Innate Immunity and Inflammation

ایمنی ذاتی و التهاب

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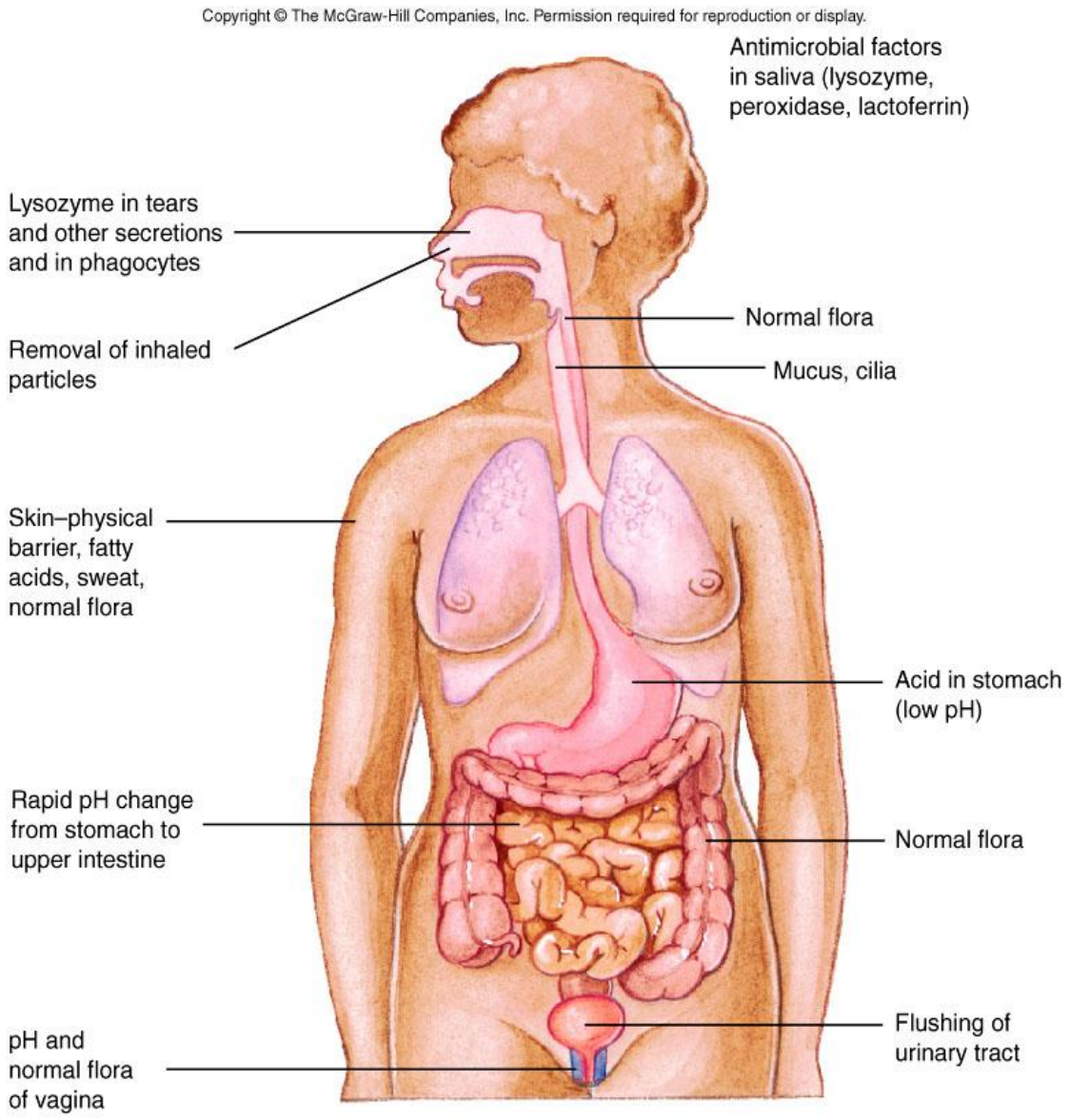
Roles of innate immunity

- Innate immunity is the first line of host defense against infections (immediately upon infection).
- The innate immune response also instructs the adaptive immune system to respond to different microbes in ways that are effective for combating these microbes.
- Innate immunity is a key participant in the clearance of dead tissues and the initiation of repair after tissue damage

Innate immunity distribution



موانع اولیه در ایمنی ذاتی

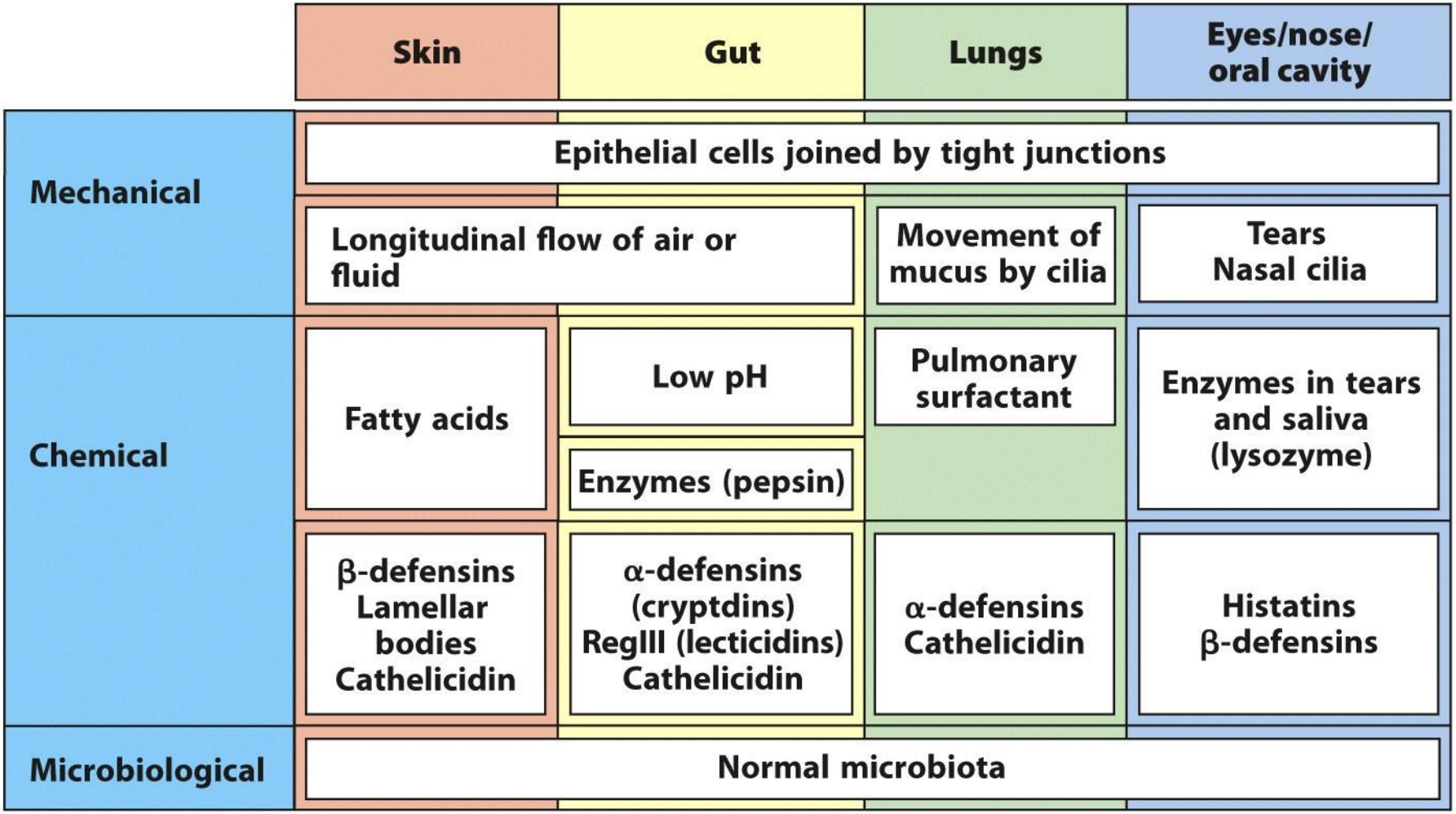


Figure 2.6 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

General features and specificity of innate immune responses

- The two principal types of reactions of the innate immune system are inflammation and antiviral defense.

- Innate immune defense against intracellular viruses, even in the absence of inflammation, is mediated by natural killer (NK) cells, which
  - kill virus-infected cells,
  - block viral replication within host cells by cytokines called type I interferons.

General features and specificity of innate immune responses

- Innate immune receptors are specific for structures of microbes that are often essential for the survival and infectivity of these microbes.

- The innate immune system also recognizes molecules that are released from damaged or necrotic host cells. Such molecules are called damage-associated molecular patterns (DAMPs).

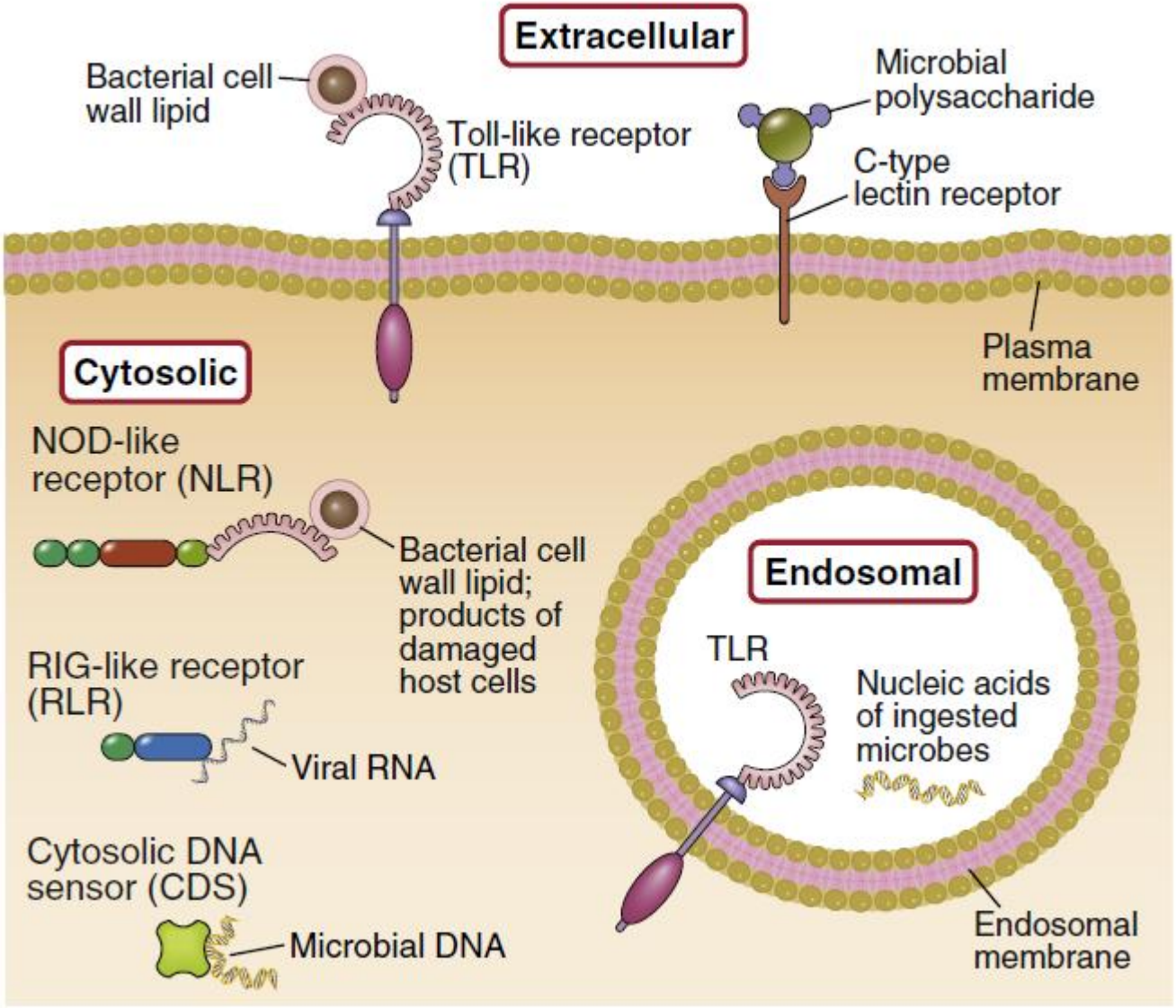
TABLE 4–2 Examples of PAMPs and DAMPs

Pathogen-Associated Molecular Patterns		Microbe Type
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	CpG	Virus, bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Dectin glucans	Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	
Crystals	Monosodium urate	
Nuclear proteins	HMGB1	

CpG, cytidine-guanine dinucleotide; dsRNA, double-stranded RNA; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; LPS, lipopolysaccharide; ssRNA, single-stranded RNA.

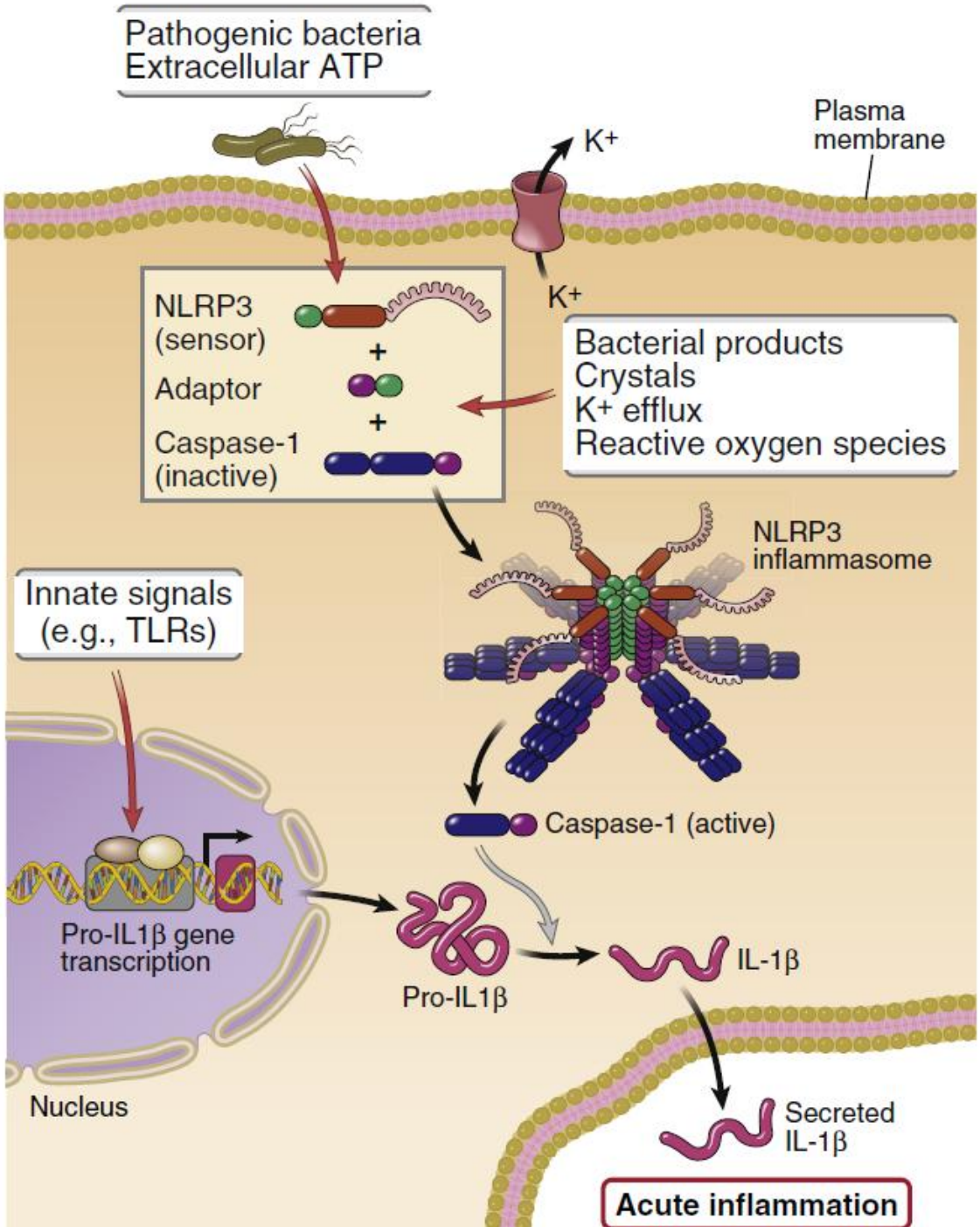
Cellular receptors for microbes and damaged cells

Cellular locations of receptors of the innate immune system



The inflammasome:

Inflammasomes are multiprotein complexes that assemble in the cytosol of cells in response to microbes or changes associated with cell injury, and proteolytically generate active forms of the inflammatory cytokines IL-1β and IL-18.



COMPONENTS OF INNATE IMMUNITY

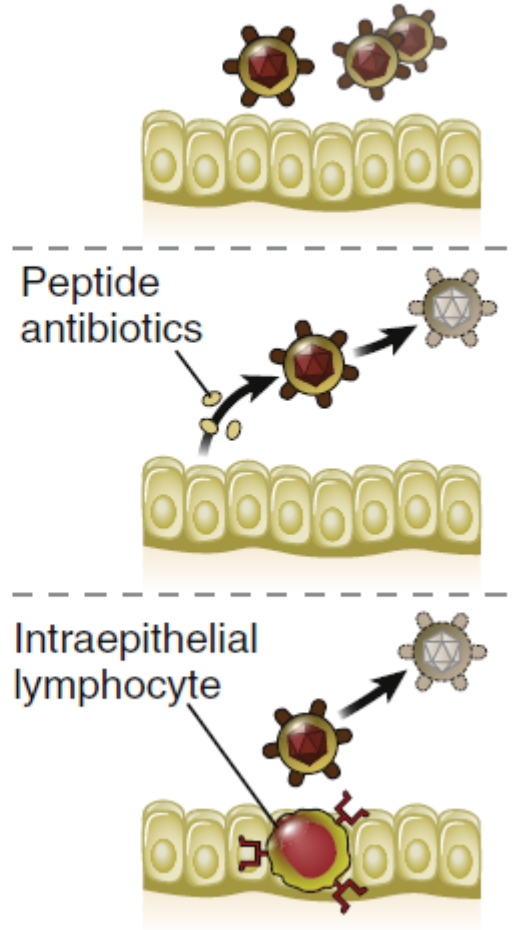
- Epithelial Barriers
- Phagocytes: Neutrophils and Monocytes/Macrophages
- Dendritic Cells
- Mast Cells
- Innate Lymphoid Cells
- Natural Killer Cells
- Lymphocytes with Limited Diversity

Functions of epithelia in innate immunity

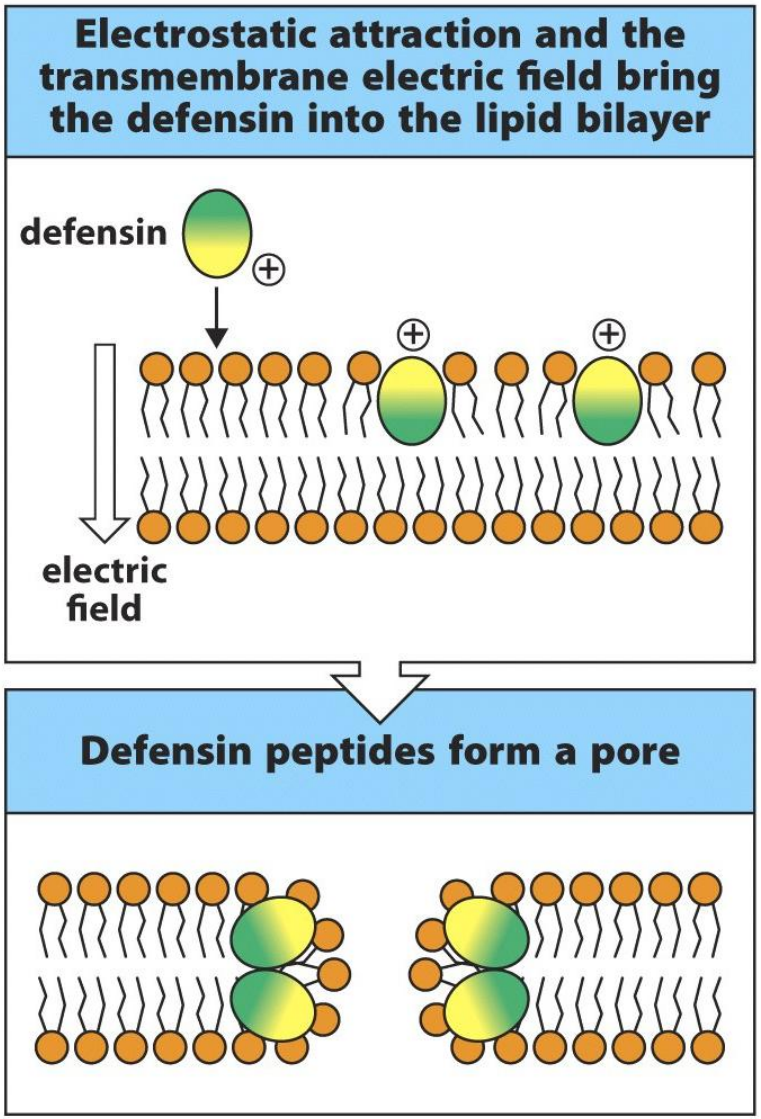
Physical barrier to infection

Killing of microbes by locally produced antibiotics

Killing of microbes and infected cells by intraepithelial lymphocytes



پپتیدهای ضد میکروبی



- دیفنسینها:

- سلول هاي اپي تليال در سطوح مخاطي
- گرانولوسیت
- توکسیسیته مستقیم براي عوامل باکتریایي، قارچي

- کاتلیسیدینها:

- توکسیسیتی مستقیم
- خنثی سازی LPS

- هیستاتینها:

- مایعات سروزی و بزاق

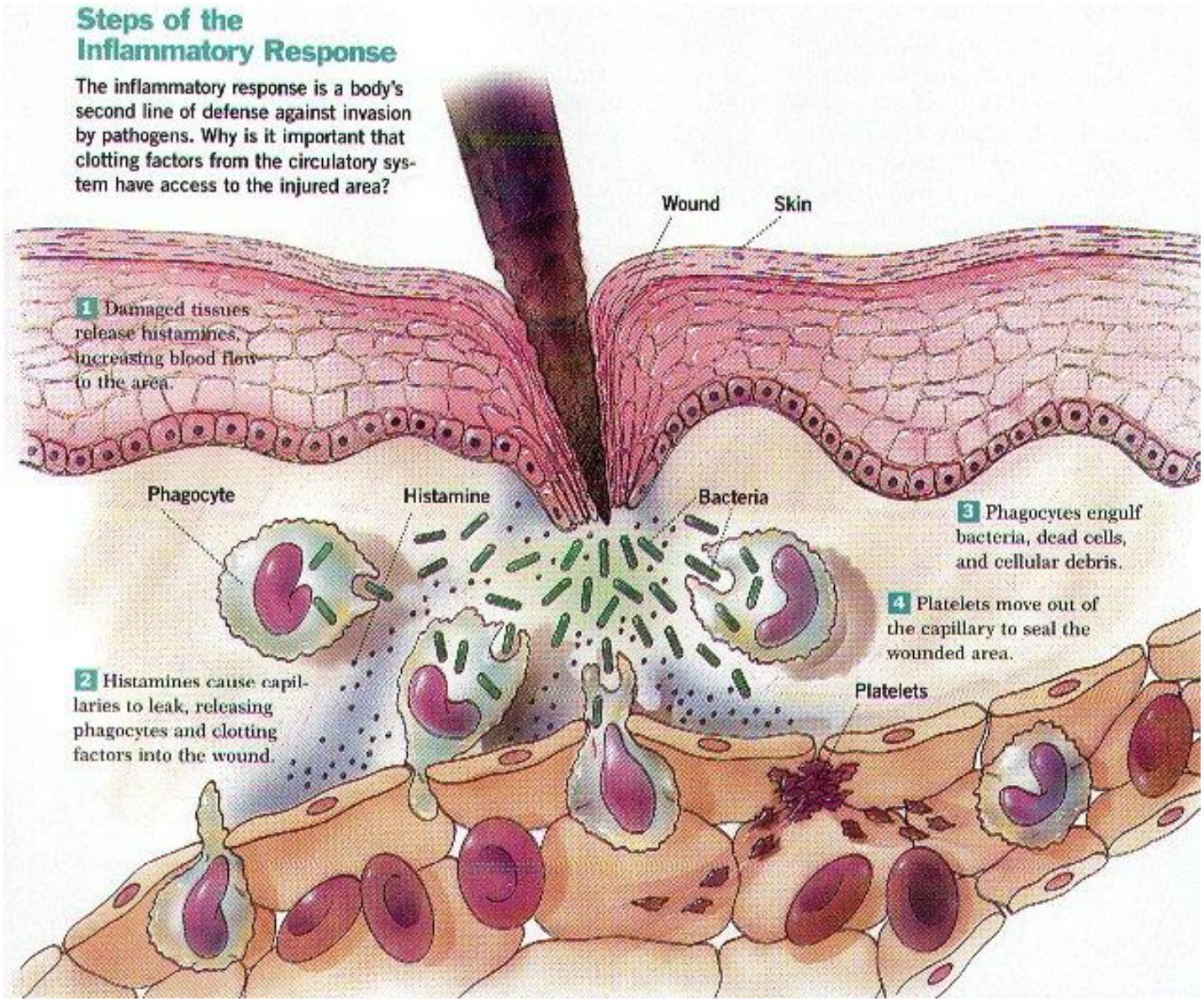
Inflammation

Inflammation

- Pathology:
- Inflammation is the reaction of blood vessels, leading to the accumulation of fluid (serum) and leukocytes in extra vascular tissue.

- Immunology:
- Inflammation is the body's attempt at **self-protection**; the aim being to remove harmful stimuli, including damaged cells, irritants, or pathogens - and begin the **healing** process.

Inflammation

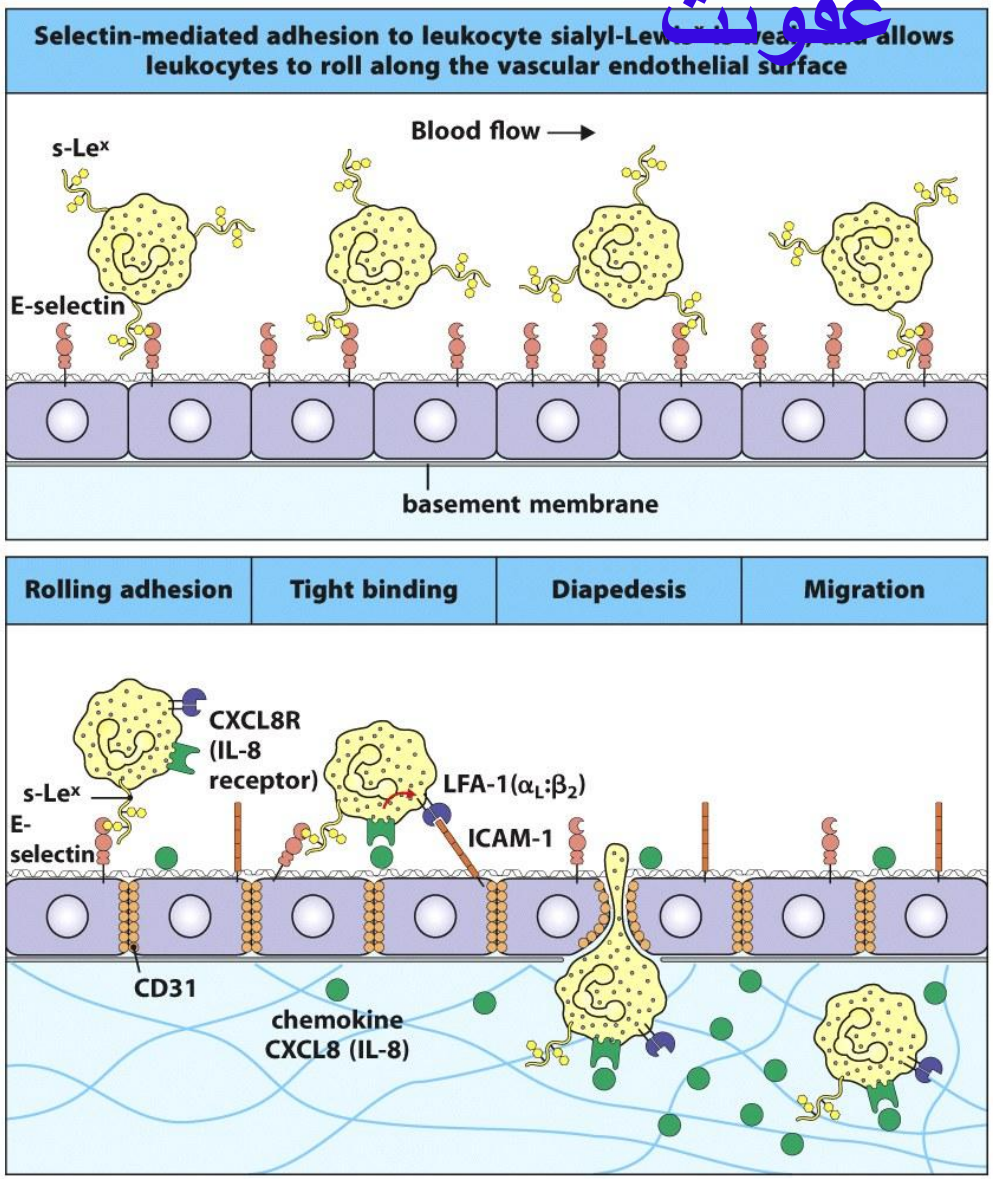


Inflammation

- *Inflammation* results in:
  - Increased blood supply to the area.
  - Increased capillary permeability.
  - Migration of leukocytes into the surrounding tissue.

- These three events manifest symptoms which include pain, heat, redness and swelling.

مهاجرت نوتروفیلها و مونوسیتها به محل عفونت



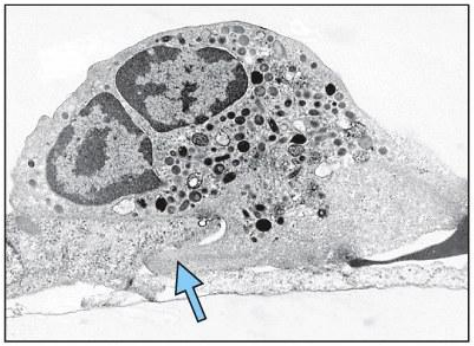
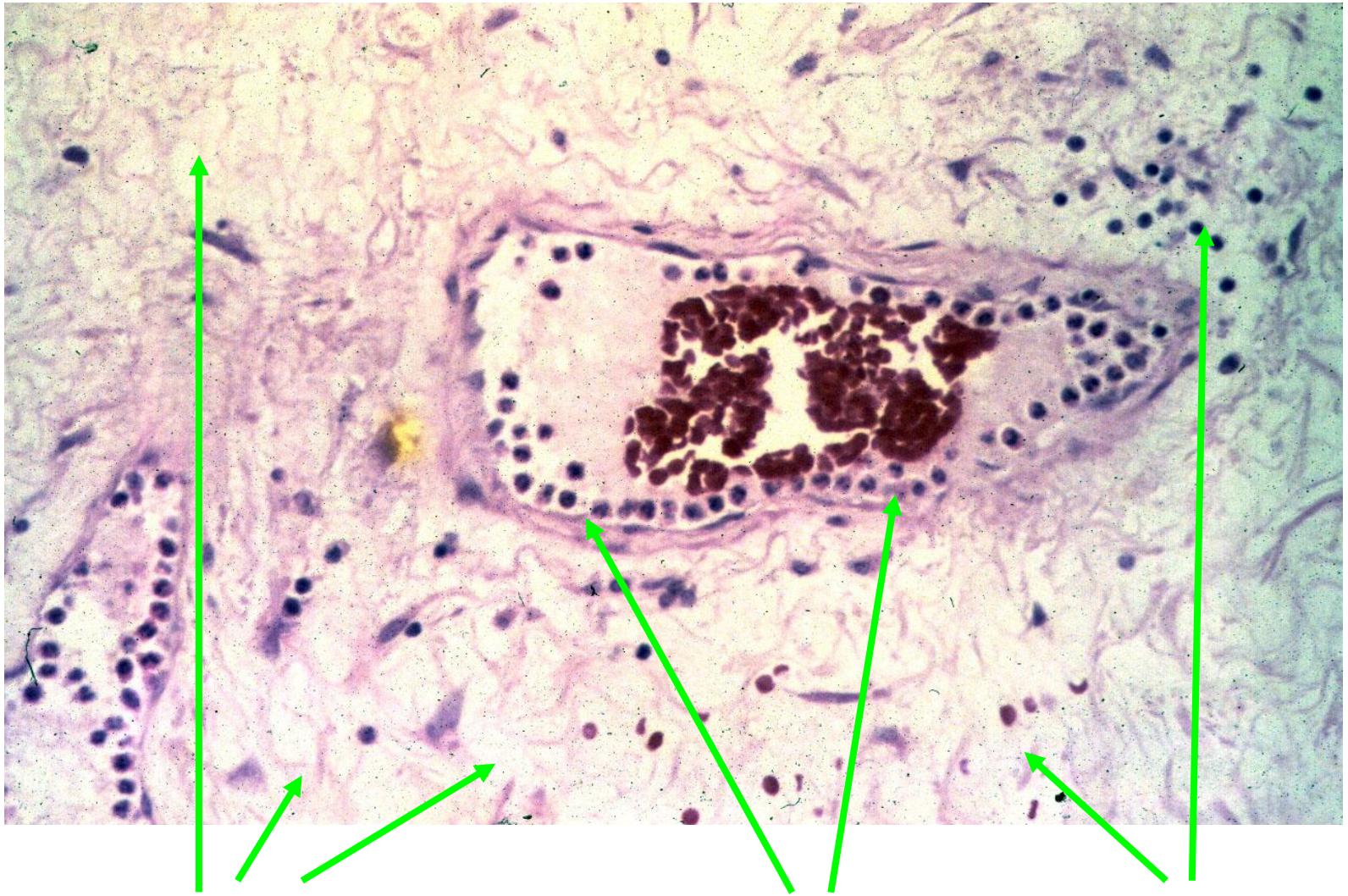


Figure 3.25 Janeway's Immunobiology, 8ed. (© Garland Science 2012)


Tissue oedema
Neutrophil margination …. And emigration

Adhesion Molecules In Leukocyte Recruitment

- Selectins
- Integrins
- their ligands

Selectins and Selectin Ligands

- **Selectins** are plasma membrane carbohydrate-binding adhesion molecules (promote adhesive interactions with other cells or the extracellular matrix).

- Selectins mediate an initial step of low affinity adhesion of circulating leukocytes to endothelial cells lining **post capillary venules**.

- **Endothelial cells** express two types of selectins, called **P-selectin** (CD62P) and **E-selectin** (CD62E).

- **Leukocytes** express **L-selectin** (CD62L)

P-selectin

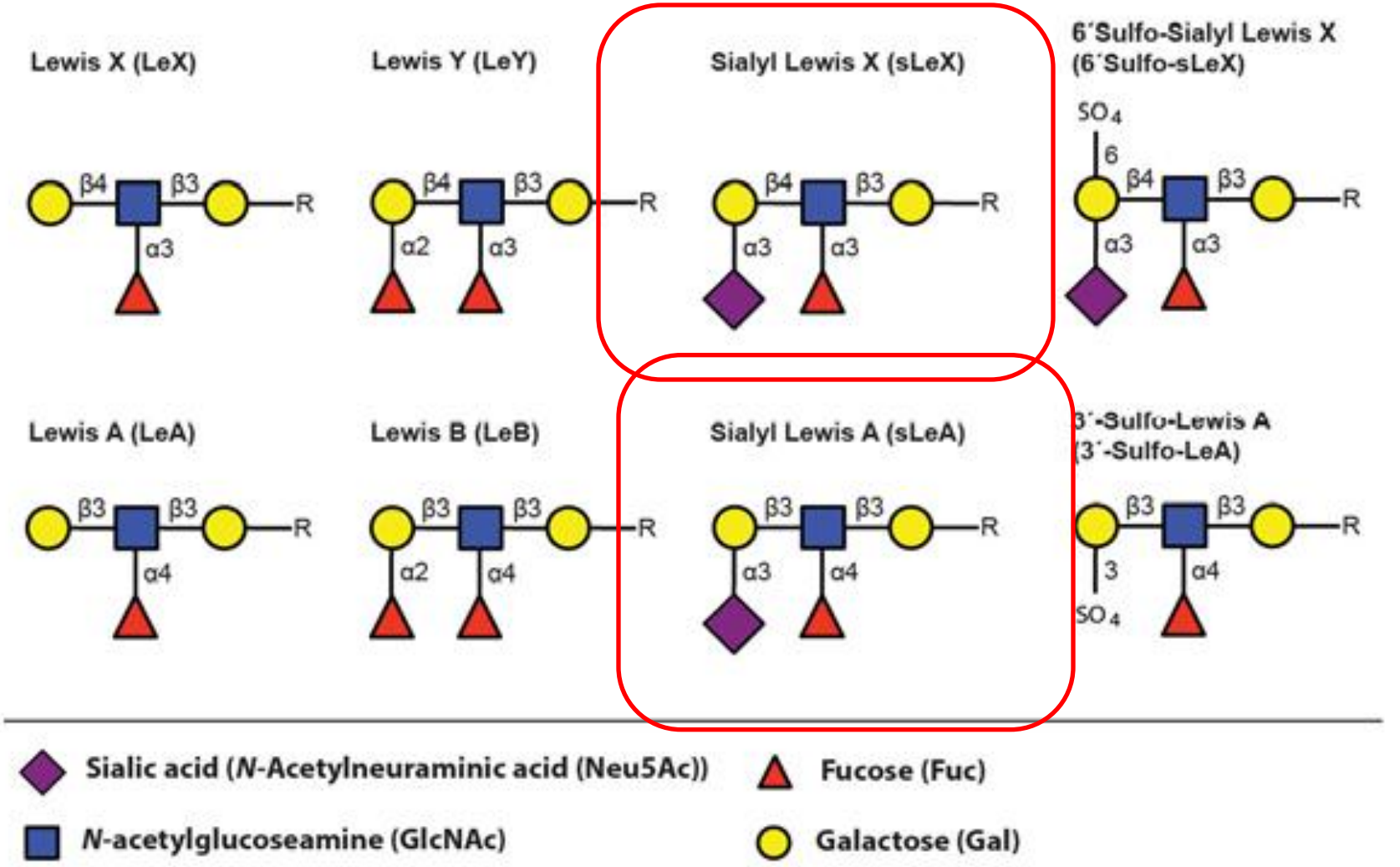
- P-selectin so named because it was first found in platelets.

- It is stored in cytoplasmic **granules** of endothelial cells and is rapidly redistributed to the luminal surface in response to
  - **histamine** from mast cells and
  - **thrombin** generated during blood coagulation.

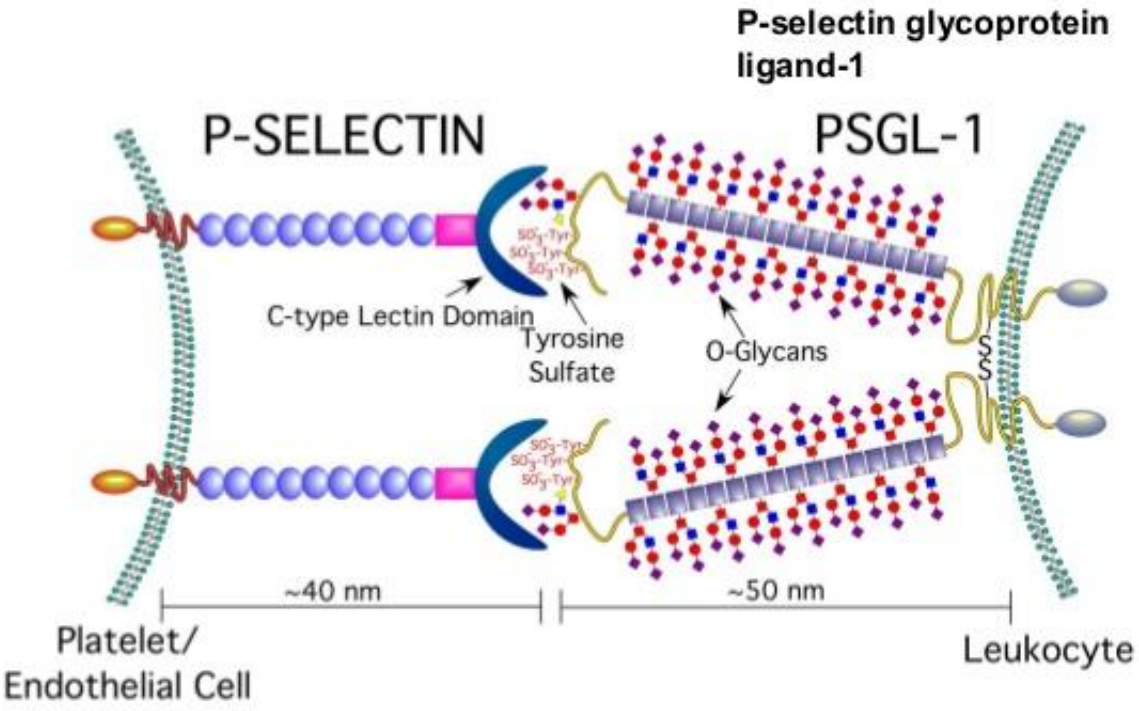
E-selectin

- E-selectin is synthesized and expressed on the endothelial cell surface within 1 to 2 hours in response to the cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF), which are produced by tissue sentinel cells (**DCs and macrophages**) in response to infection.

- **The ligands** on leukocytes that bind to E-selectin and P-selectin on endothelial cells are complex sialylated carbohydrates related to the Lewis X or Lewis A family of blood group molecules.


Lewis X (LeX)
β4
β3
α3
R
Lewis Y (LeY)
β4
β3
α2
α3
R
Sialyl Lewis X (sLeX)
β4
β3
α3
α3
R
6´Sulfo-Sialyl Lewis X
(6´Sulfo-sLeX)
SO4
6
β4
β3
α3
α3
R
Lewis A (LeA)
β3
β3
α4
R
Lewis B (LeB)
β3
β3
α2
α4
R
Sialyl Lewis A (sLeA)
β3
β3
α3
α4
R
3´-Sulfo-Lewis A
(3´-Sulfo-LeA)
β3
β3
3
SO4
α4
R
Sialic acid (N-Acetylneuraminic acid (Neu5Ac))
Fucose (Fuc)
N-acetylglucoseamine (GlcNAc)
Galactose (Gal)

P-selectin ligand



Integrins and Integrin Ligands

- Integrins are cell surface proteins that mediate adhesion of cells to other cells or to extracellular matrix, through **specific binding** interactions with various ligands.

- The name integrin for this family of proteins derives from the idea that these proteins integrate signals triggered by extracellular ligands with cytoskeleton-dependent motility, shape change, and phagocytic responses.

مولکولهای چسبان دخیل در پاسخ التهابی

		Name	Tissue distribution	Ligand
Selectins Bind carbohydrates. Initiate leukocyte–endothelial interaction	P-selectin	P-selectin (PADGEM, CD62P)	Activated endothelium and platelets	PSGL-1, sialyl-Lewis^x
		E-selectin (ELAM-1, CD62E)	Activated endothelium	Sialyl-Lewis^x
Integrins Bind to cell-adhesion molecules and extracellular matrix. Strong adhesion	LFA-1 (α, β)	α_L:β_2 (LFA-1, CD11a:CD18)	Monocytes, T cells, macrophages, neutrophils, dendritic cells, NK cells	ICAMs
		α_M:β_2 (CR3, Mac-1, CD11b:CD18)	Neutrophils, monocytes, macrophages, NK cells	ICAM-1, iC3b, fibrinogen
		α_X:β_2 (CR4, p150.95, CD11c:CD18)	Dendritic cells, macrophages, neutrophils, NK cells	iC3b
		α_5:β_1 (VLA-5, CD49d:CD29)	Monocytes, macrophages	Fibronectin
Immunoglobulin superfamily Various roles in cell adhesion. Ligand for integrins	ICAM-1	ICAM-1 (CD54)	Activated endothelium, activated leukocytes	LFA-1, Mac1
		ICAM-2 (CD102)	Resting endothelium, dendritic cells	LFA-1
		VCAM-1 (CD106)	Activated endothelium	VLA-4
		PECAM (CD31)	Activated leukocytes, endothelial cell–cell junctions	CD31

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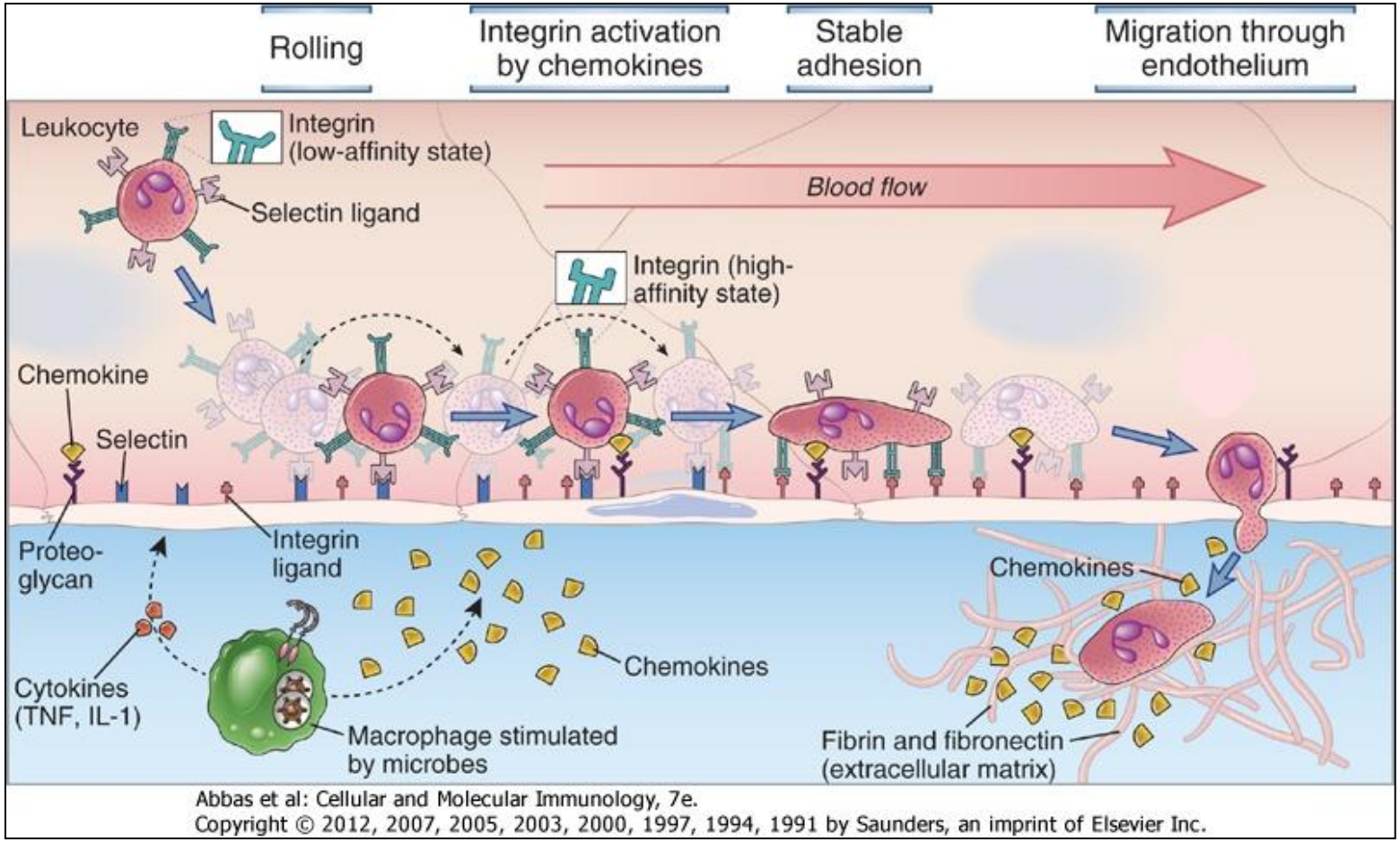
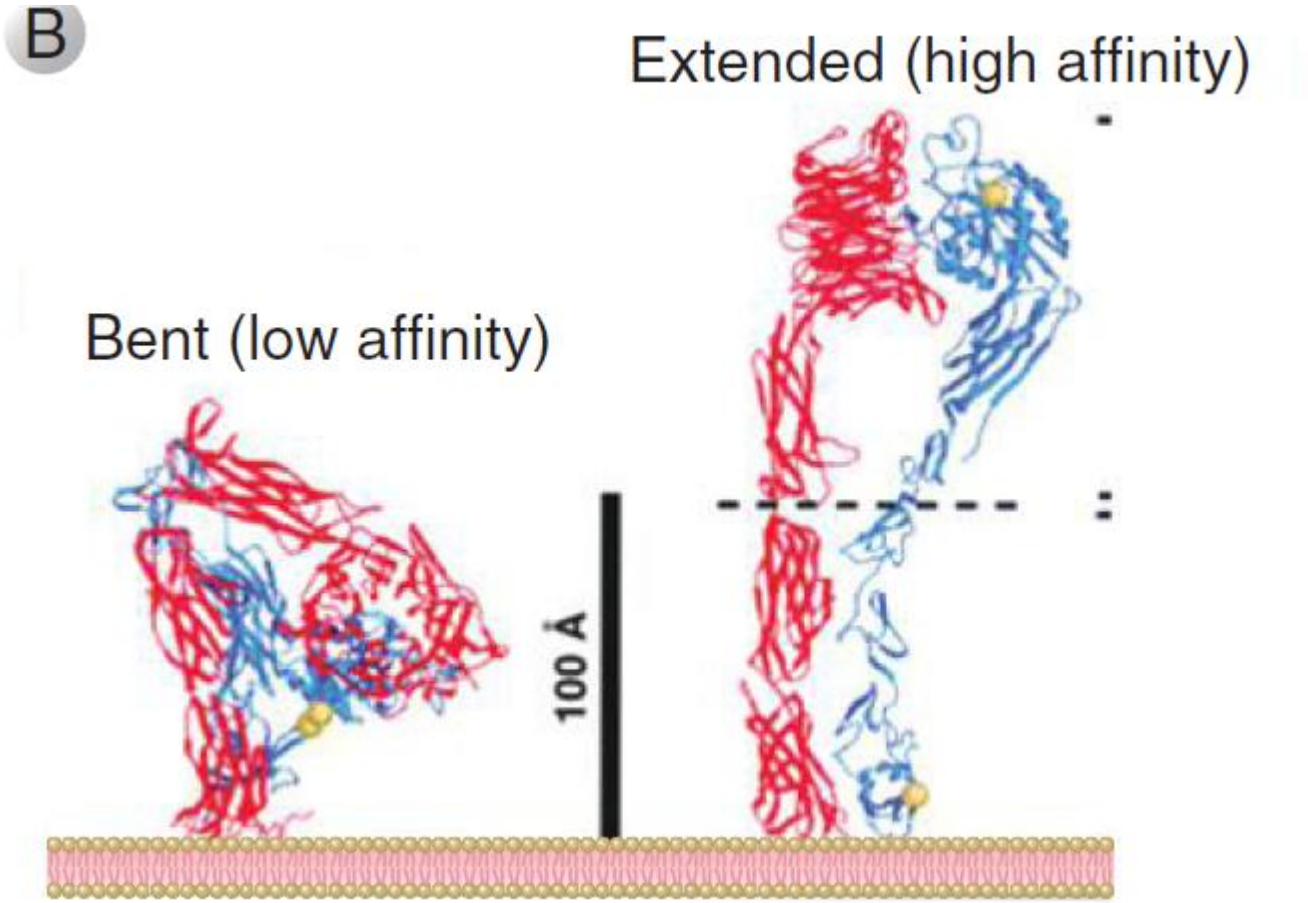
VLA-4 (very late antigen 4)

LFA-1 (leukocyte function-associated antigen 1

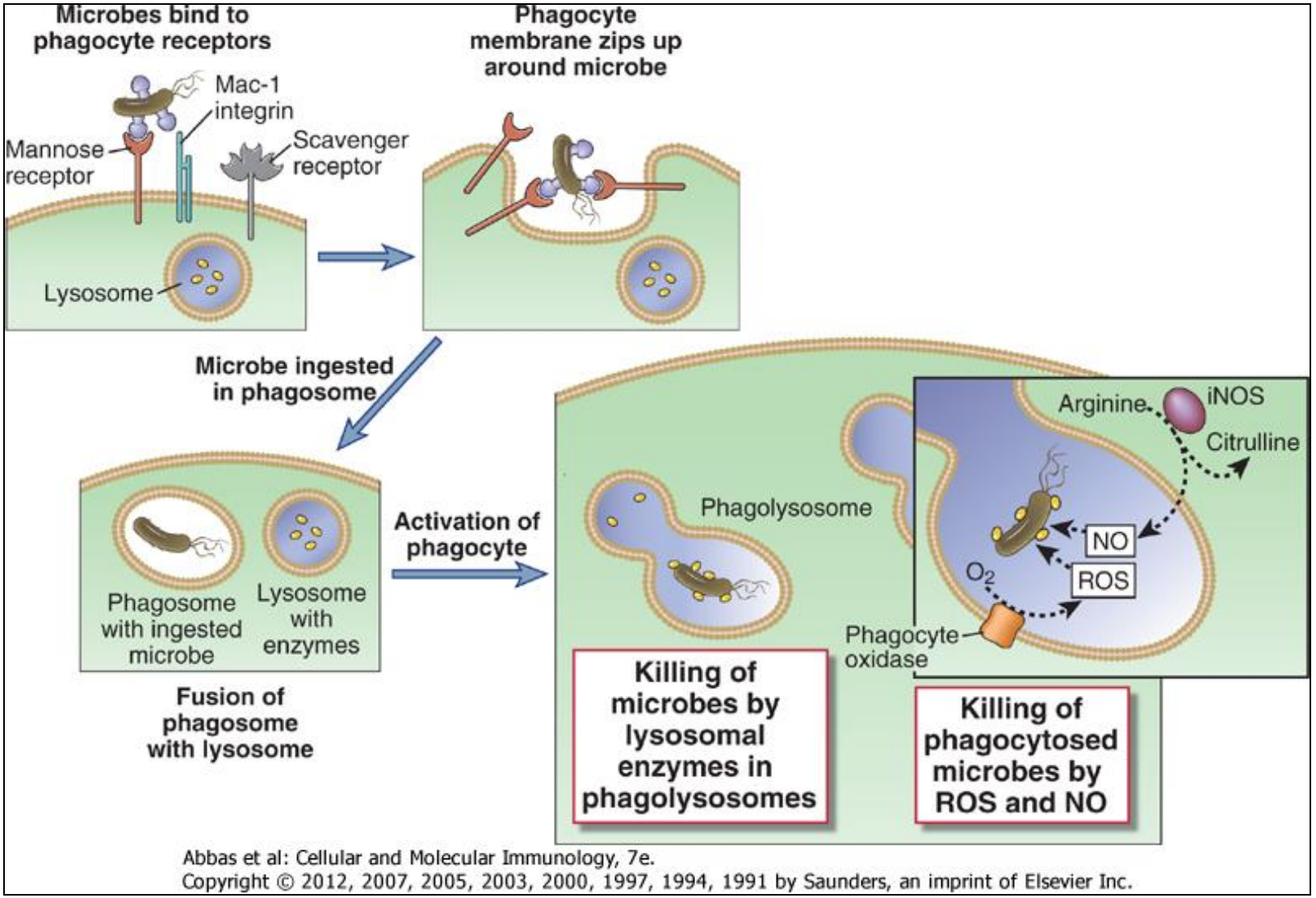
Platelet endothelial cell adhesion molecule (PECAM-1)

مهاجرت لوکوسیتها به محل عفونت

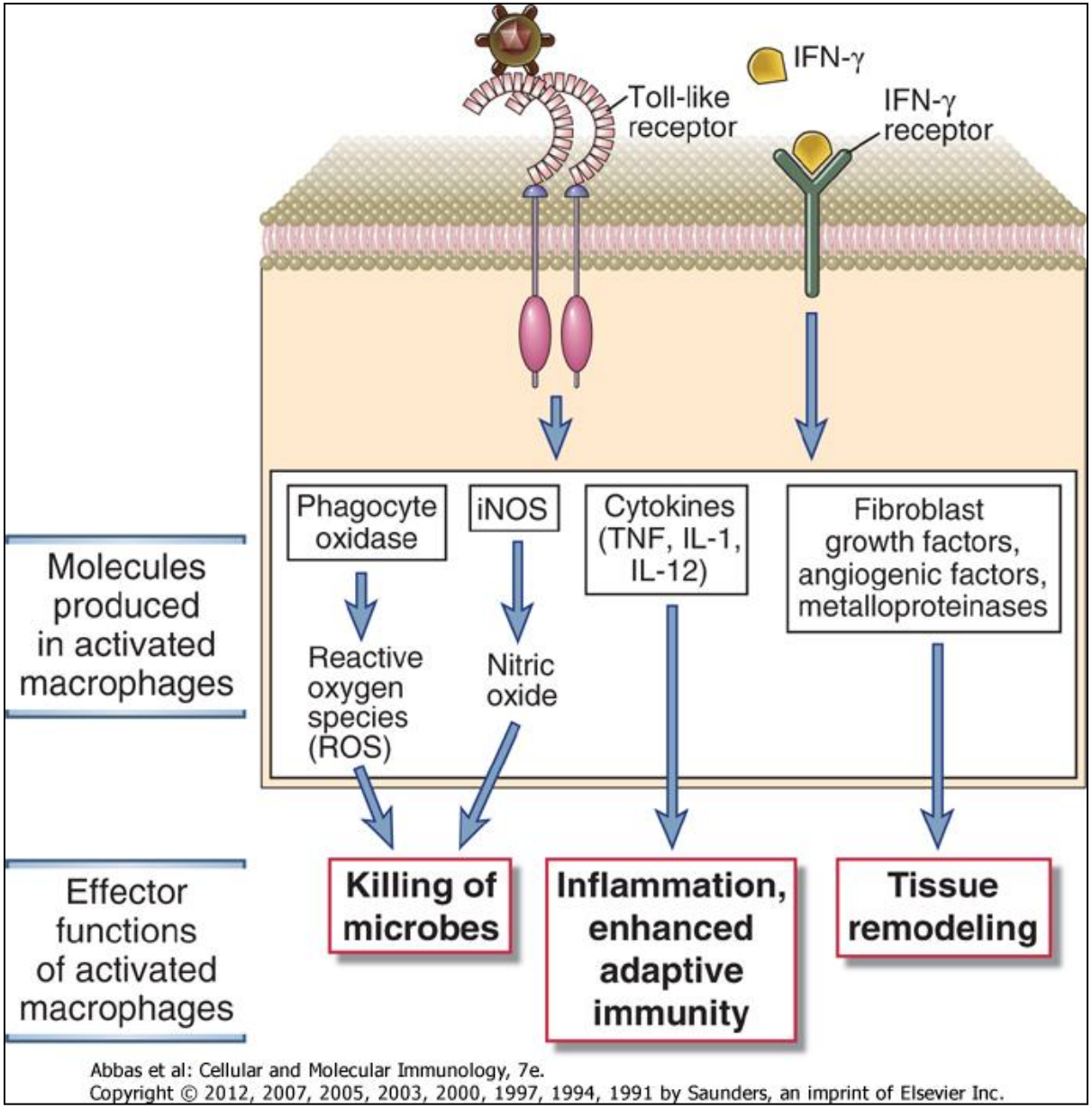



B
Extended (high affinity)
Bent (low affinity)
100 Å

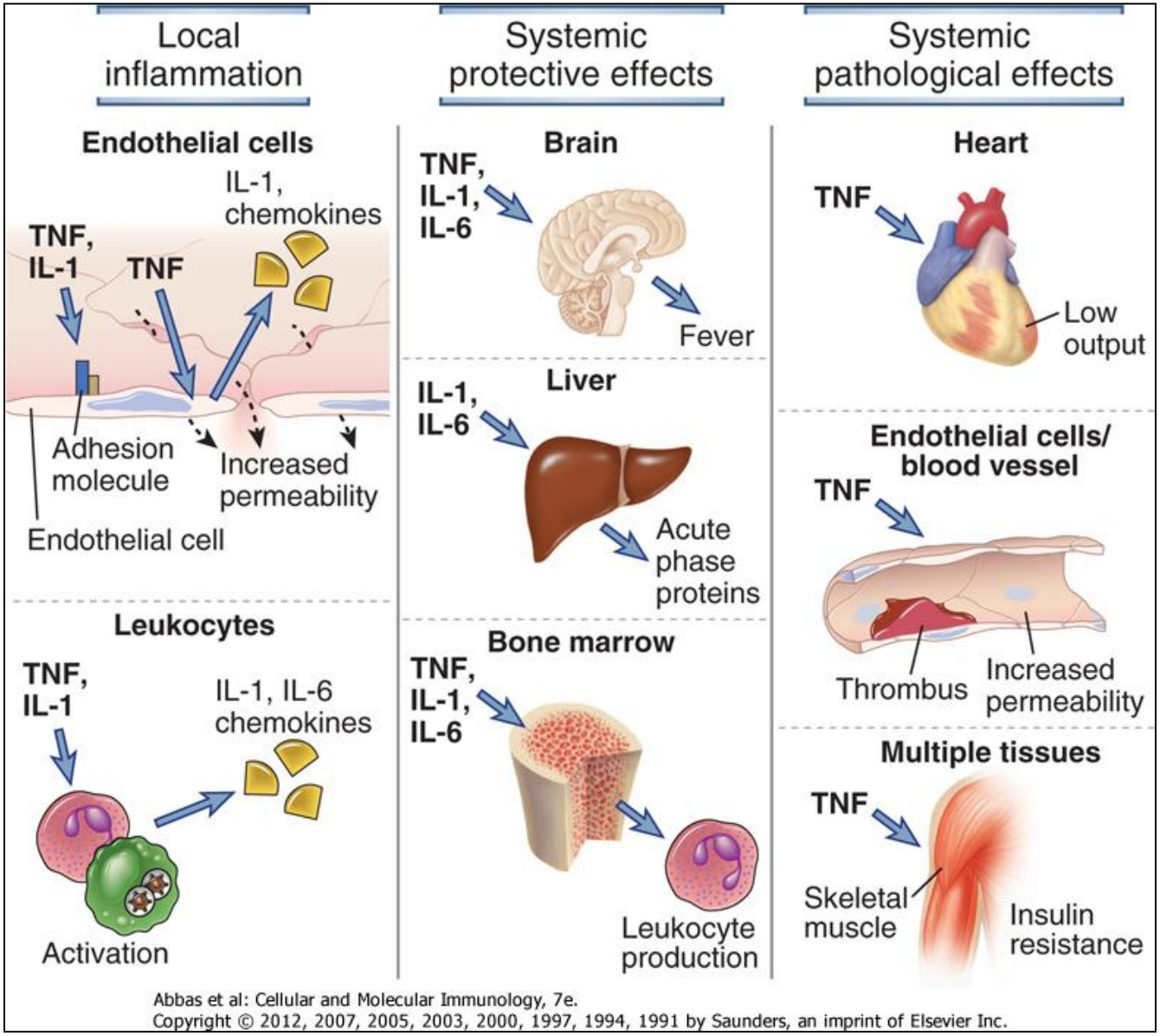
فاگوسیتوز و تخریب داخل سلولی میکروبها



اعمال اجرایی ماکروفاژها در التهاب

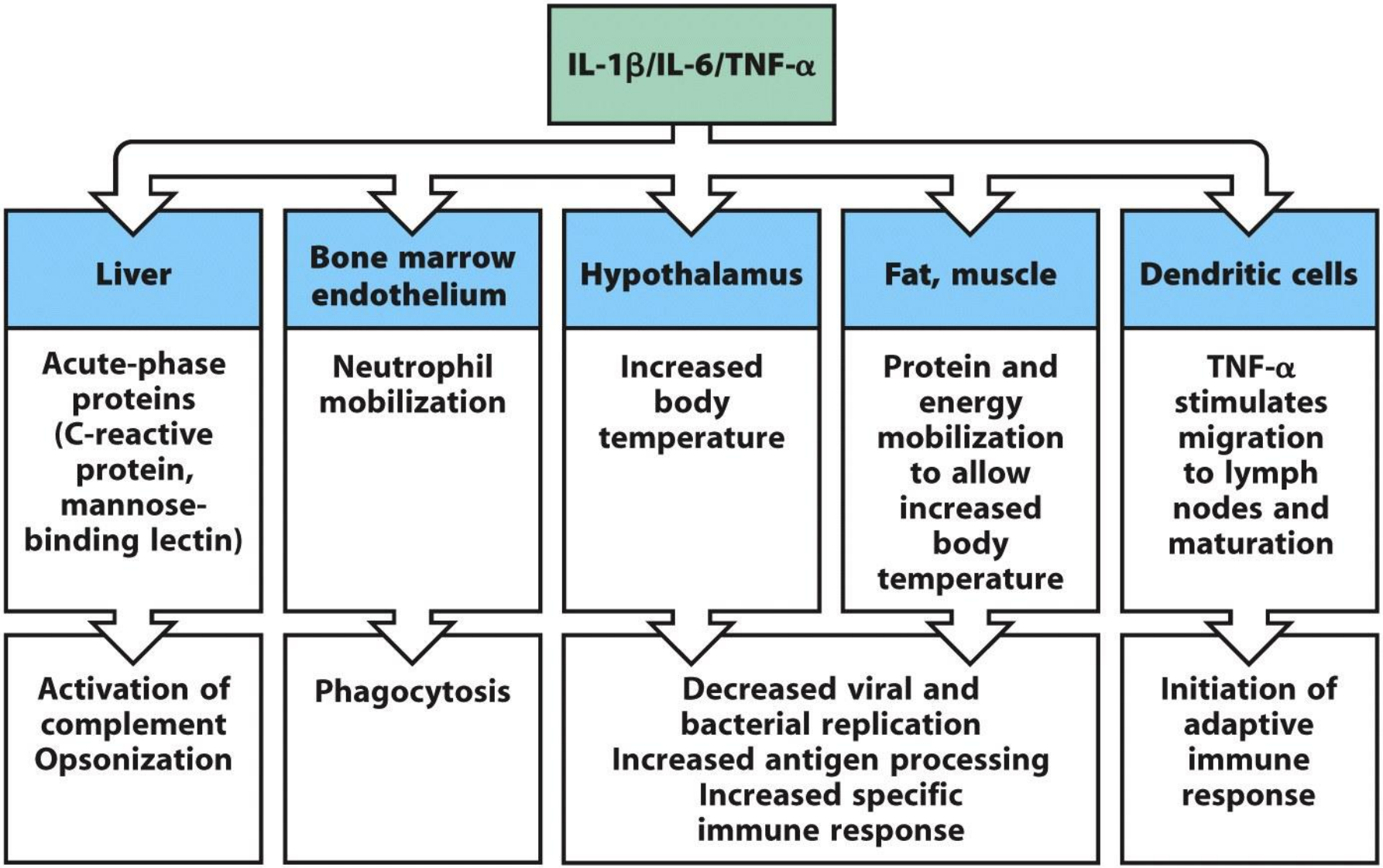


اعمال موضعی و سیستمیک سایتوکاینها در التهاب



septic shock

اعمال مختلف سایتوکاینها در التهاب



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موفق باشید