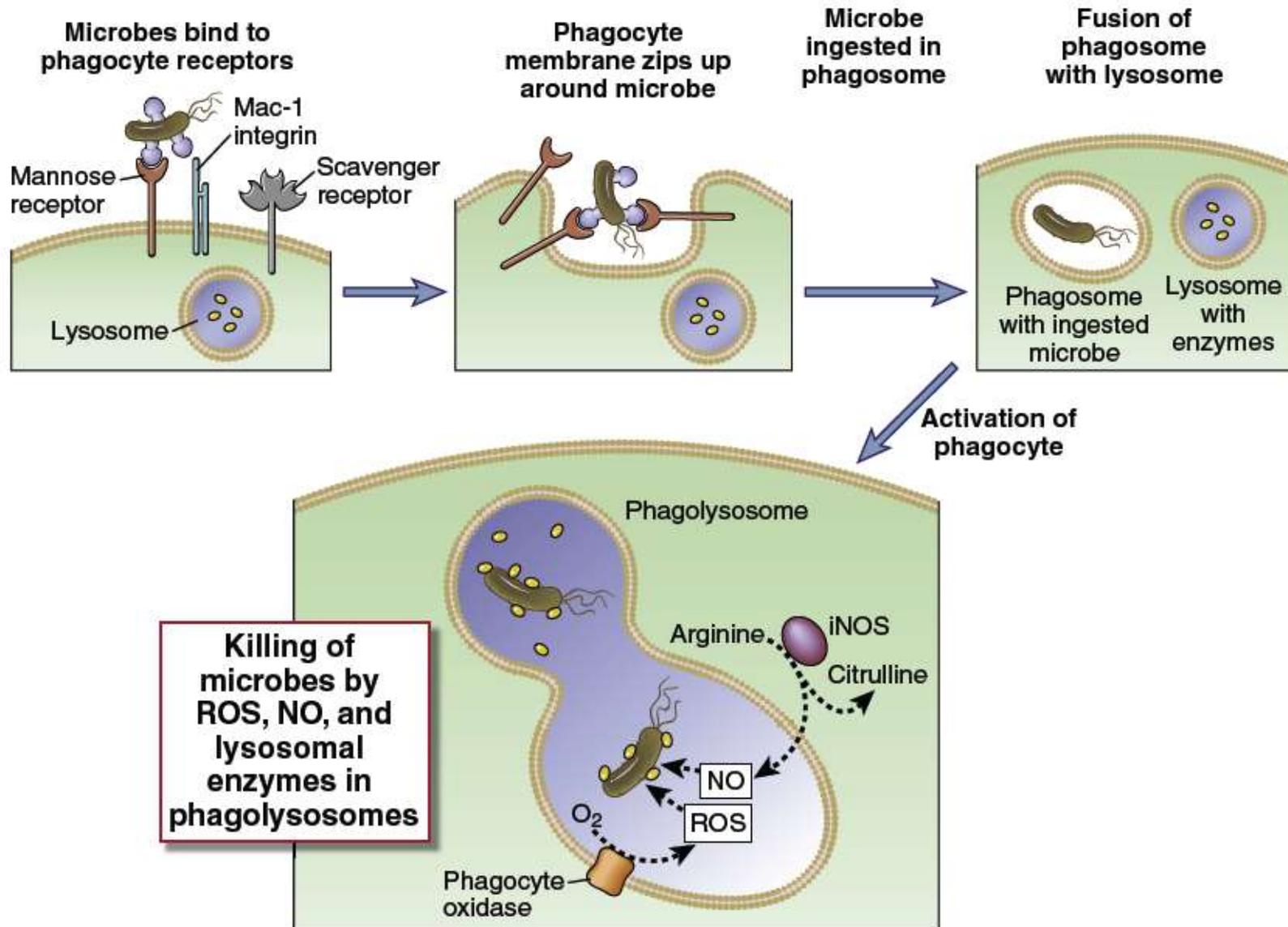
PRR= „Pattern Recognition Receptors”

→Binding to the PAMPS of microbes

PAMP=„Pathogen Associated Molecular Patterns

DAMPs = „Danger/Damage Associated Molecular Patterns”

Process of phagocytosis

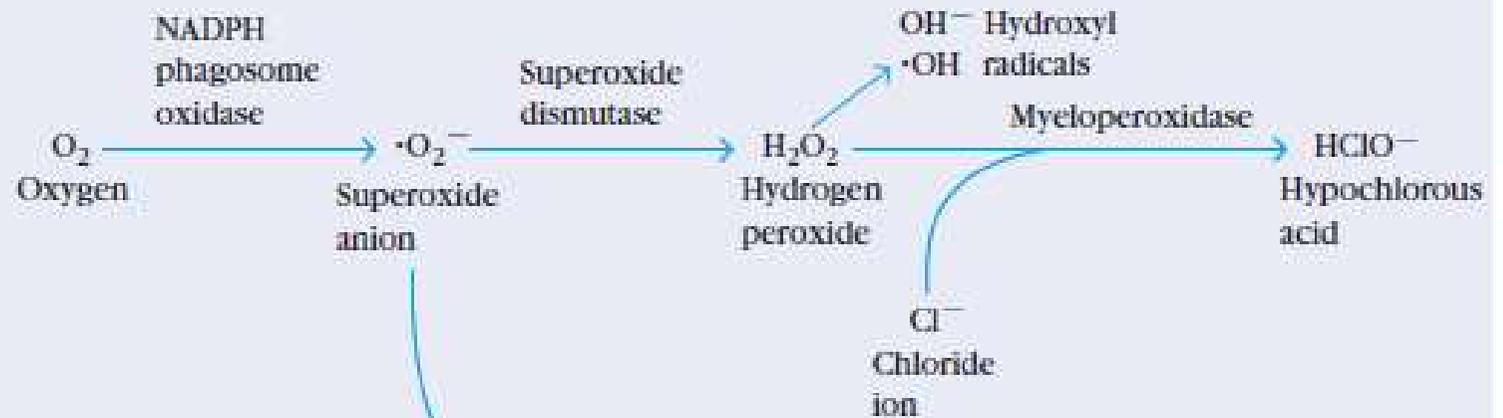


Reactive oxygen/nitrogen intermediers

Antimicrobial species generated from oxygen and nitrogen

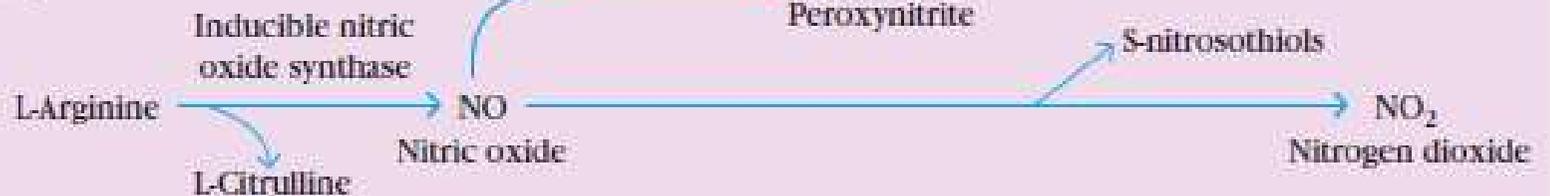
Reactive oxygen species (ROS)

$\cdot\text{O}_2^-$ (superoxide anion)
 $\text{OH}\cdot$ (hydroxyl radical)
 H_2O_2 (hydrogen peroxide)
 HClO (hypochlorous acid)

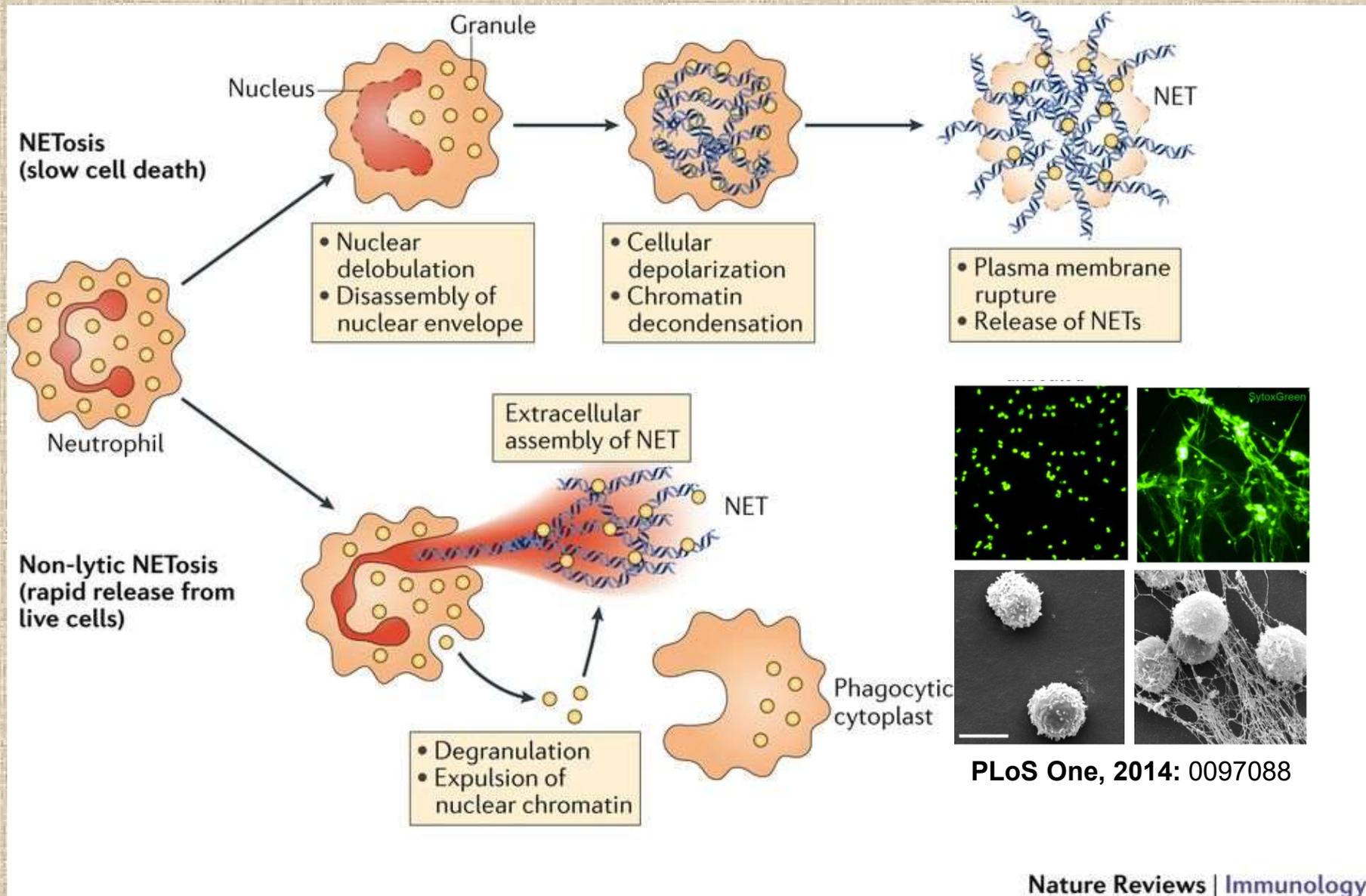


Reactive nitrogen species (RNS)

NO (nitric oxide)
 NO_2 (nitrogen dioxide)
 ONOO^- (peroxynitrite)

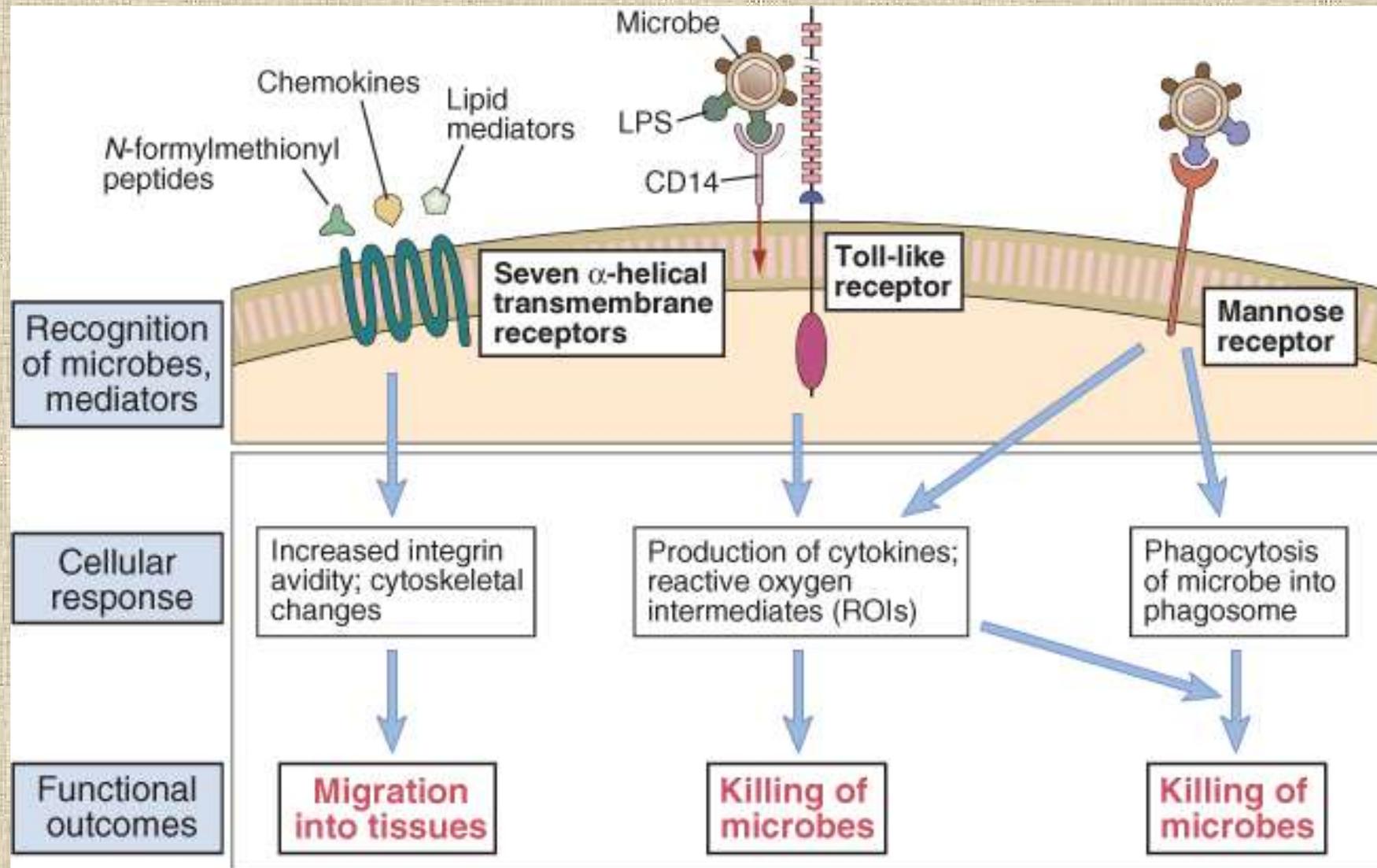


Process of NETosis



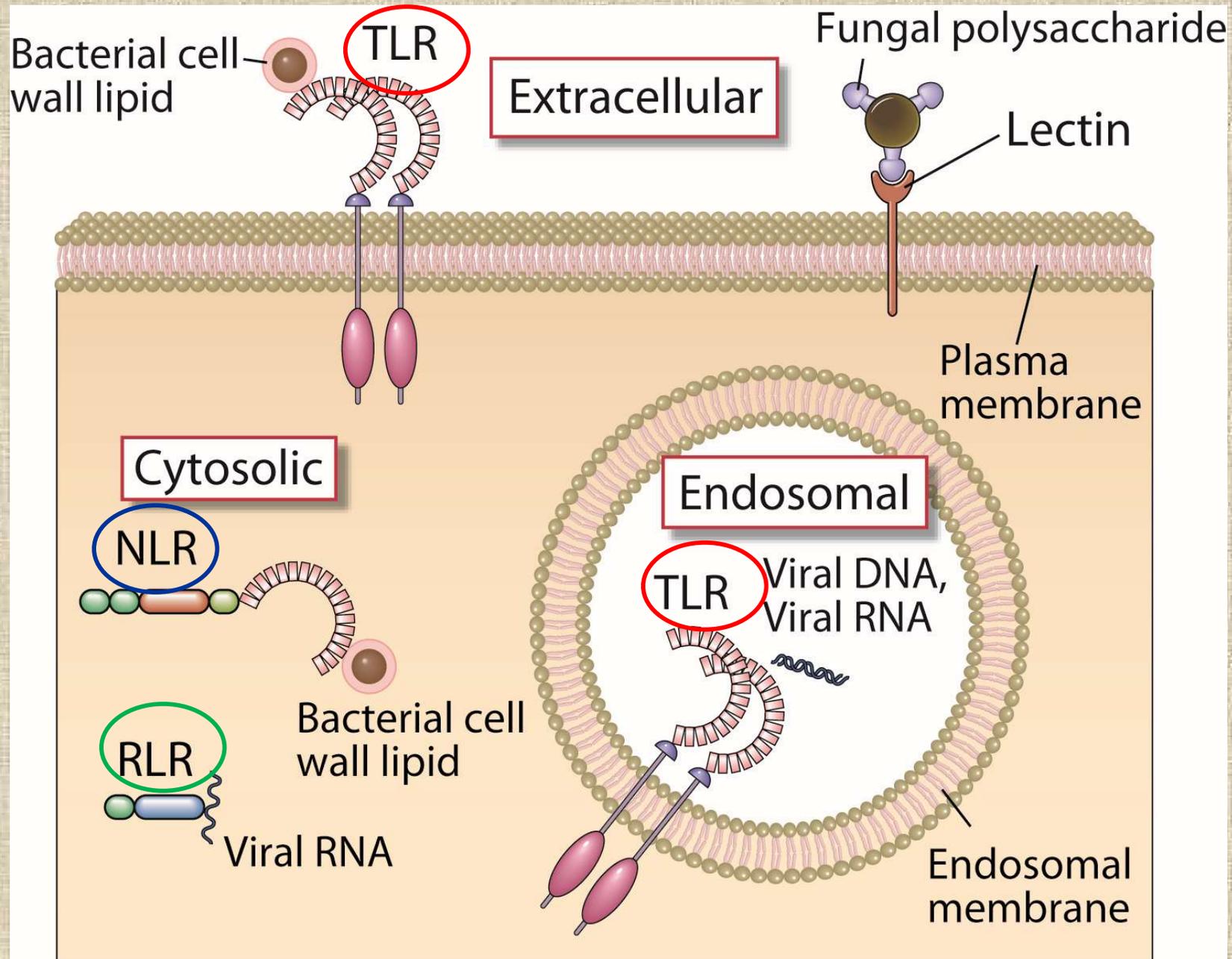
NET: neutrophyl extracellular trap

Phagocyte receptors



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Pattern recognition receptors

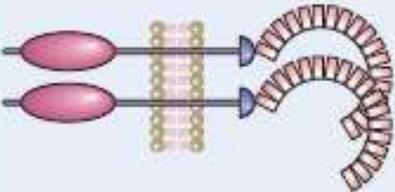
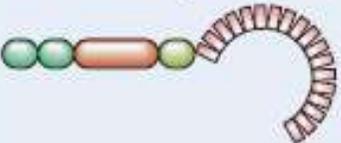
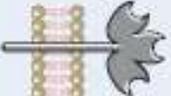


Toll-like receptors (TLR)

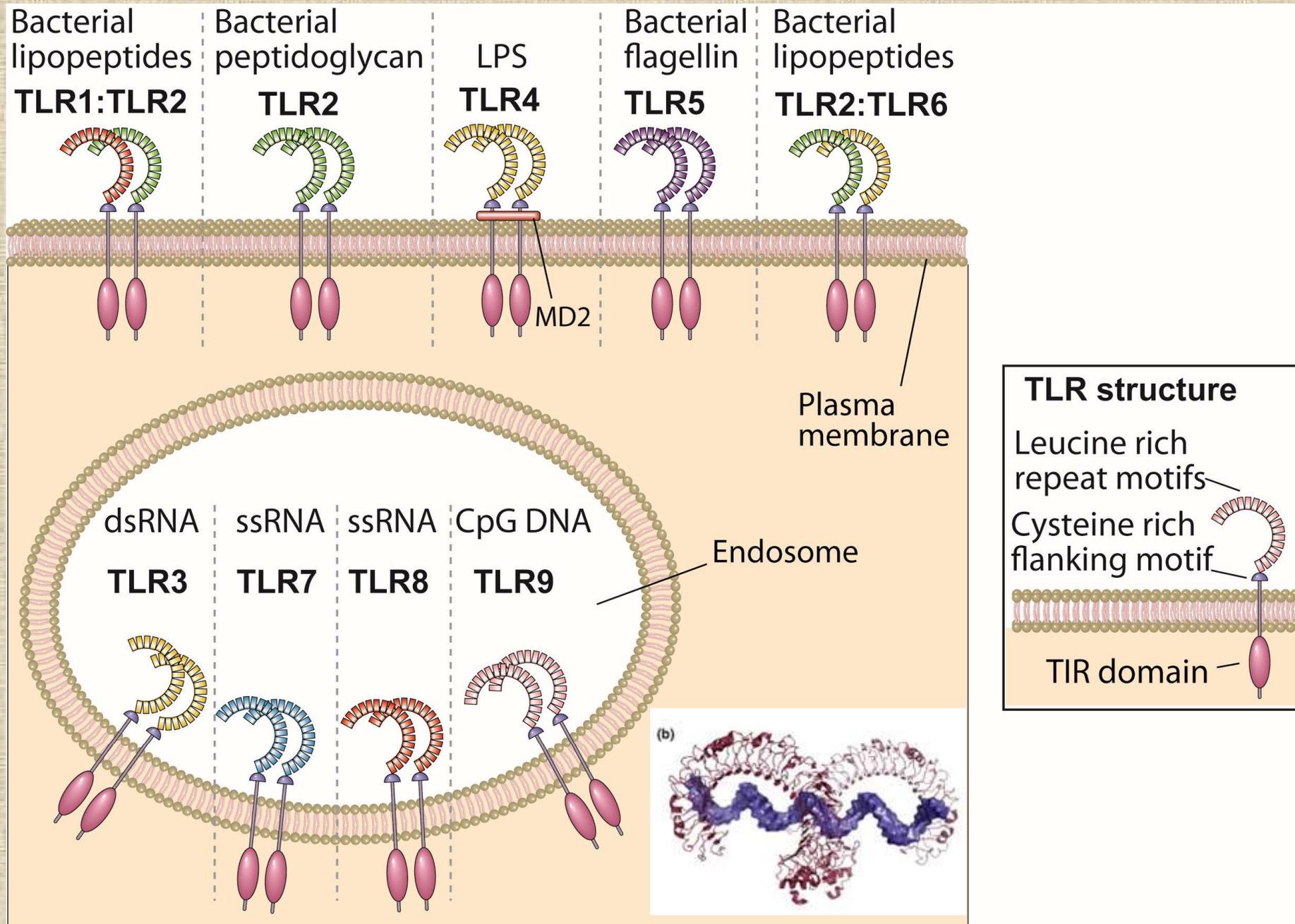
NOD-like receptors (NLR)

RIG-like receptors (RLR)

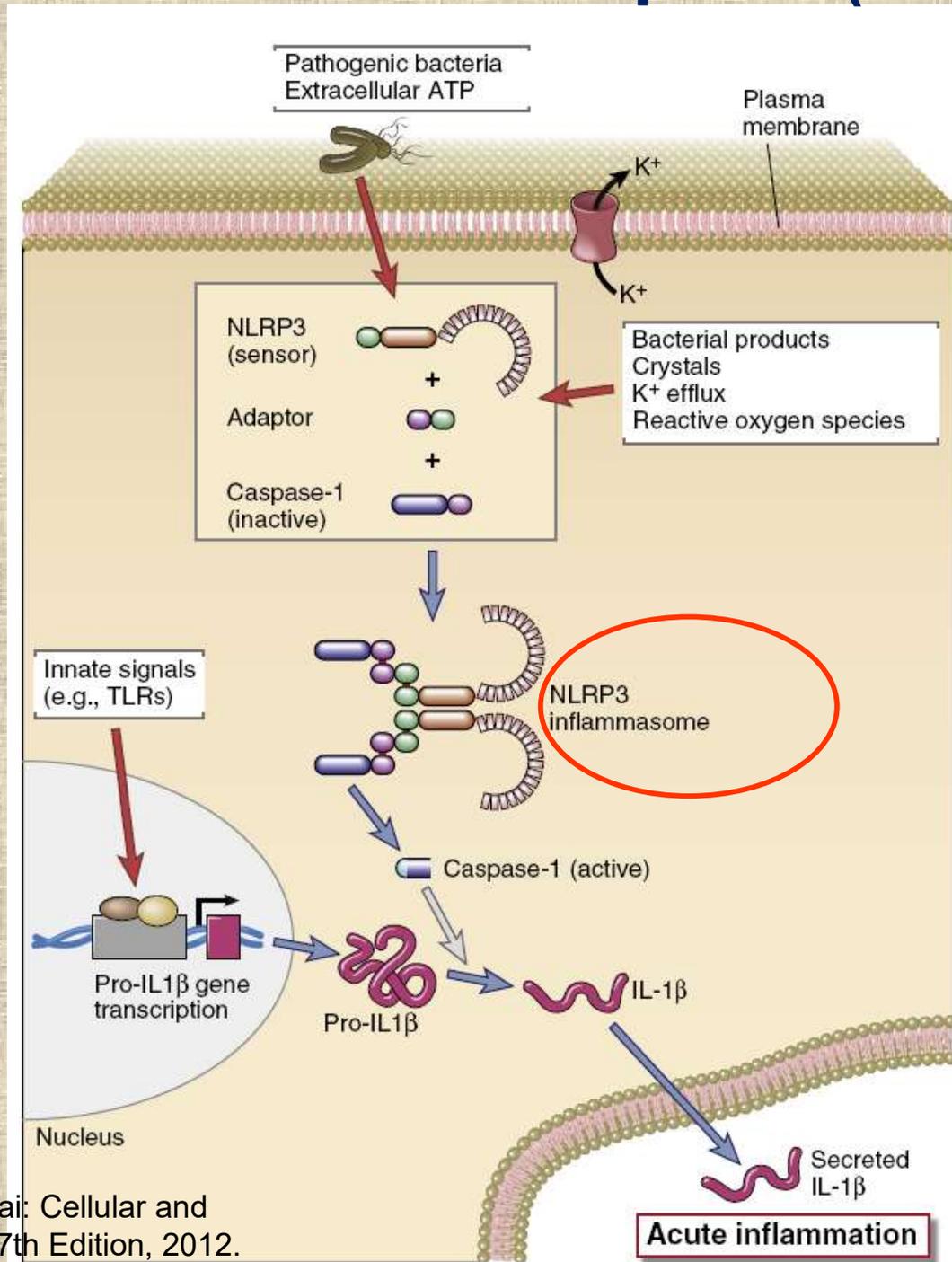
Main groups of pattern recognition receptors

<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)

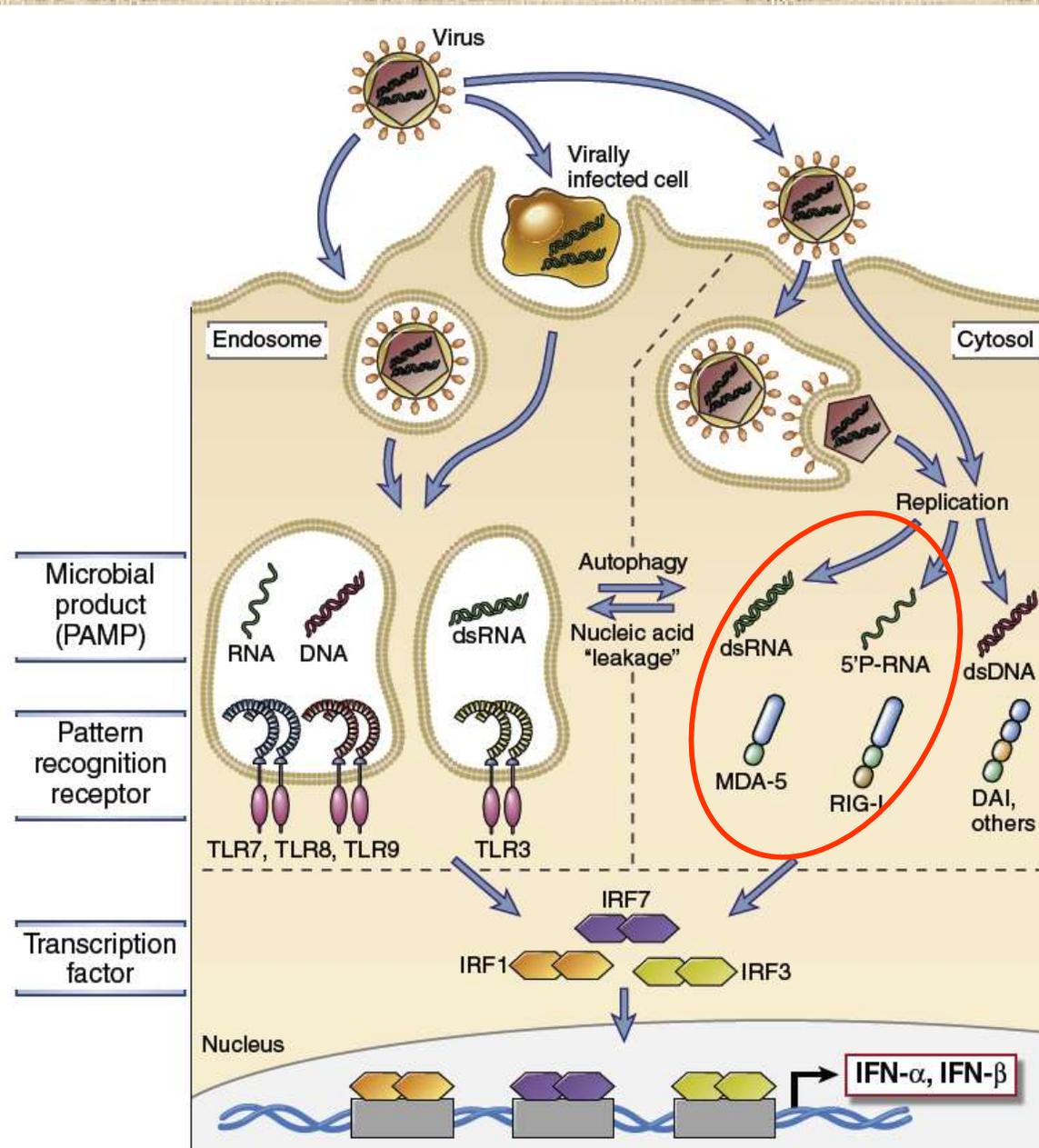


Pattern recognition receptors: NOD-like receptors (NLR)

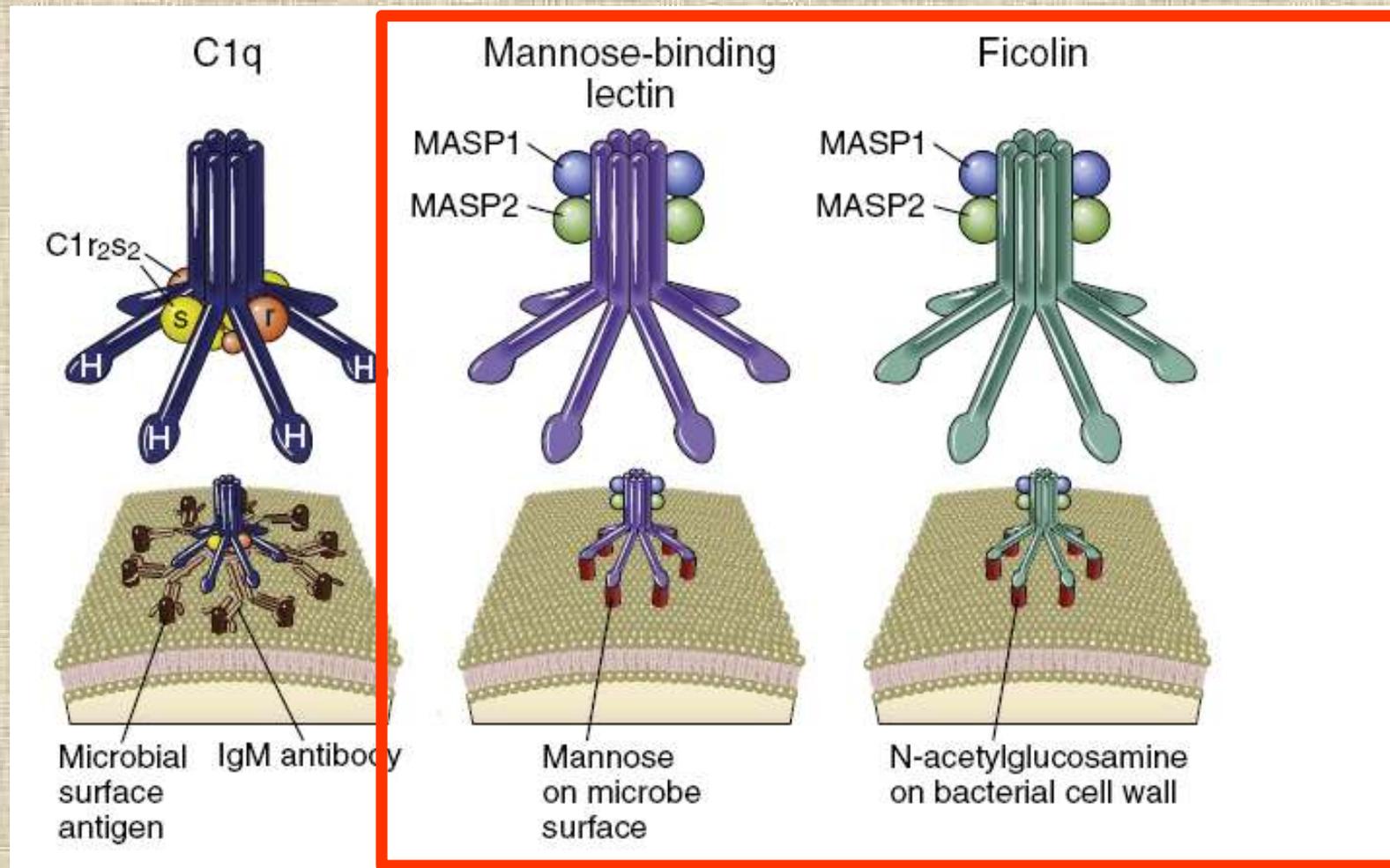


NOD: Nucleotide oligomerization domain

Pattern recognition receptors: RIG-like receptors (RLR)



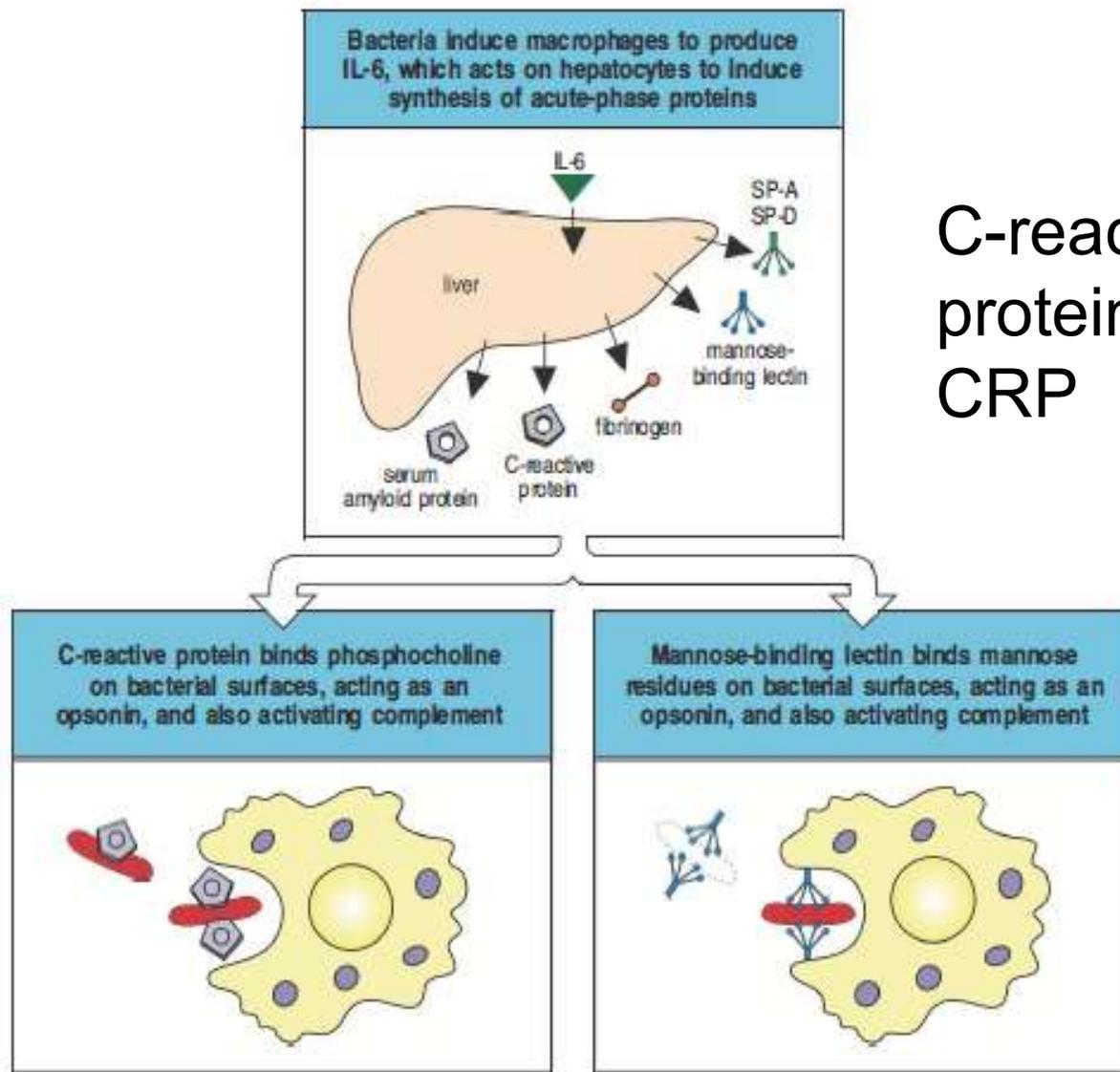
Soluble pattern recognition molecules I



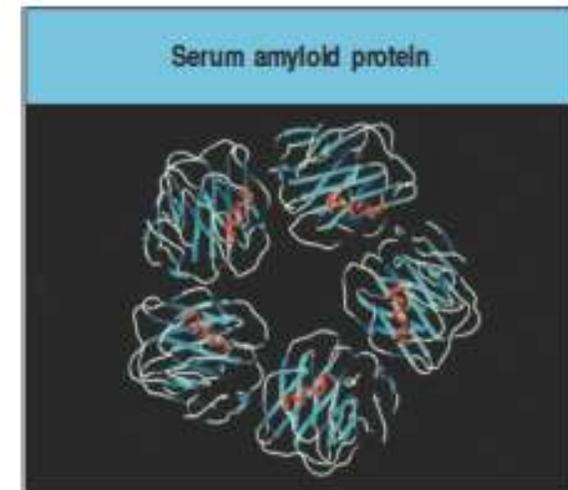
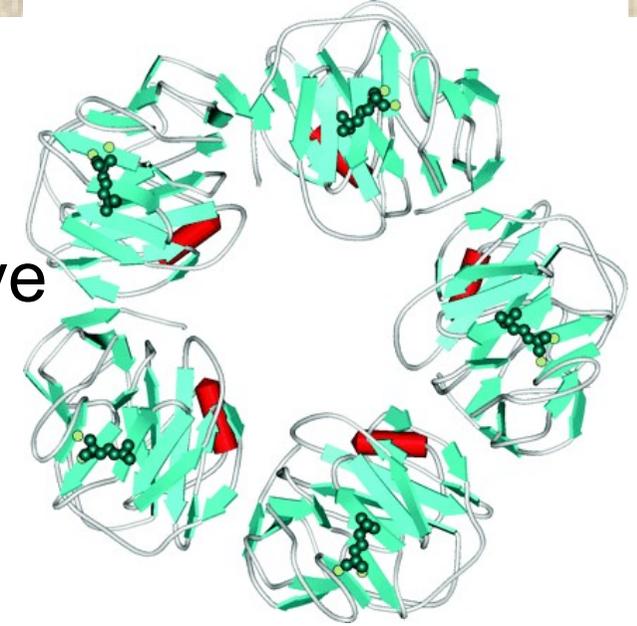
Collectin (MBL, SP-A, SP-D): C-type lectin domain

Ficolin: Fibrinogen domain

Soluble pattern recognition molecules II: pentraxins



C-reactive
protein-
CRP



Clinical significance of C-reactive protein level

Risk of infection, sepsis



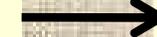
CRP test, complete blood count, blood culture
Then start Antibiotics treatment



CRP 48 hr



CRP <10 mg/L & blood culture negative



Discontinue antibiotic treatment

CRP >10 mg/L,
Continue antibiotics therapy

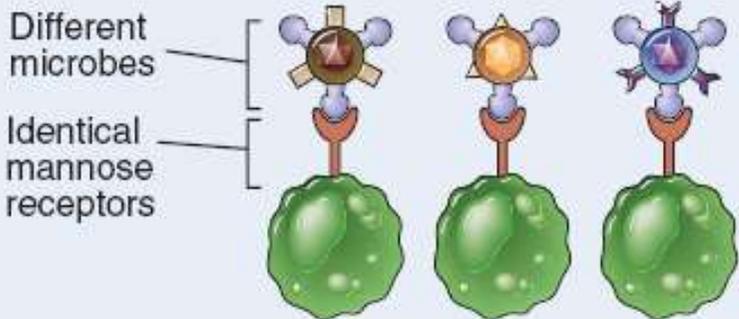
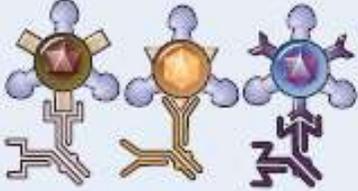
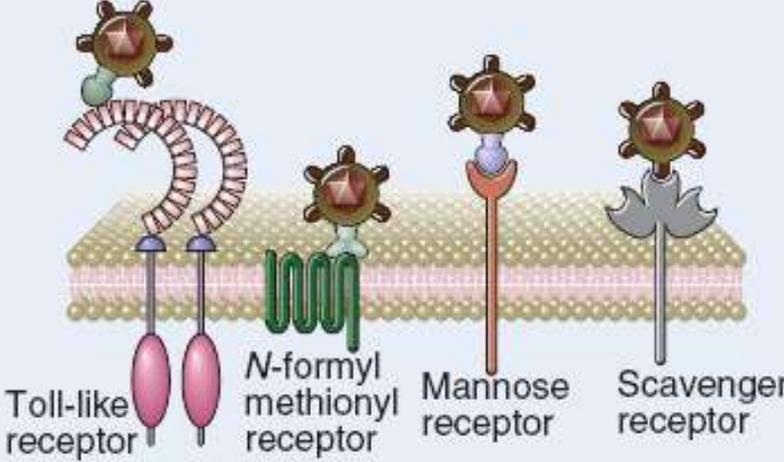
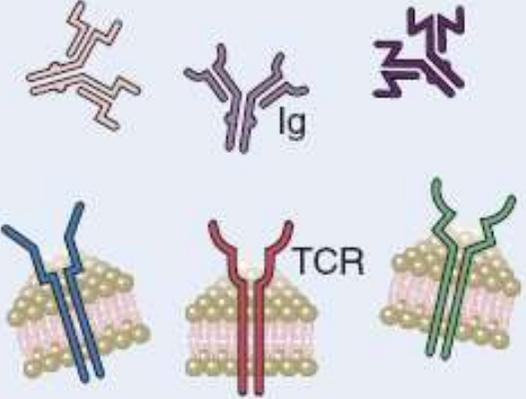


CRP at 7 days

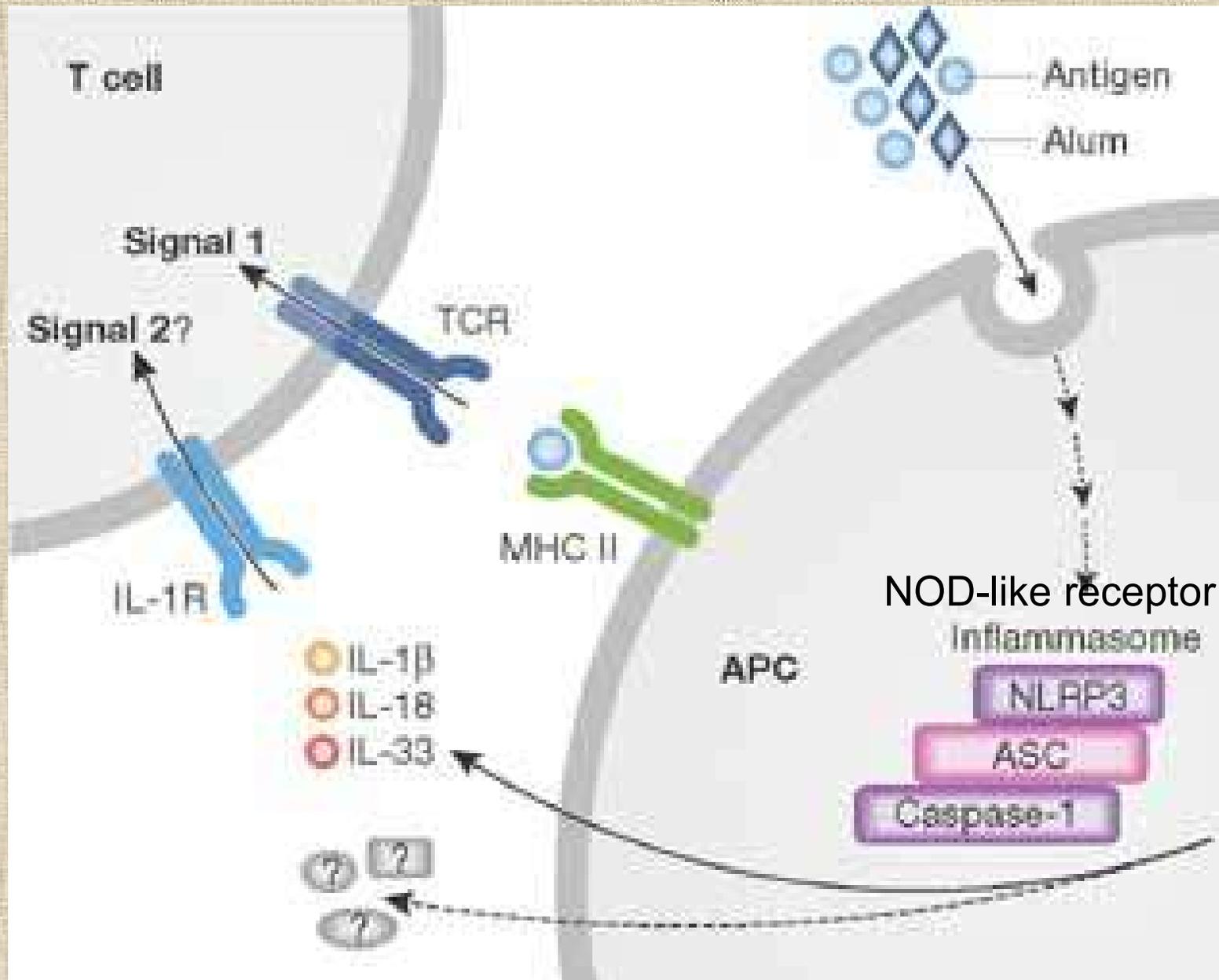
CRP <10 mg/L: discontinue antibiotic treatment

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

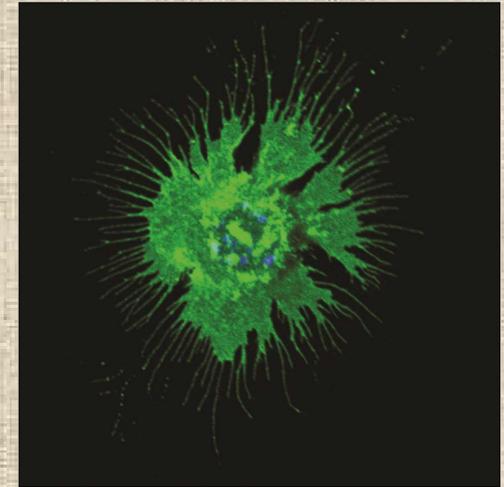
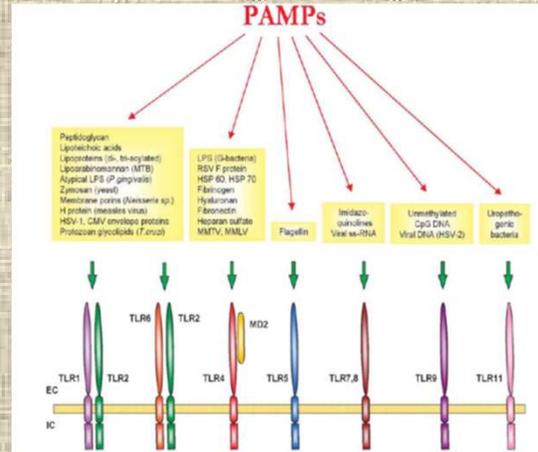
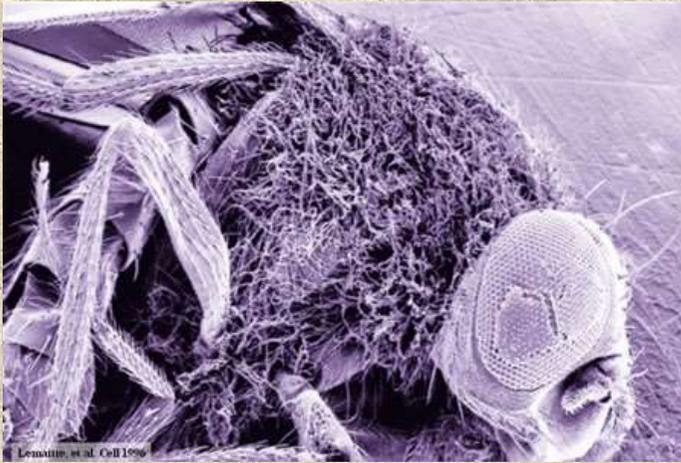
Specificity of innate and adaptive immunity

	Innate Immunity	Adaptive Immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns)	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens
	<p>Different microbes</p> <p>Identical mannose receptors</p> 	<p>Different microbes</p> <p>Distinct antibody molecules</p> 
Receptors	Encoded in germline limited diversity (pattern recognition receptors)	Encoded by genes produced by somatic recombination of gene segments ; 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	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)

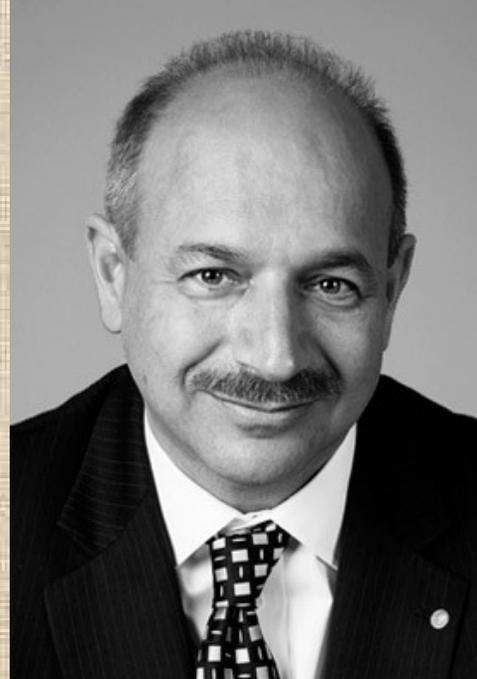
Vaccination and the role of adjuvants



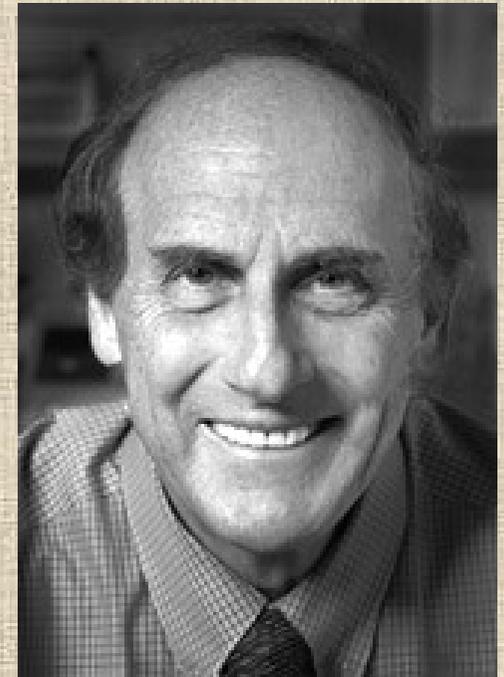
Nobel Laureates in 2011 for medicine and physiology



Jules A. Hoffmann



Bruce A. Beutler



Ralph M. Steinmann