# Basic immunology

*Lecture 5.*

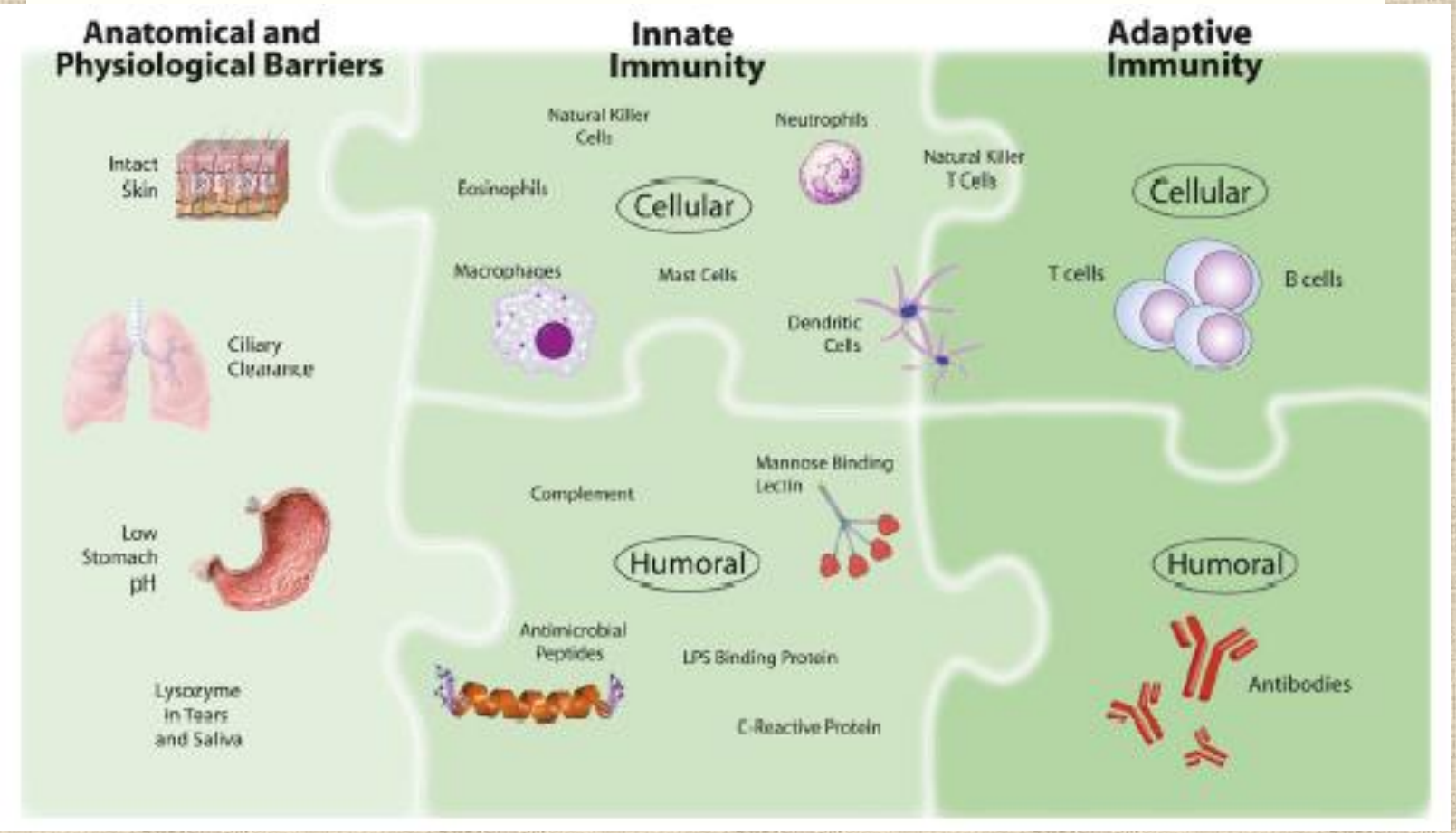
**Innate immunity: inflammation, leukocyte migration**

**Péter Engelmann**

- Different levels of the immune response
- Recognition molecules of the innate immunity
- Initiation of local and systemic inflammation
- Extravasation, homing

# The levels of host defense

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




J Allergy Clin Immunol. 2010 ;125:S24–S32.

# The levels of host defense

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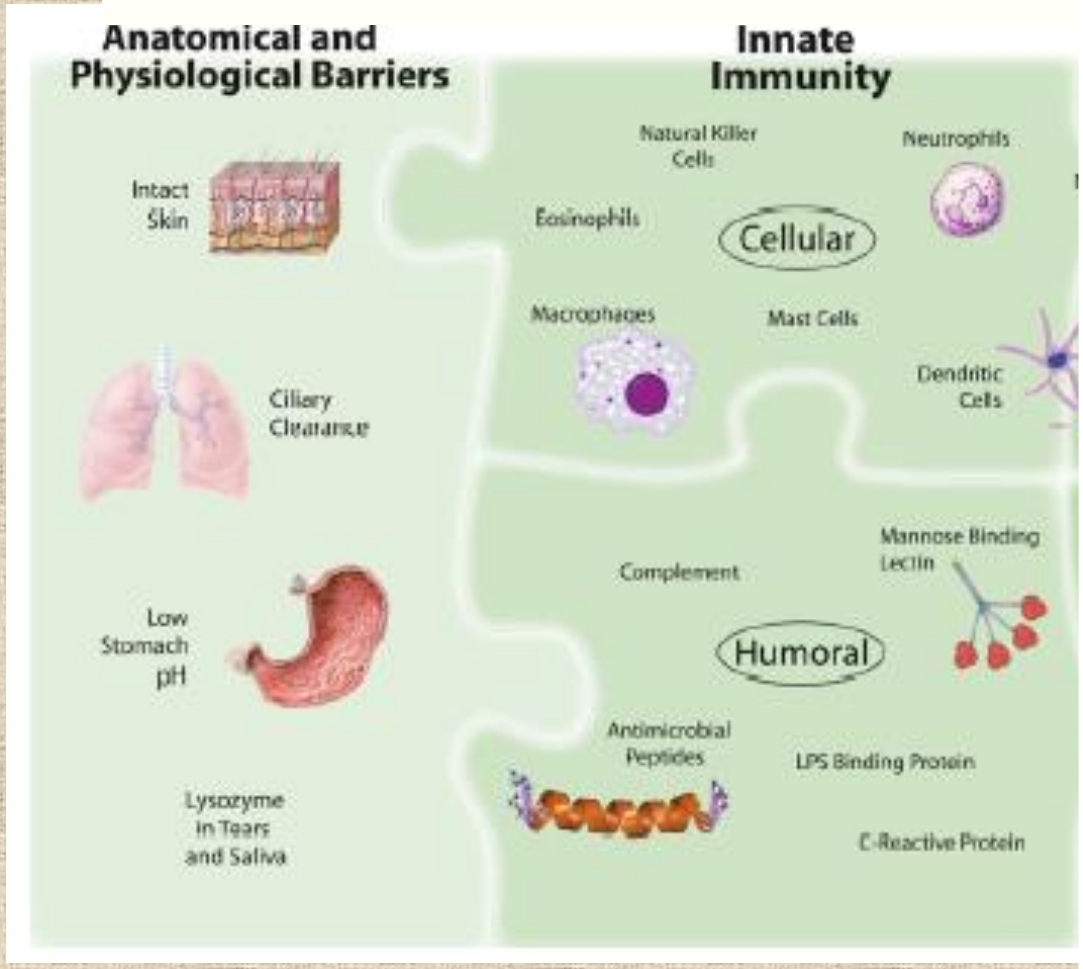


# I. First line of defense: anatomic „barriers”

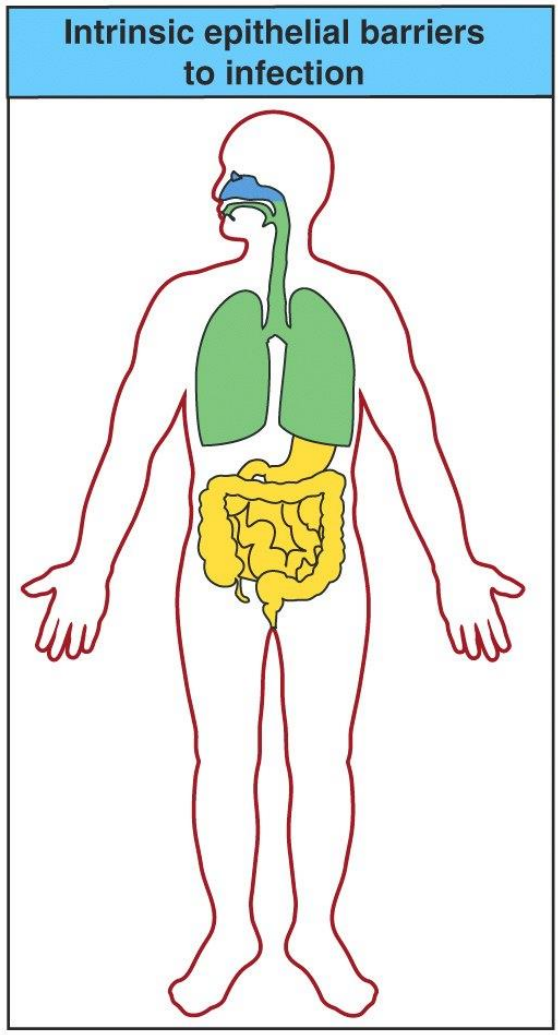


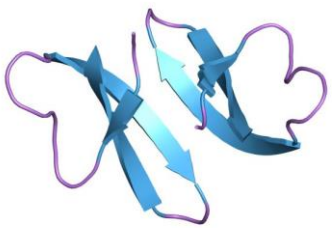

Figure 2-4 Immunobiology, 6/e. (© Garland Science 2005)

| | 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<br>Nasal cilia |
| Chemical | Fatty acids | Low pH | Pulmonary surfactant | Enzymes in tears and saliva (lysozyme) |
| | | Enzymes (pepsin) | | |
| | β-defensins<br>Lamellar bodies<br>Cathelicidin | α-defensins (cryptdins)<br>RegIII (lecticidins)<br>Cathelicidin | α-defensins<br>Cathelicidin | Histatins<br>β-defensins |
| Microbiological | Normal microbiota | | | |

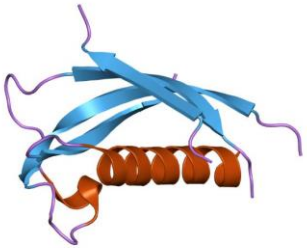
1. Mechanical defense
2. Slightly acidic environment
3. Normal (commensal) microorganisms
4. Antimicrobial factors in the body fluids, on the skin.
5. Cilia

Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

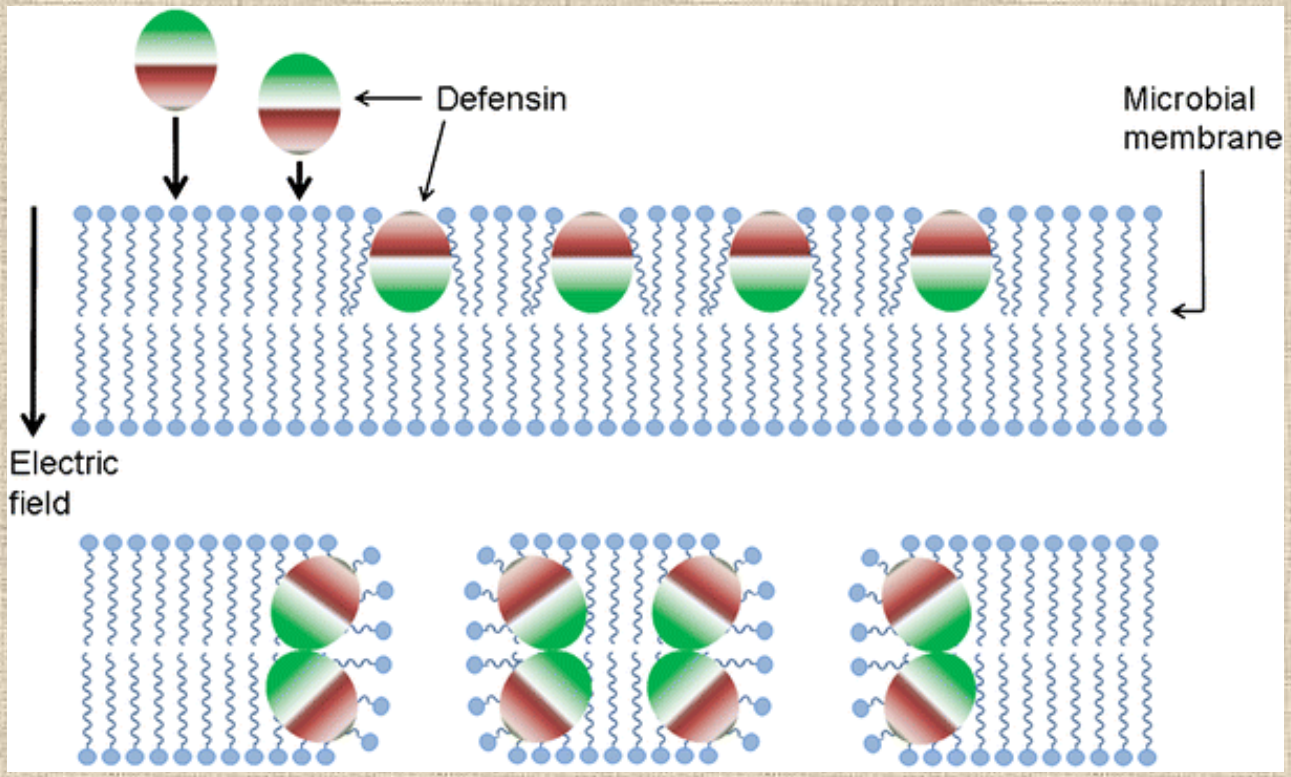
# Antimicrobial peptides

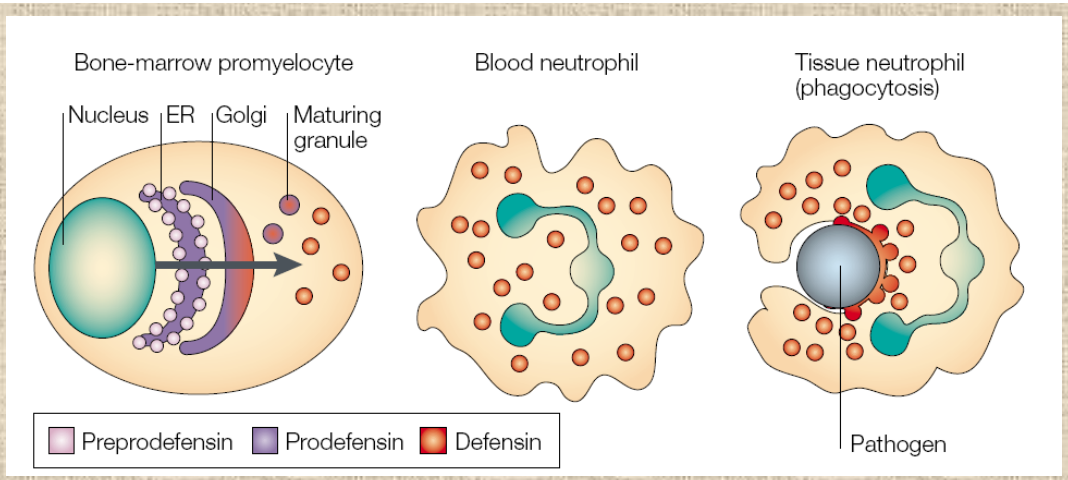


Defensin



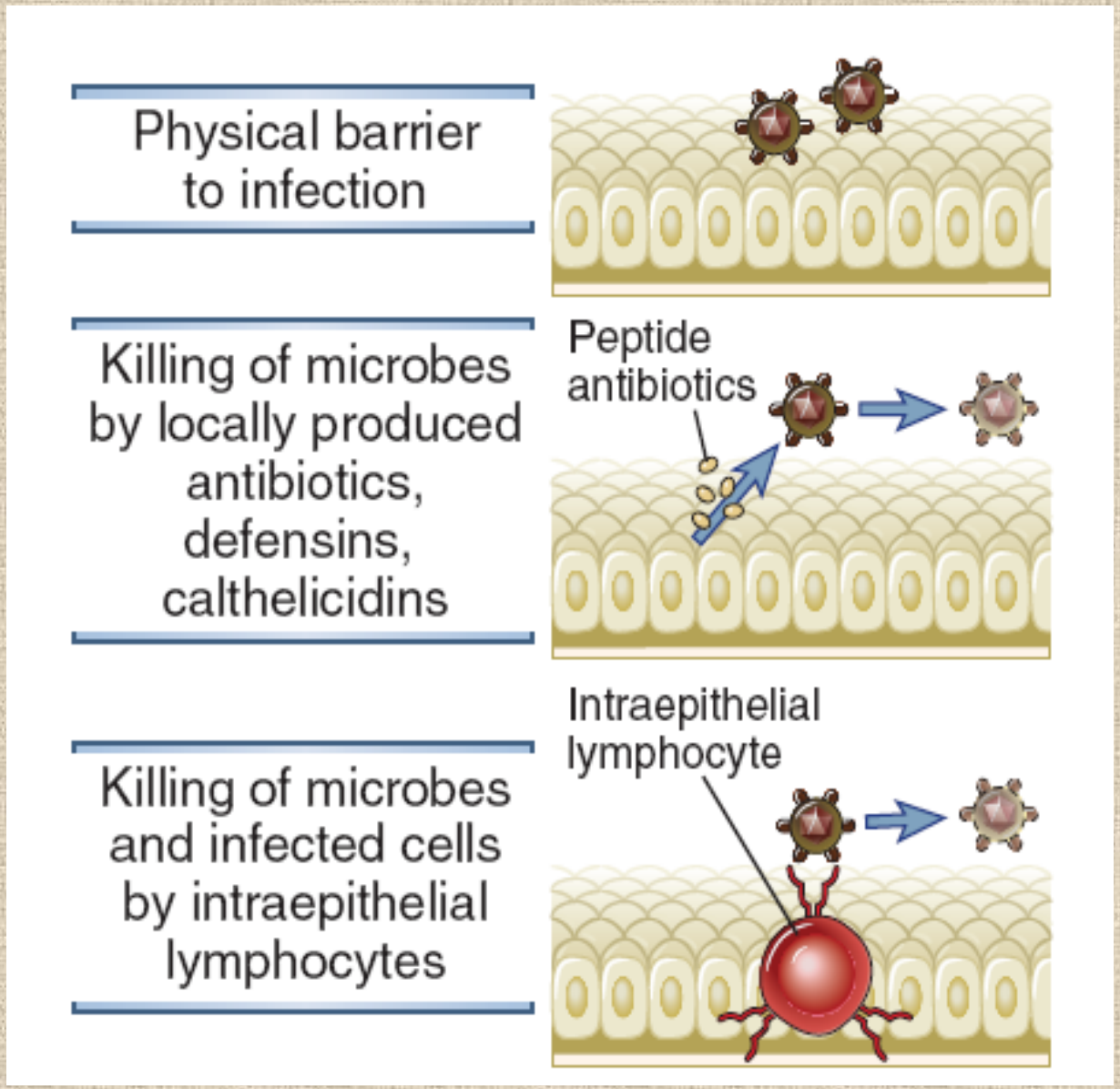
Cathelicidin




Nat Rev Immunol. 2003 ;3:710-720. Cell Tissue Res. 2011 ;343:175-88.

# The role of epithelial barriers

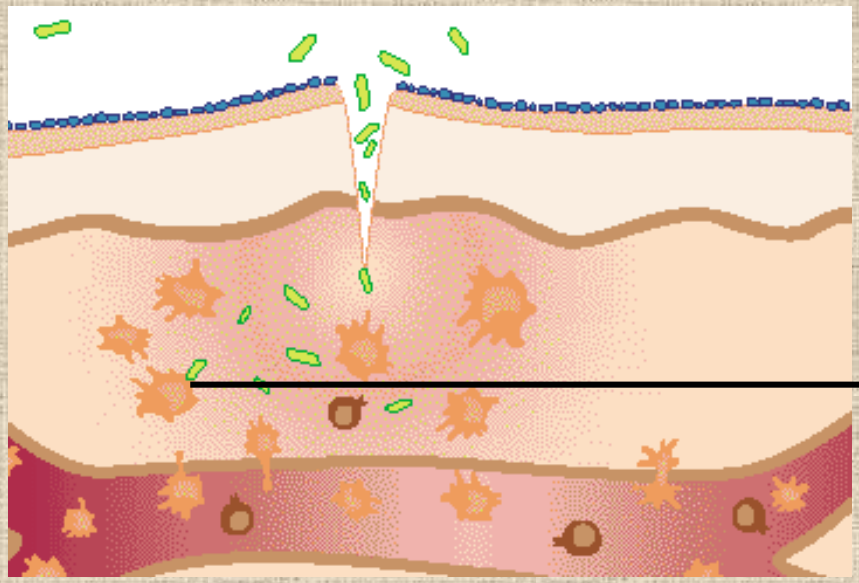


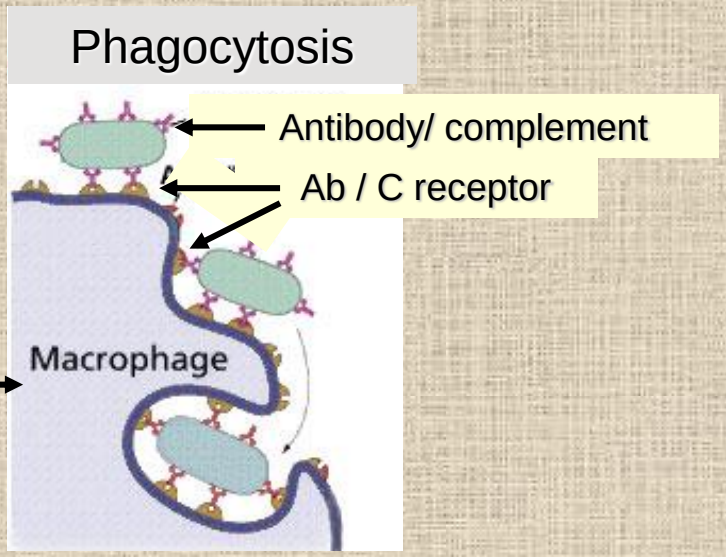

Defensins, cathelicidins

Mast cells, IEL: γδ T cells

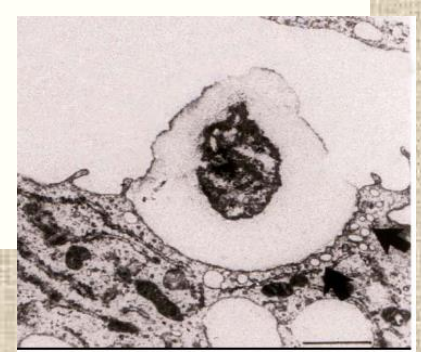
Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition , 2012.

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





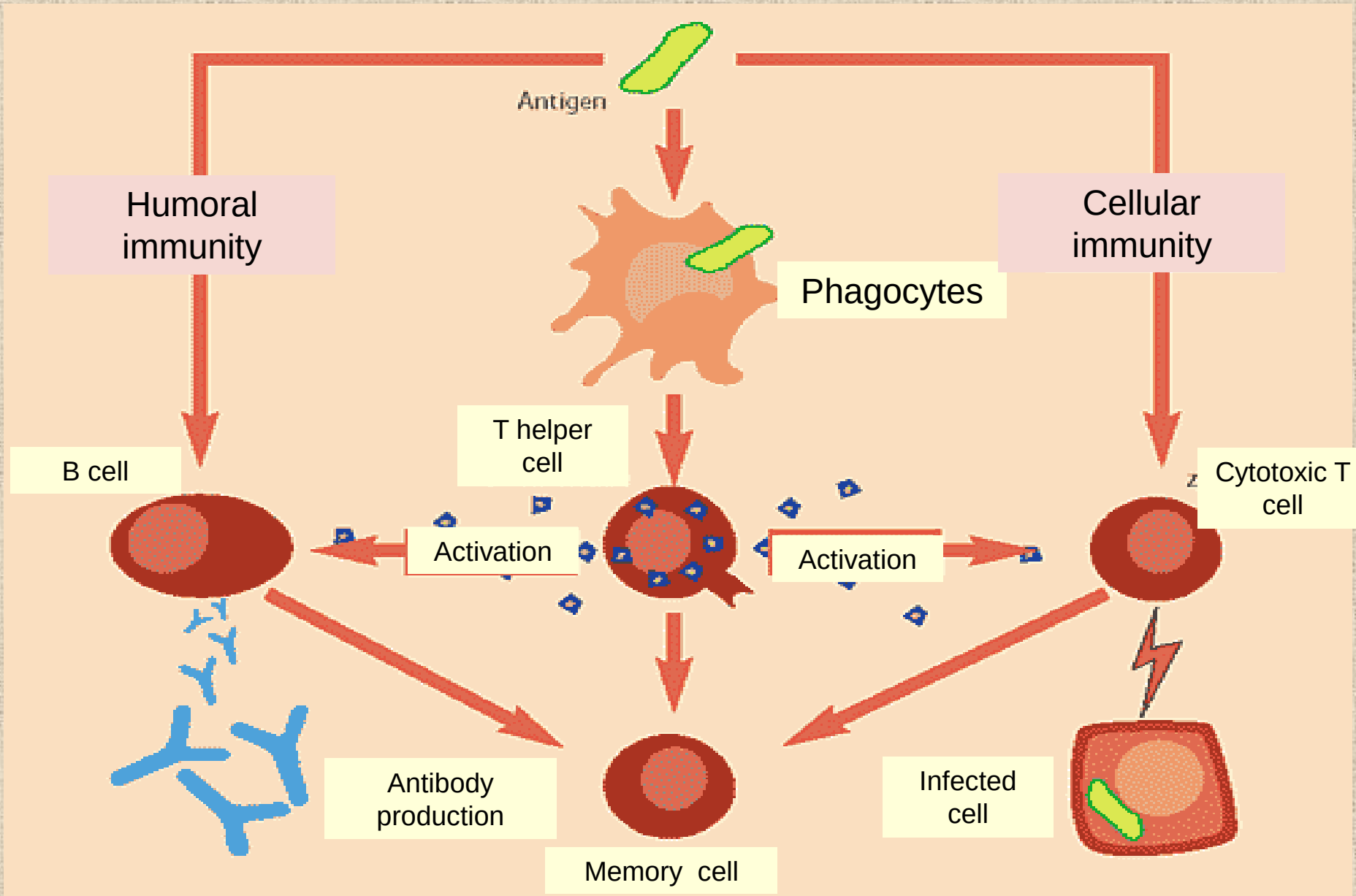

1. Phagocytes in the blood and tissues.
2. Soluble proteins (immunglobulin and complement), bind to microbe surface (opsonisation) to enhace the phagocytosis.



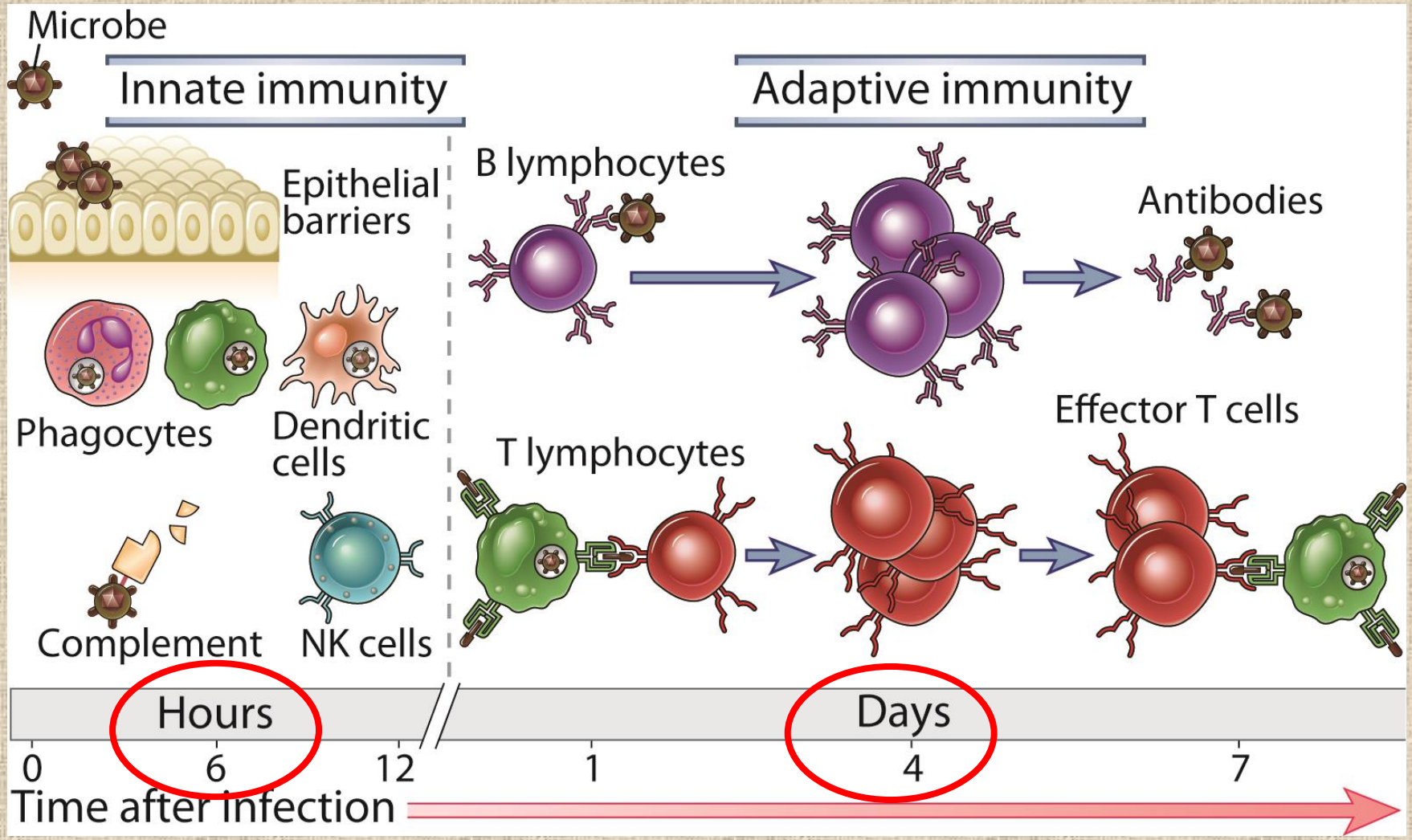
# Functions of innate immunity

- 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



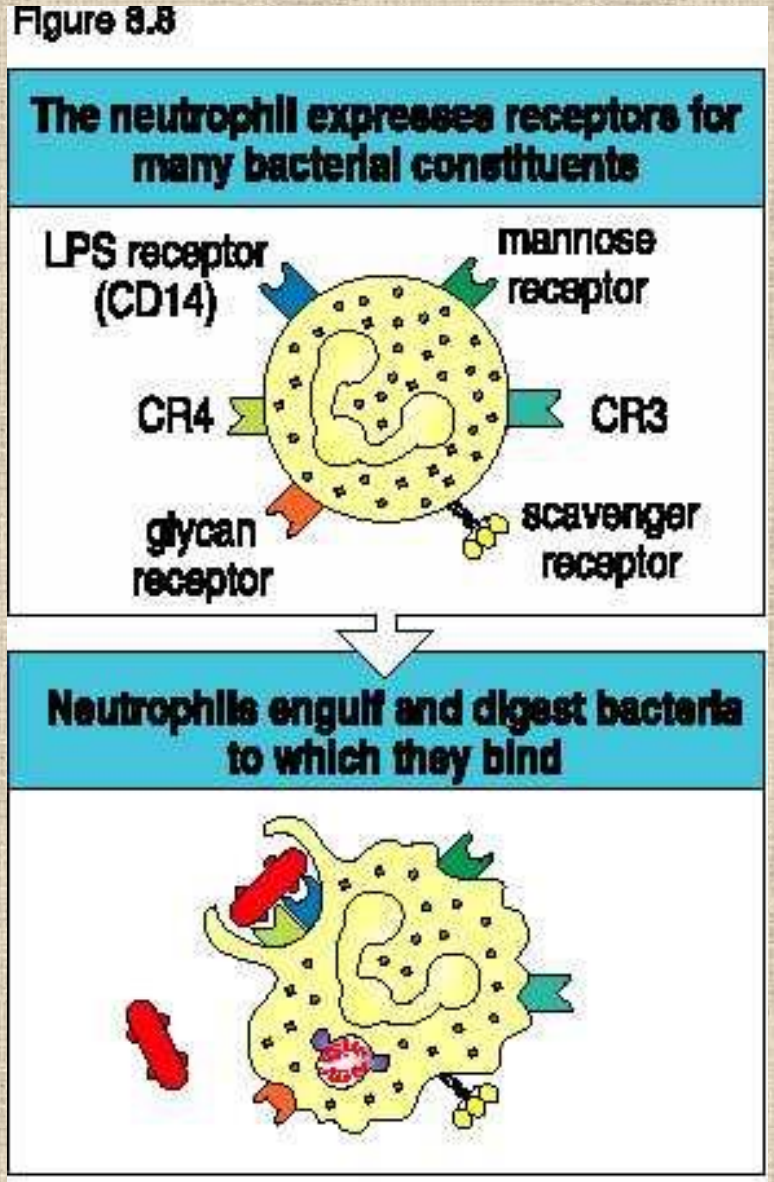
# The kinetics of innate and adaptive immune response




Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

- Different levels of the immune response
- Recognition molecules of innate immunity
- Initiation of local and systemic inflammation
- Extravasation, homing

# Recognition of pathogens, phagocytosis



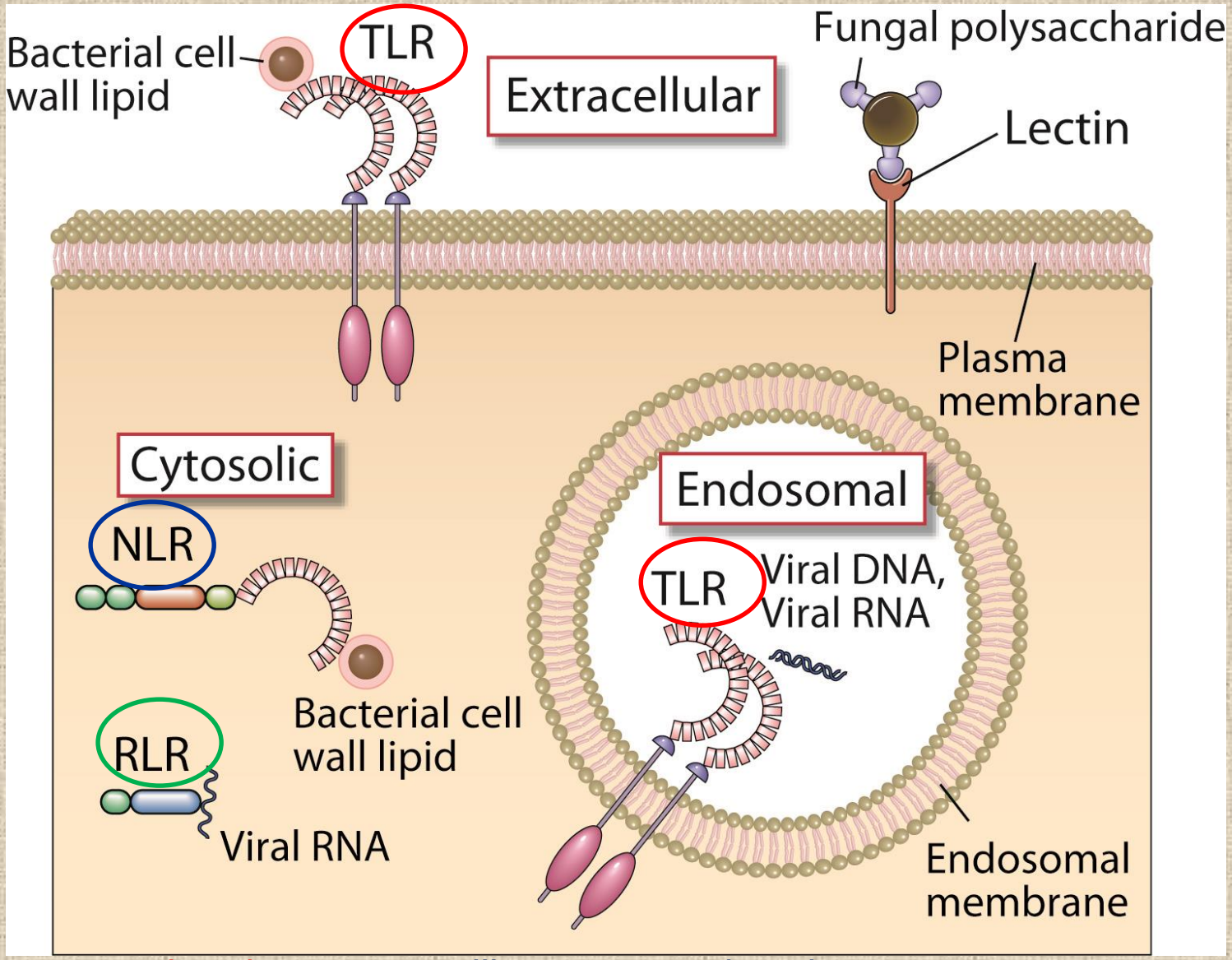

PRR= „Pattern Recognition Receptors”

→Binding to the PAMPS of microbes

PAMP=„Pathogen Associated Molecular Patterns

Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

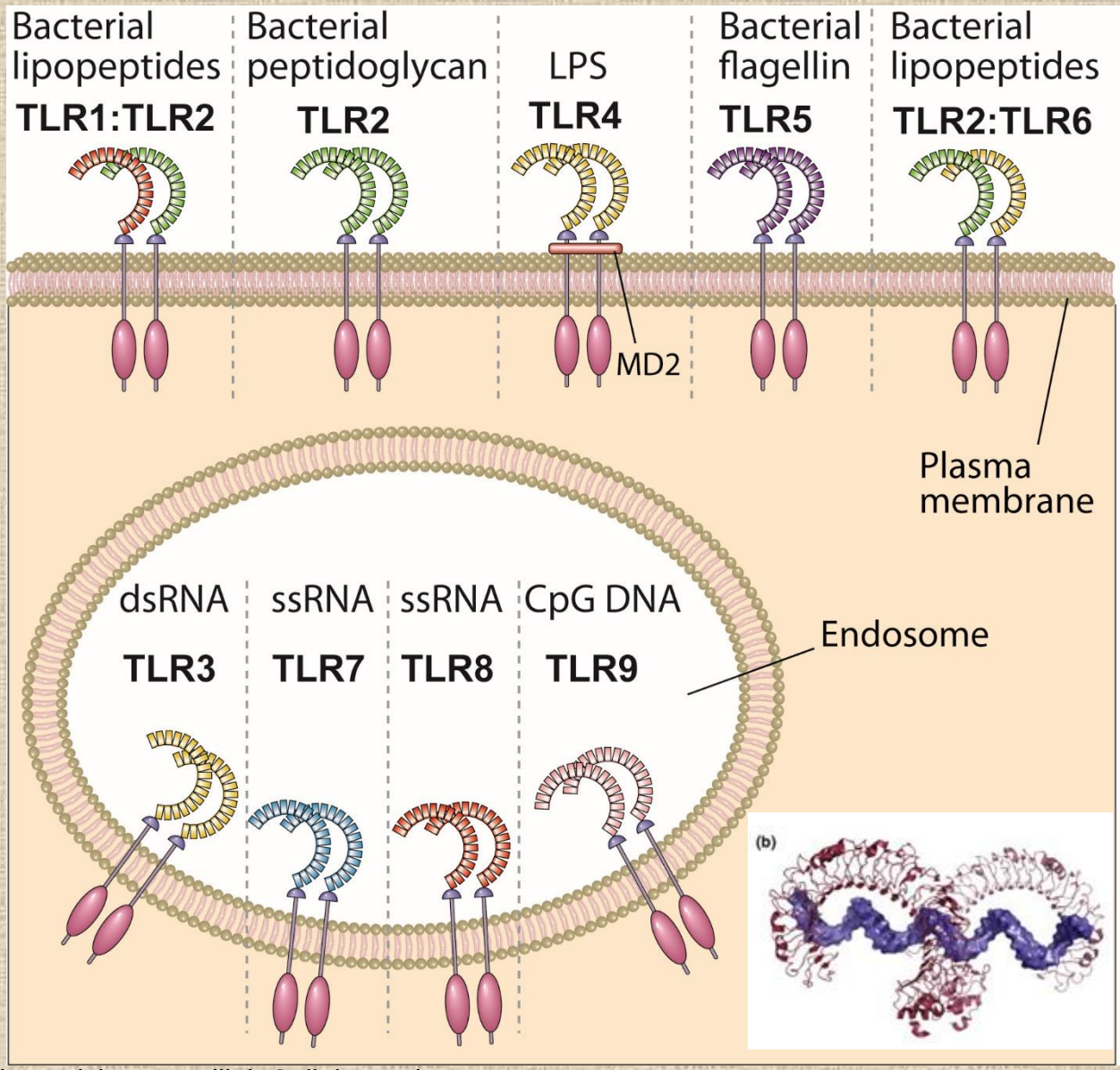
# Pattern recognition receptors

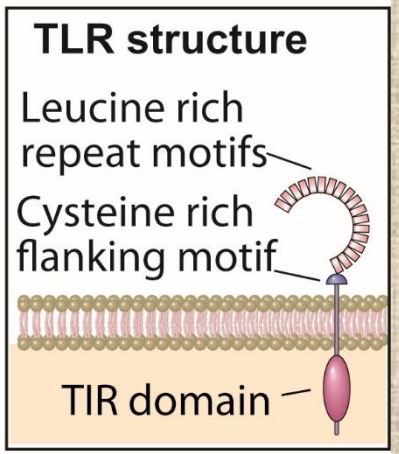



Toll-like receptors (TLR) NOD-like receptors (NLR) RIG-like receptors (RLR)

Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

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

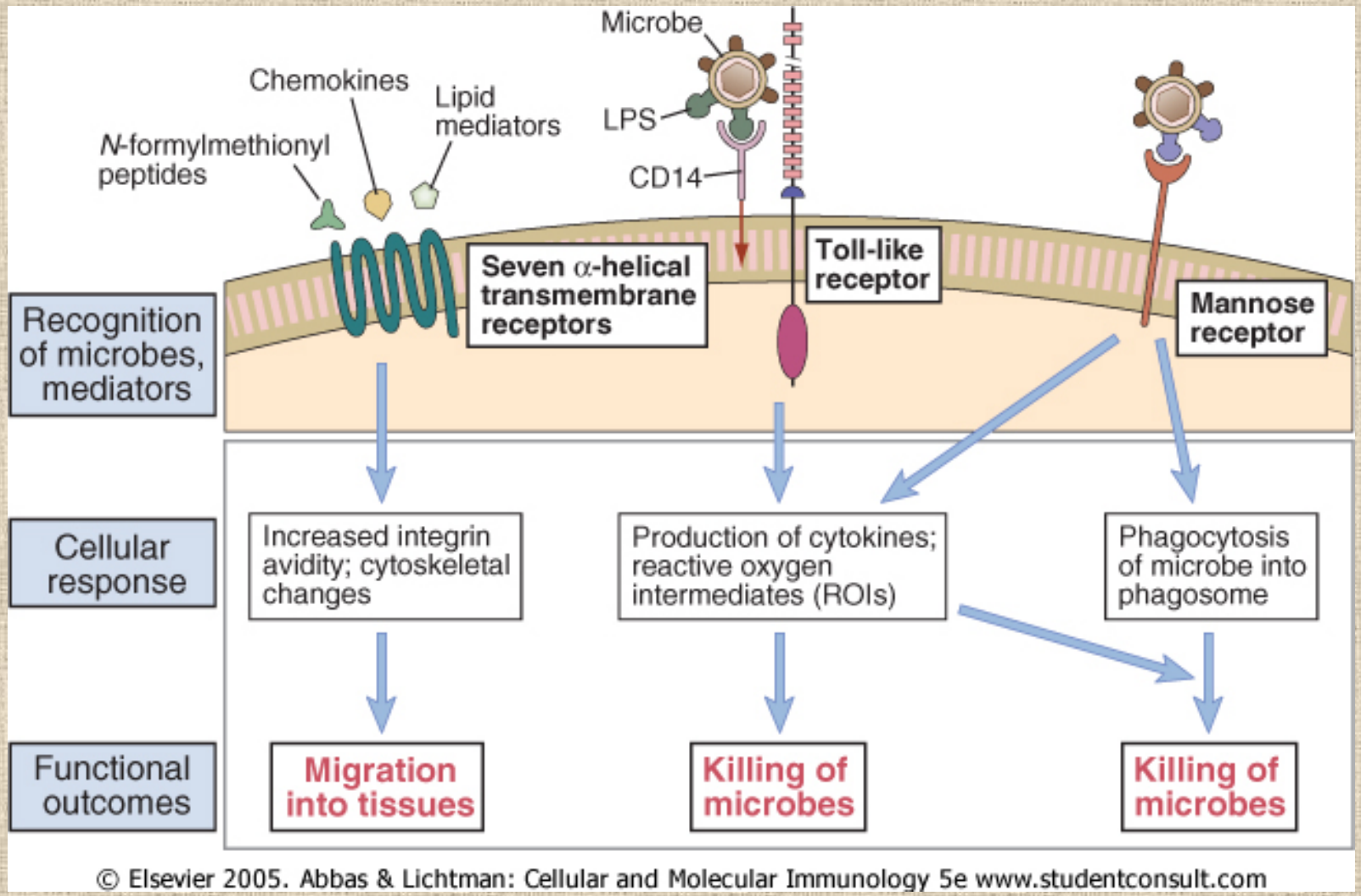



Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

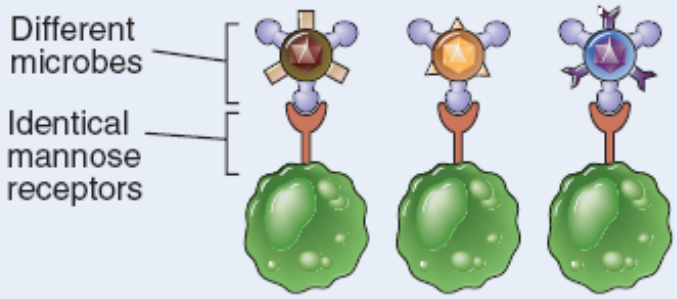
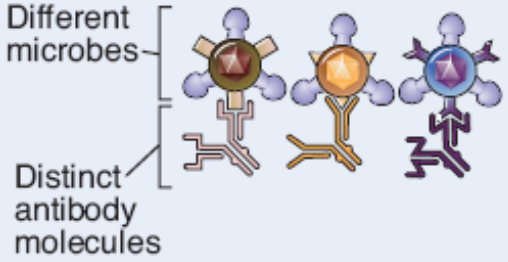
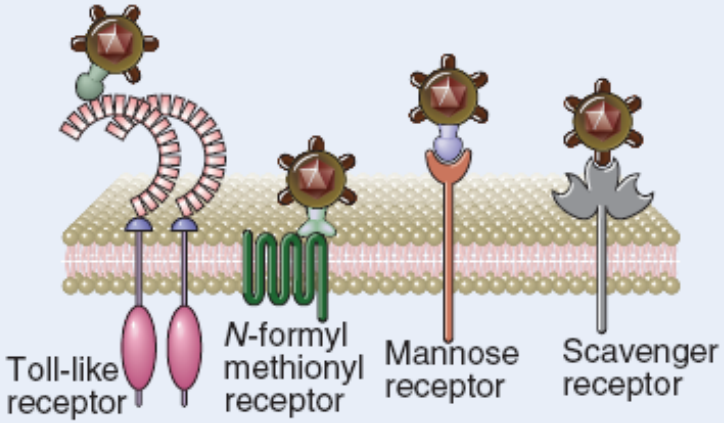
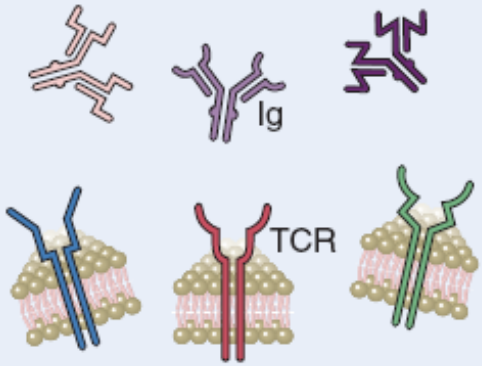
Trends in Biochemical Sciences 2009; 34: 553-561.

# Phagocyte receptors



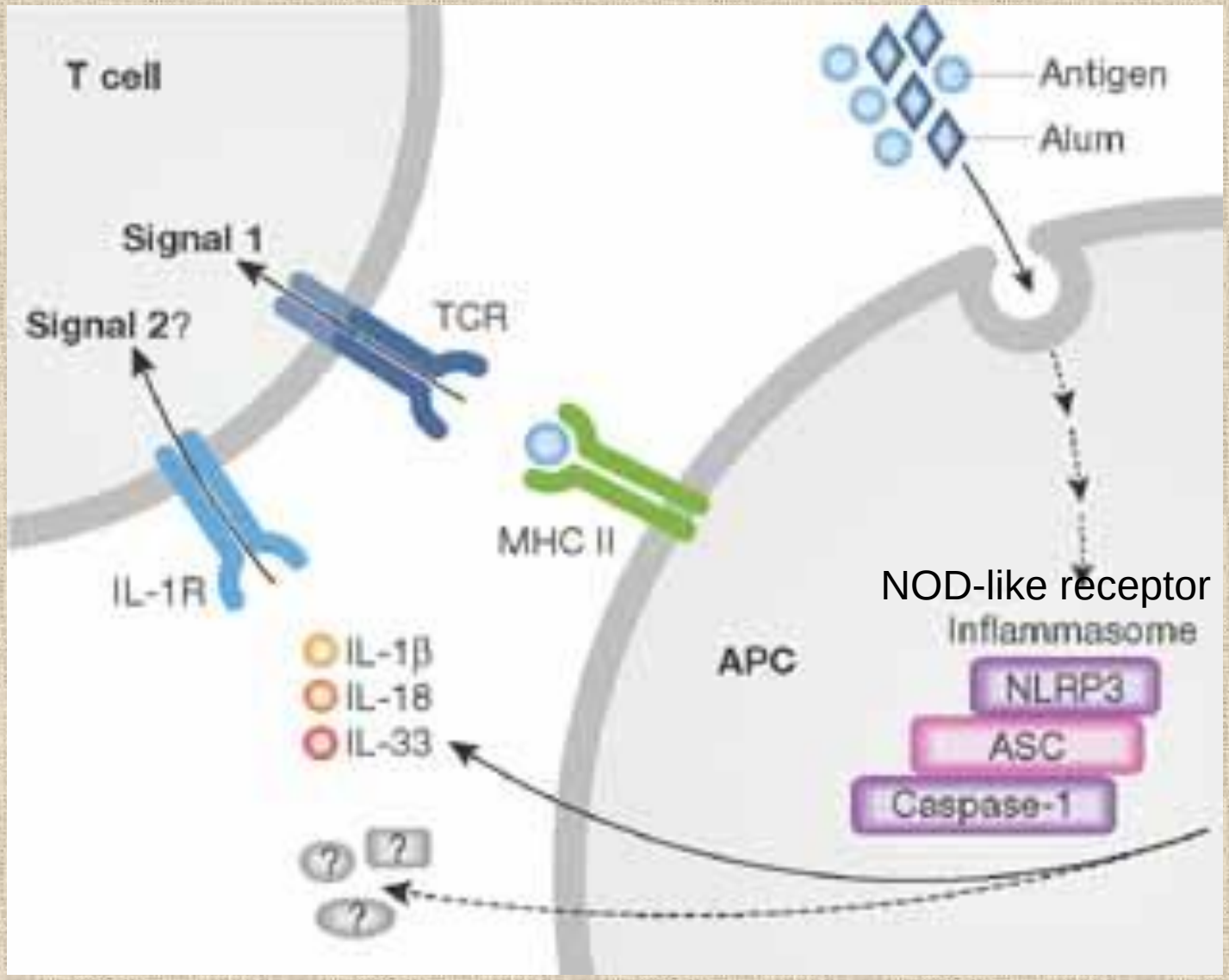

Abbas, Lichtman: Cellular and Molecular Immunology 5th Edition, 2005.

# Specificity of innate and adaptive immunity

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

Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

# Vaccination and the role of adjuvants

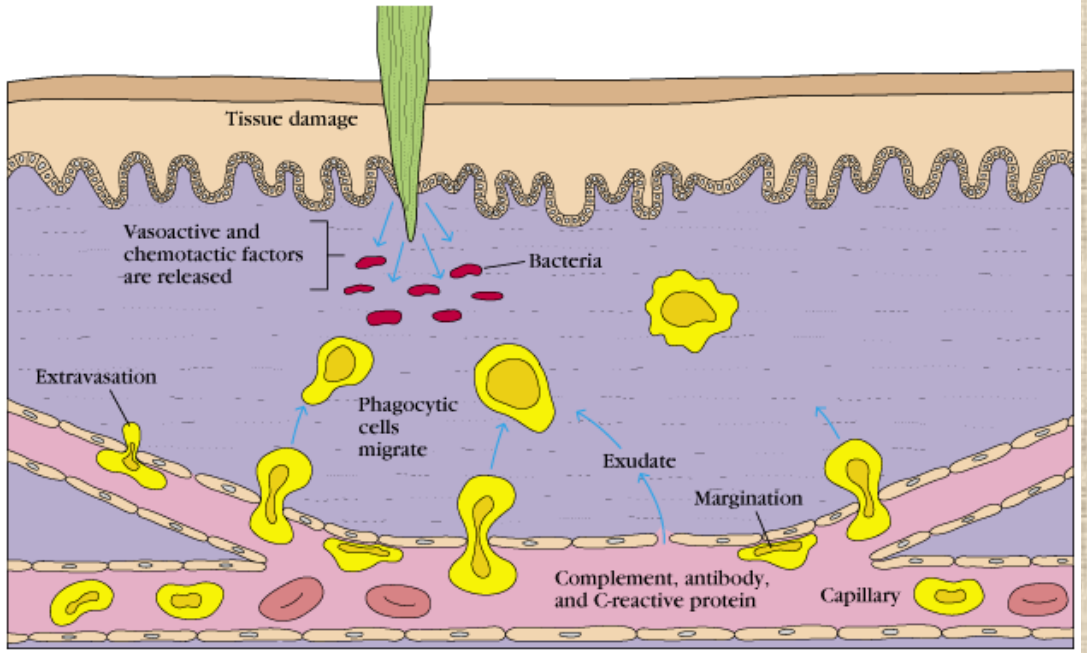



EMBO Mol Med. 2009;1: 92-8.

- Different levels of the immune system
- Recognition molecules of the innate immunity
- Local and systemic inflammation
- Extravasation, homing

# **Acute inflammation**:

- Infection or tissue-injury initiate the cascade of non-specific reactions
- Immediate reaction
- its role to inhibit the spreading of infection and tissue injury




Celsus: 4 signs of inflammation: - rubor (red), calor (hot), dolor (painfull), tumor (swelling) + functio laesa (loss of function)

3 main events:
- Vasodilation – w/in minutes
- higher capillary permeability, fluid efflux, initation of oedema
- Phagocytes migration: - hours

Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

# Molecular mediators of inflammation

Plasma enzyme mediators:

- kinin kallikrein system
- Fibrinolytic system
- Complement cascade
- Clotting cascade

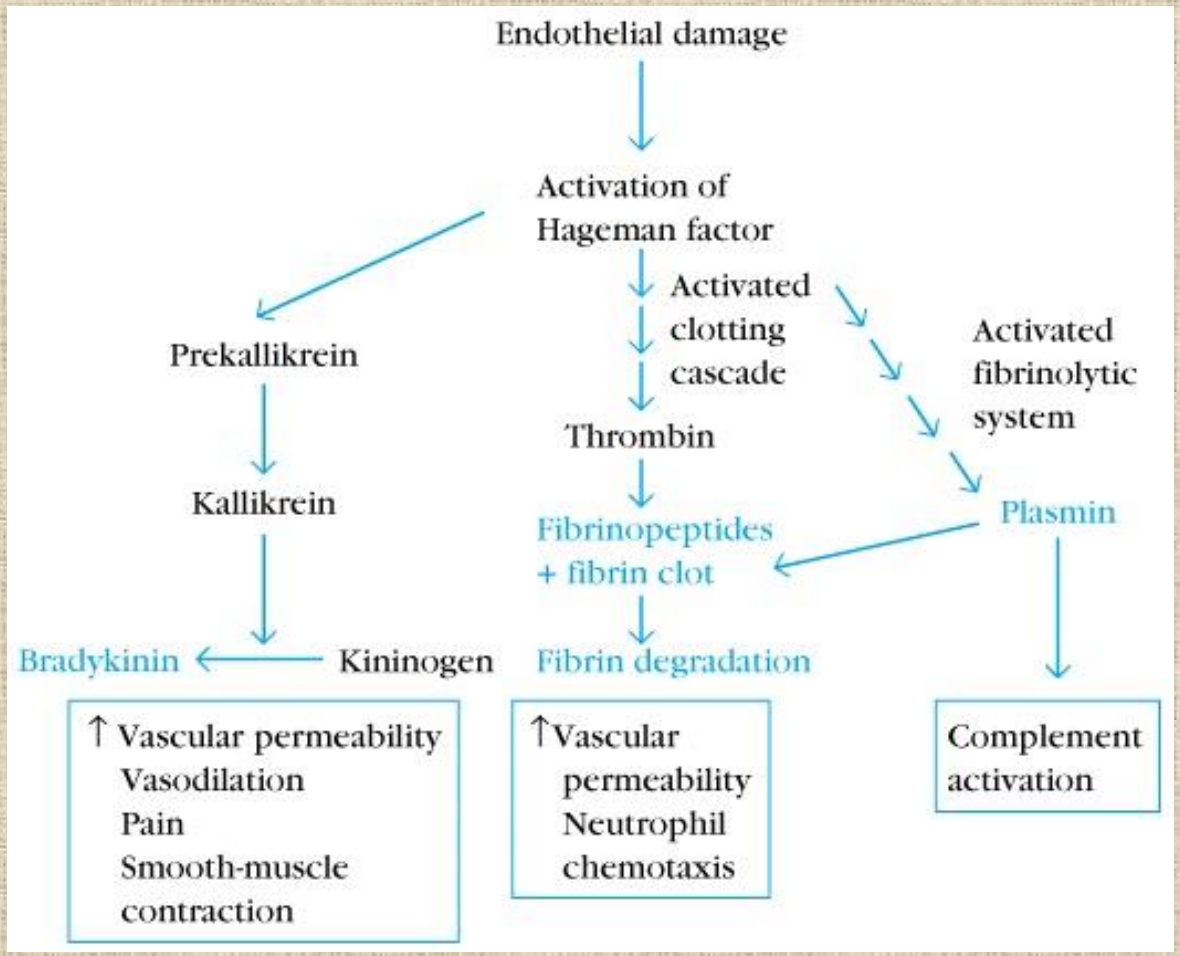
Lipid mediators:

leukotrienes,
prostaglandins (PGE)

Chemoattractants:

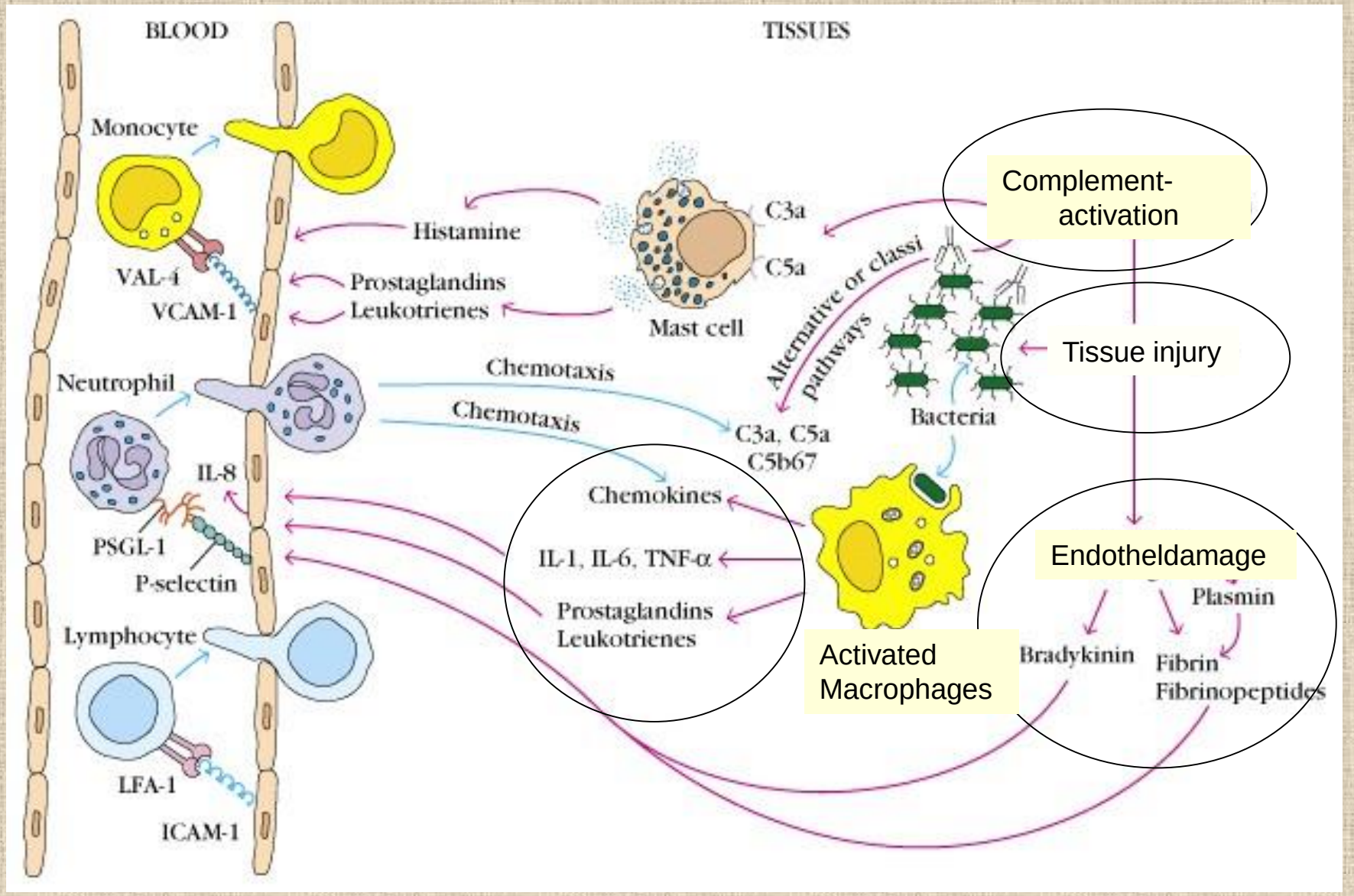
-Chemokines: IL-8
-Complement components
- PAF (platelet activating factor)

Inflammatory cytokines




Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

# Initation of acute inflammation




Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

- Different levels of the immune response
- Recognition molecules of the innate immunity
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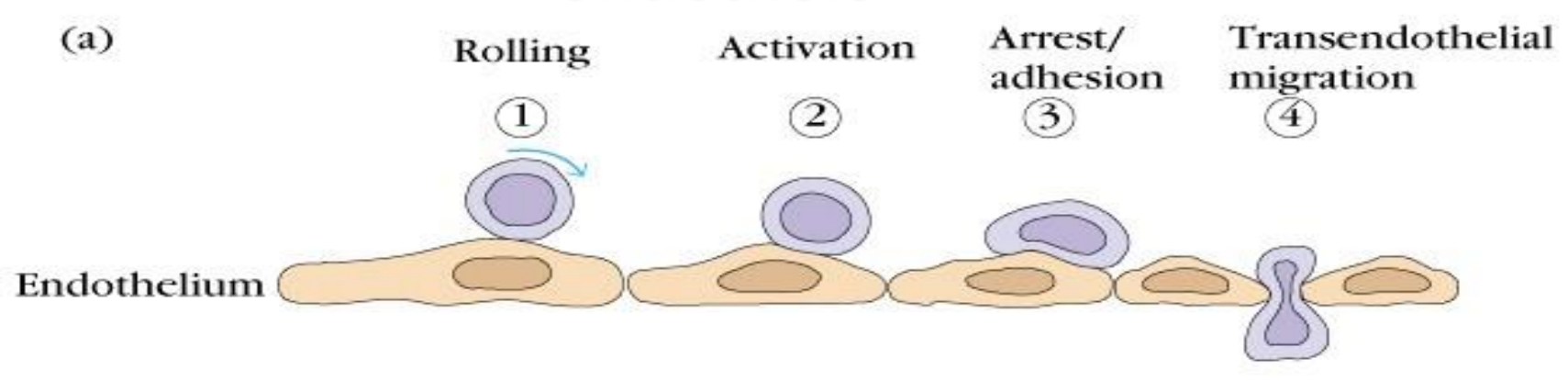
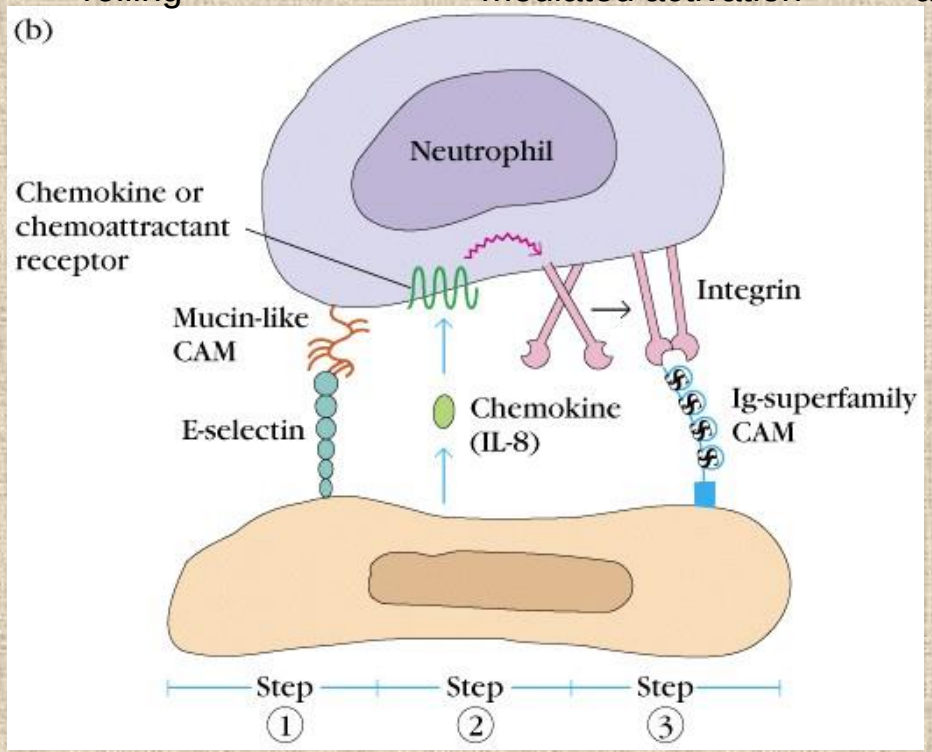
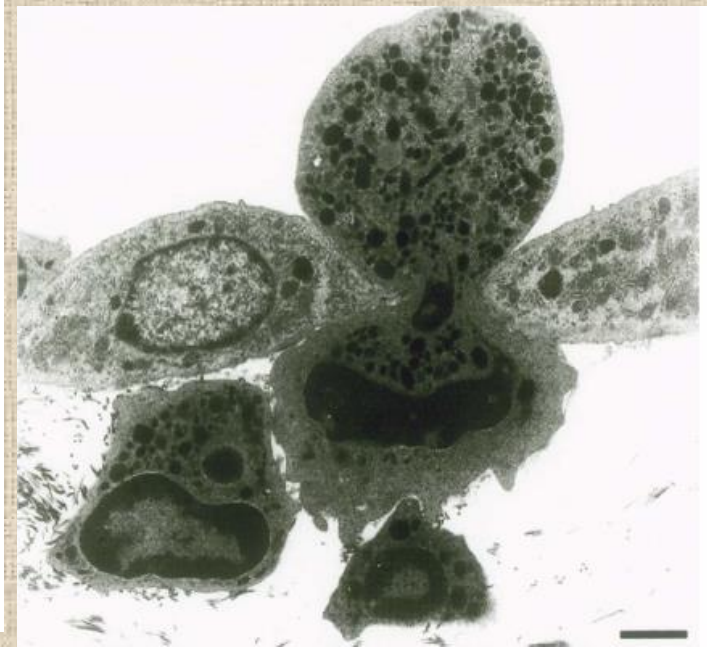
# Neutrophils extravasation through the inflamed endothels



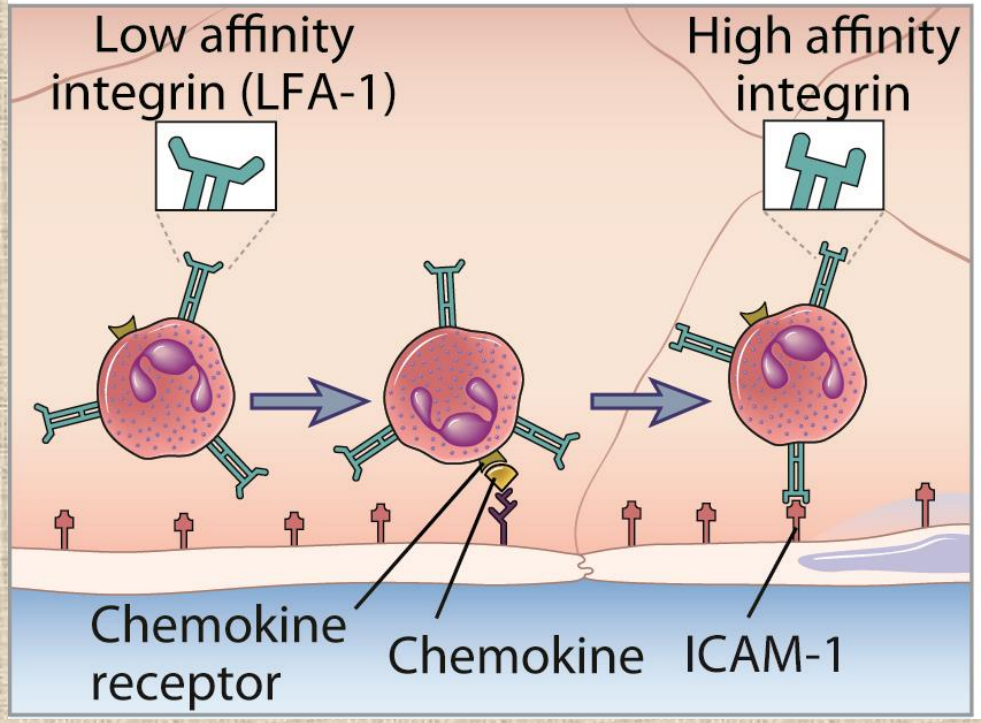

1. Selectin-mediated rolling
2. Chemoattractant mediated activation
3. Integrin-mediated adhesion
4. Transendothelial migration

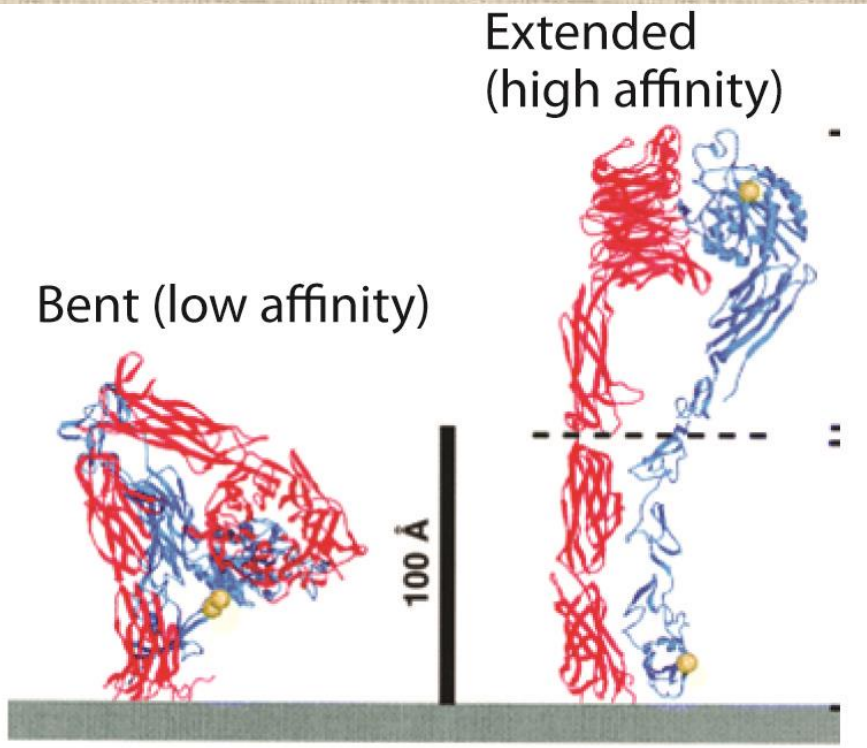


Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

# Chemokines accelerate conformational changes in integrins




Leukocyte functional antigen 1 (LFA-1)

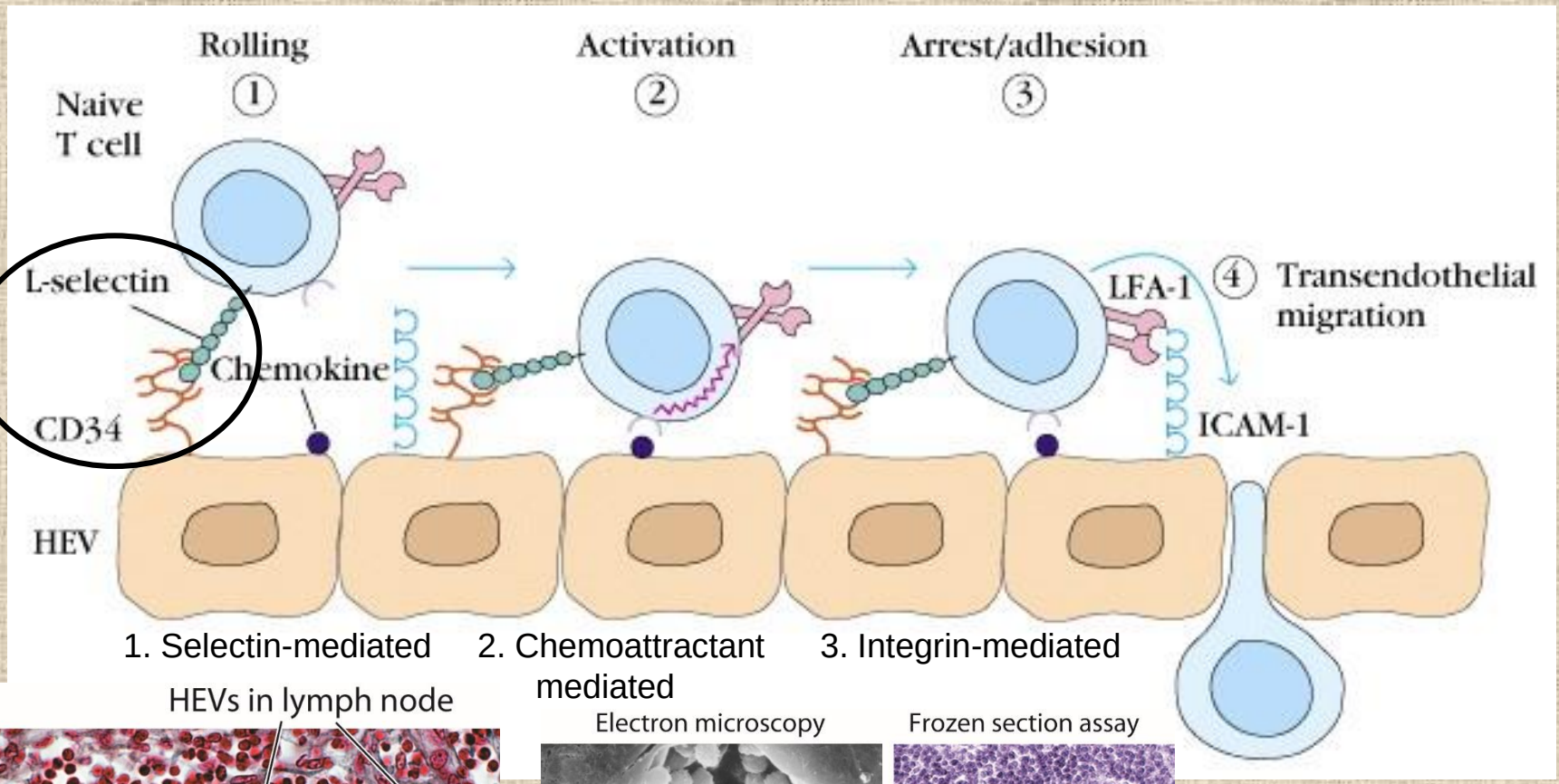
↕

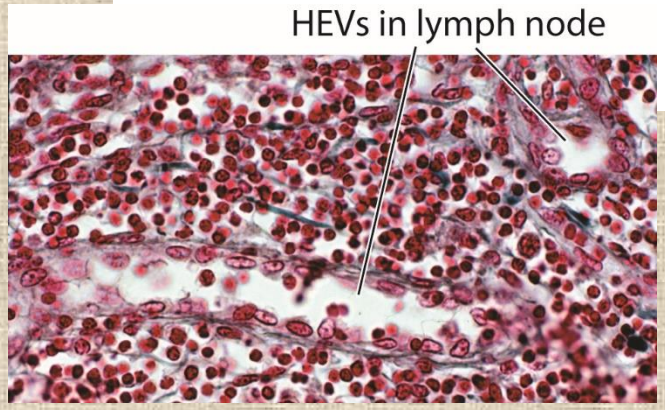
Intercellular adhesion molecule 1 (ICAM-1)

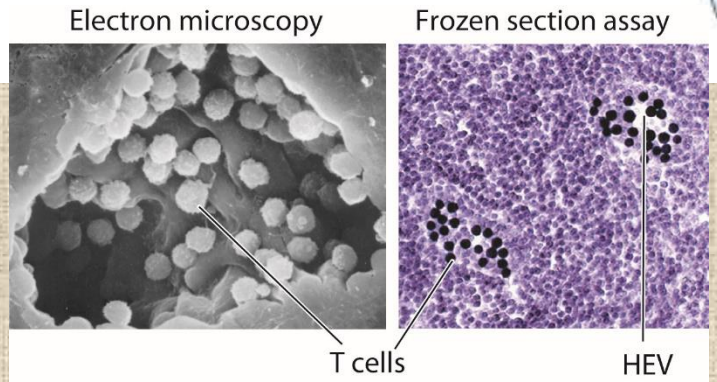
Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

# Naive lymphocytes migrate into the peripheral lymphoid tissues:

Role of high endothel venules (HEV) and adhesion molecules:



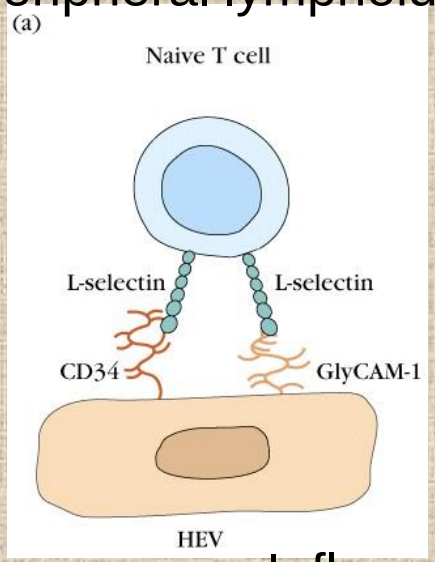



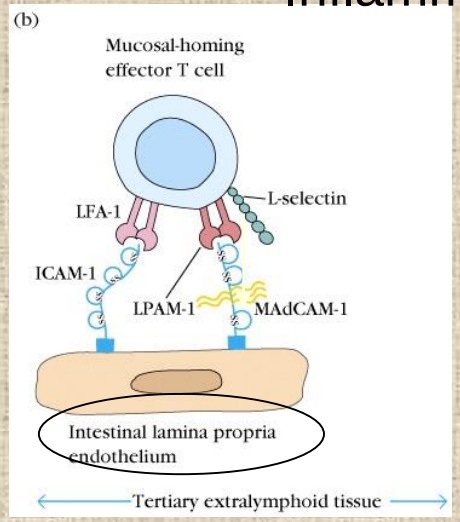

Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000

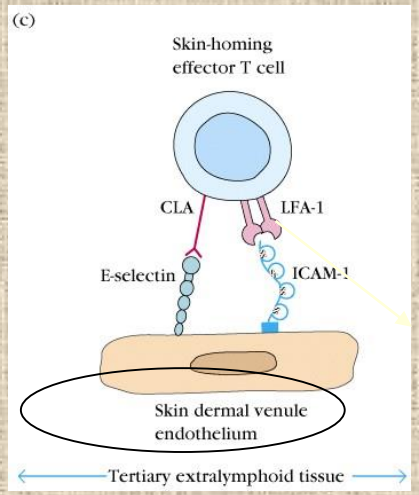
# Different adhesion molecules determine the migration of naive and memory (effector) cells

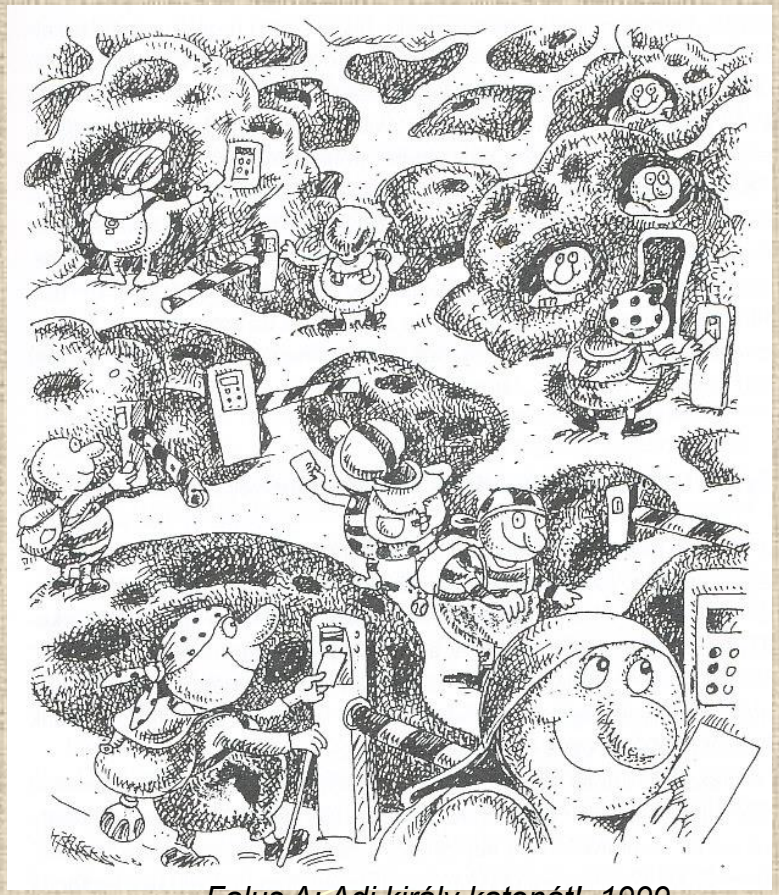
Peripheral lymphoid tissue




Inflammatory tissue



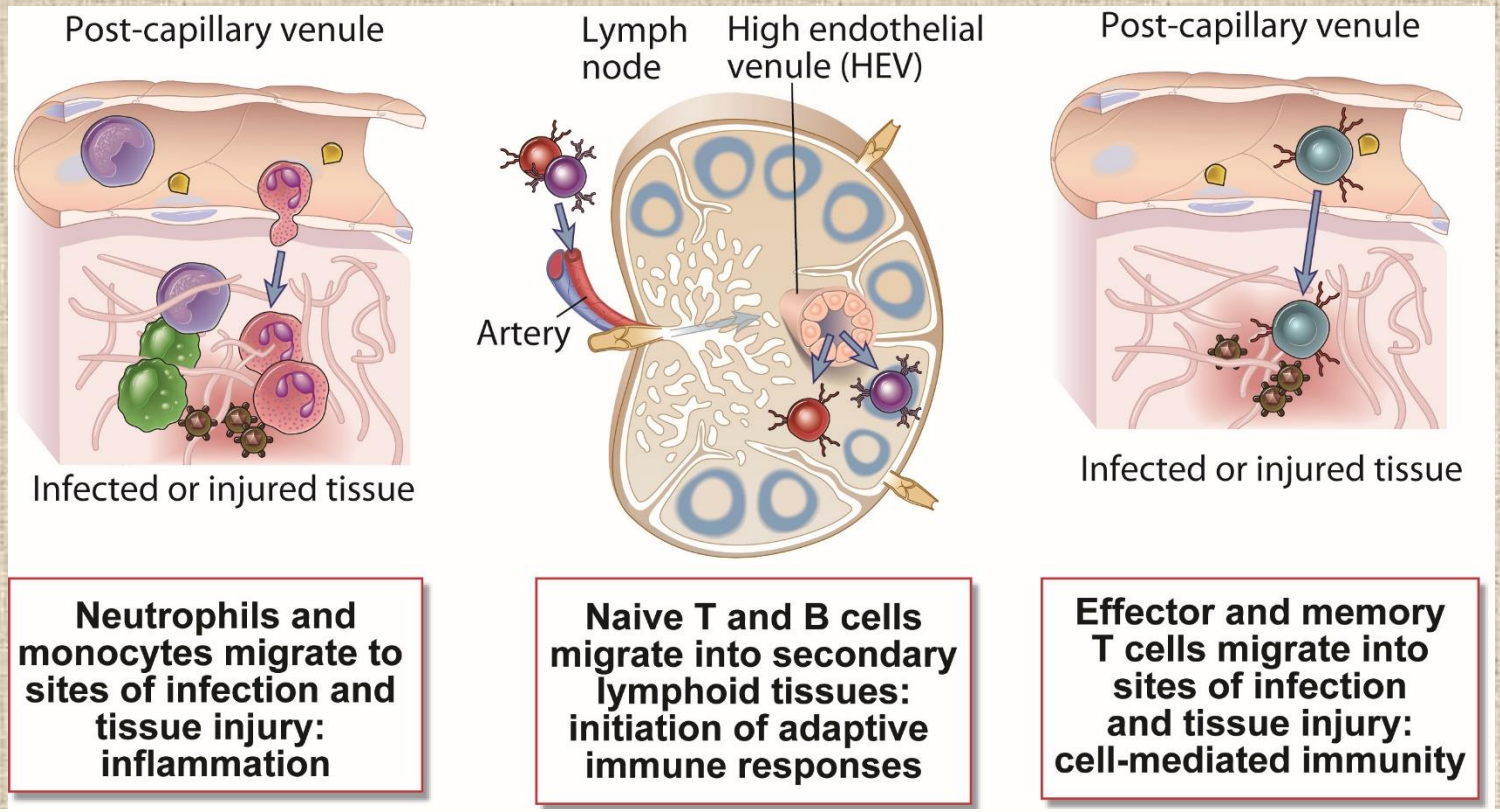



*Falus A: Adj király katonát!, 1999.*

Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

# **Lymphocyte recirculation**: continous 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:

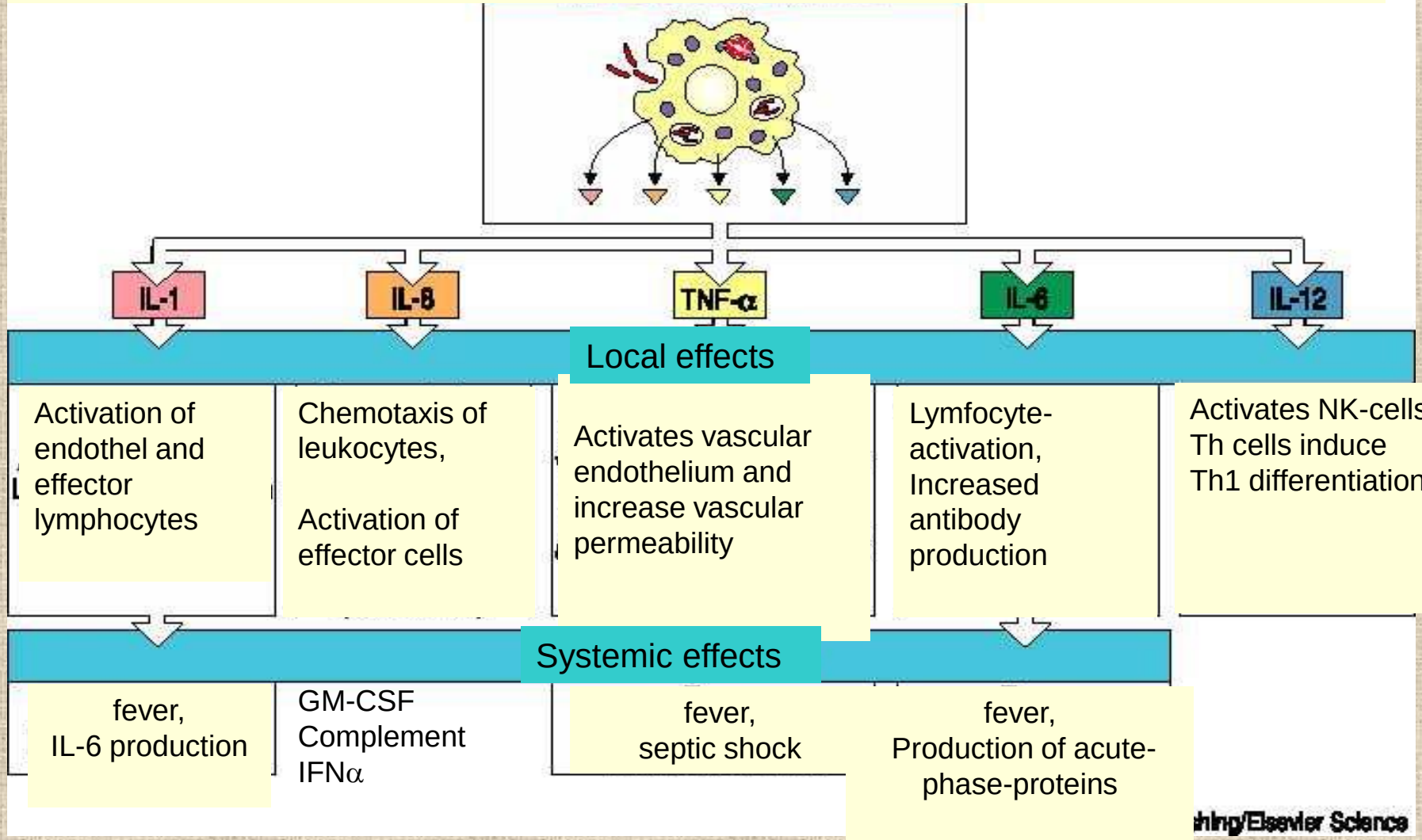
-Extravasation: adhesion then transmigration of leukocytes through the endothel from the bloodgflow into the tissue.

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

Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

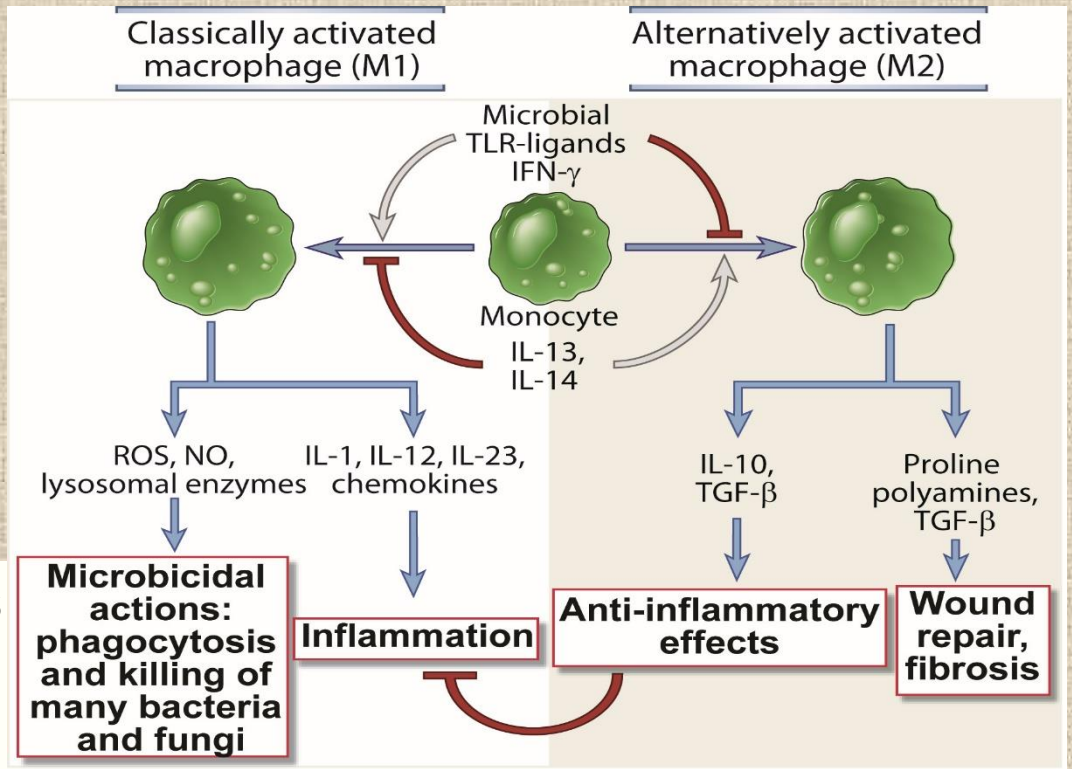
# Role of macrophages in acute inflammation I

LPS originated from Gram – bacterium LPS activates the macrophages, those produce various cytokines




Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

# Role of macrophages in acute inflammation II: classical and alternative activations




## Classical activation

Resting macrophage: → Phagocytosis

↓ LPS

Activated macrophage: → antigenpresentation, MHCII ↑
cytokine-production

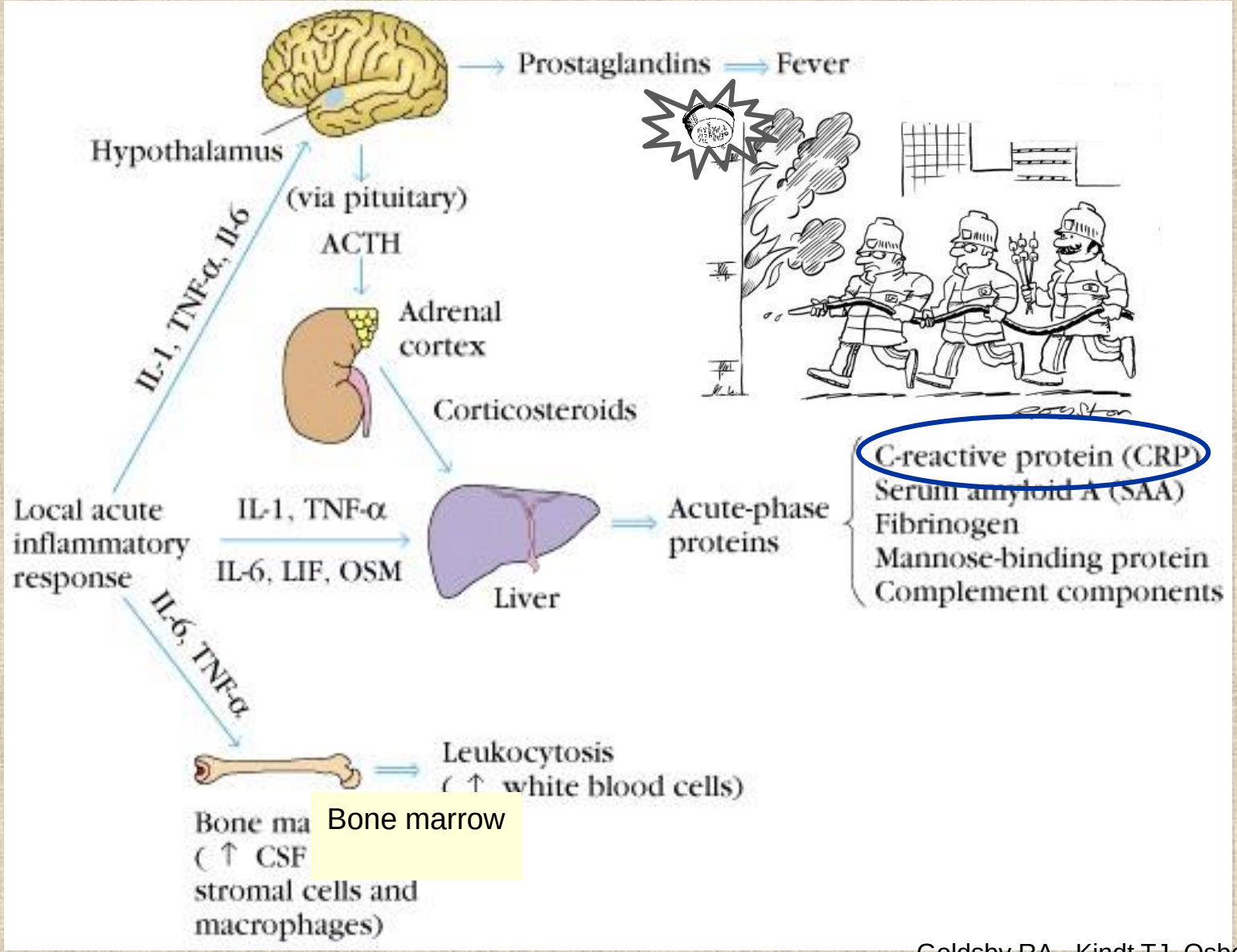
↓ IFNγ

Hyperactivated macrophage: → citotoxicity MHCII ↓
(TNFα)

Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

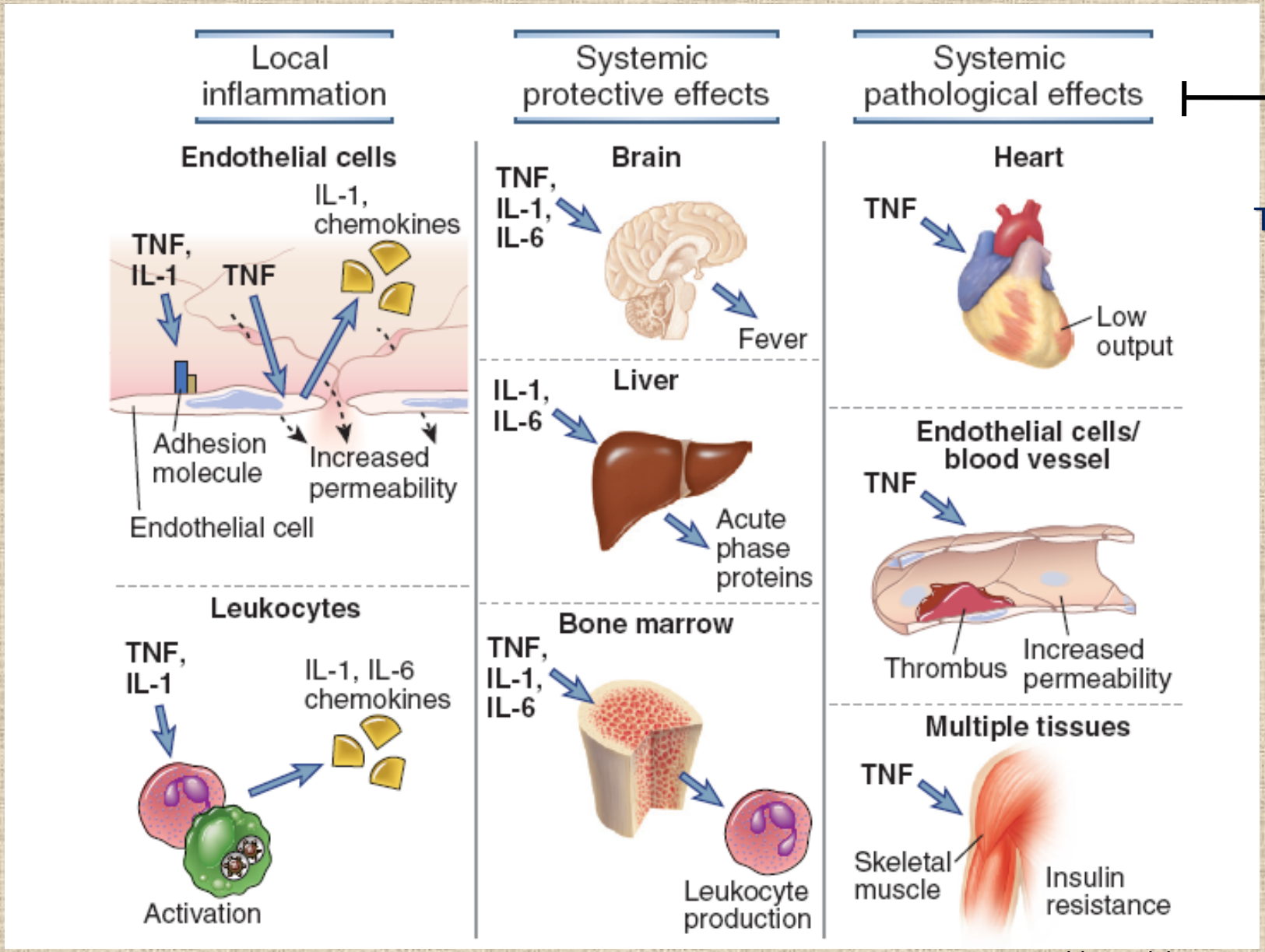
Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

# Systemic acute inflammation = acute phase reaction



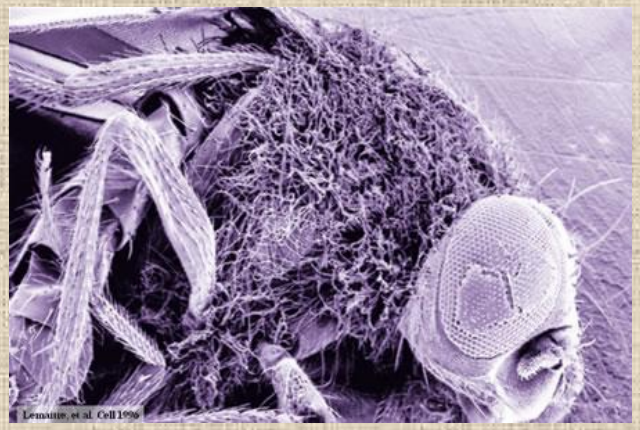

Goldsby RA, Kindt TJ, Osborne BA: Kuby Immunology 4th Edition, 2000.

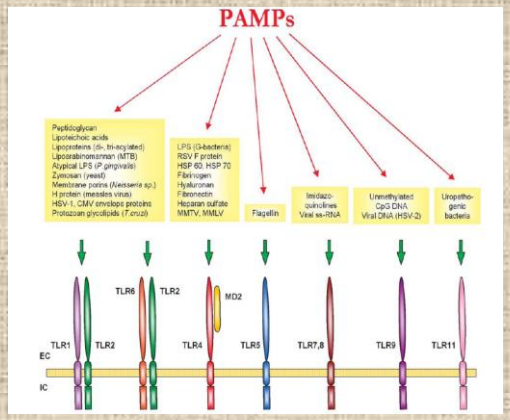
# Acute inflammation / Chronic inflammation

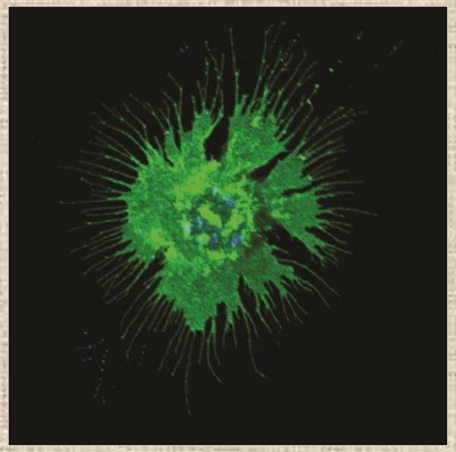



Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

# Nobel Laureates in 2011 for medicine and physiology

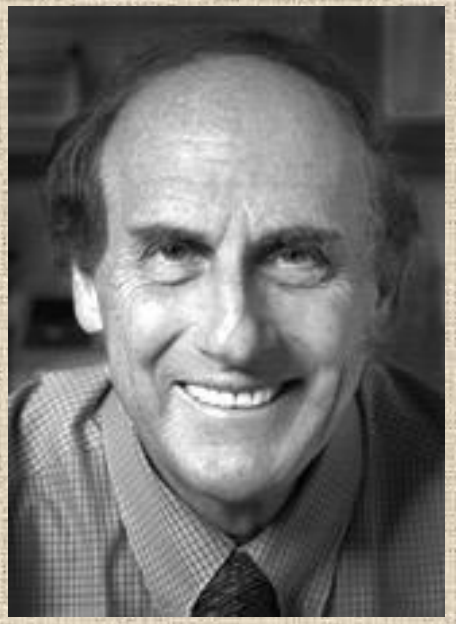




Jules A. Hoffmann

Bruce A. Beutler



Ralph M. Steinmann