

Basic immunology

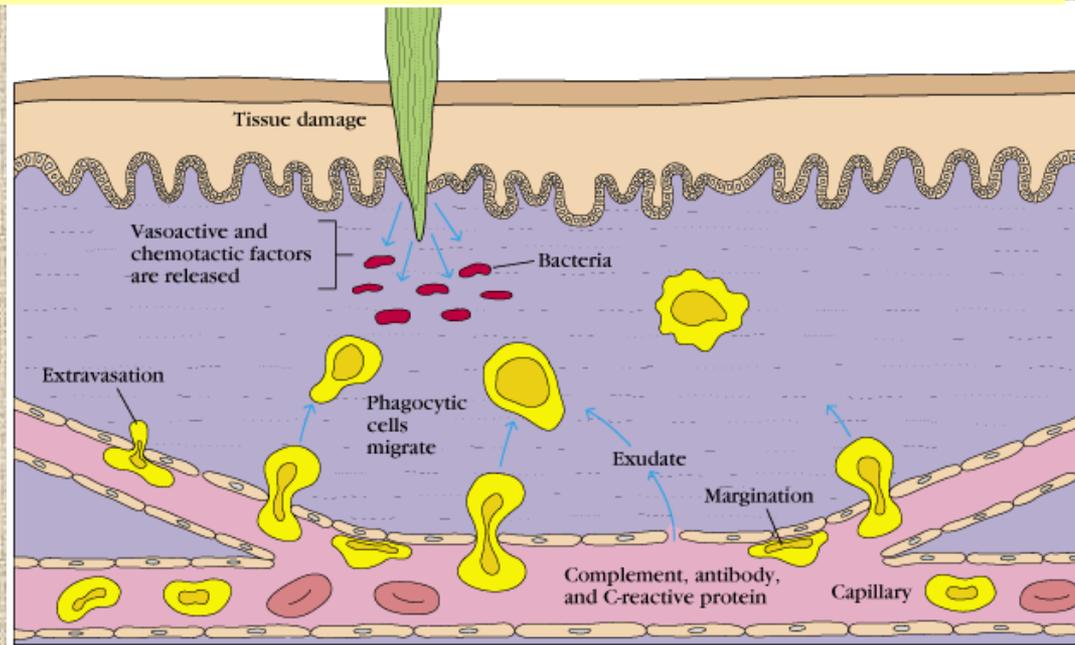
Lecture 5.

Inflammatory reaction

Timea Berki

Acute, local inflammation:

- Infection or tissue-injury initiate the cascade of non-specific reactions
- Immediate reaction
- Its role is 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 – minutes
 - Increased capillary permeability, fluid efflux, oedema
 - Phagocytes migration: - hours

Innate and Adaptive Immunity

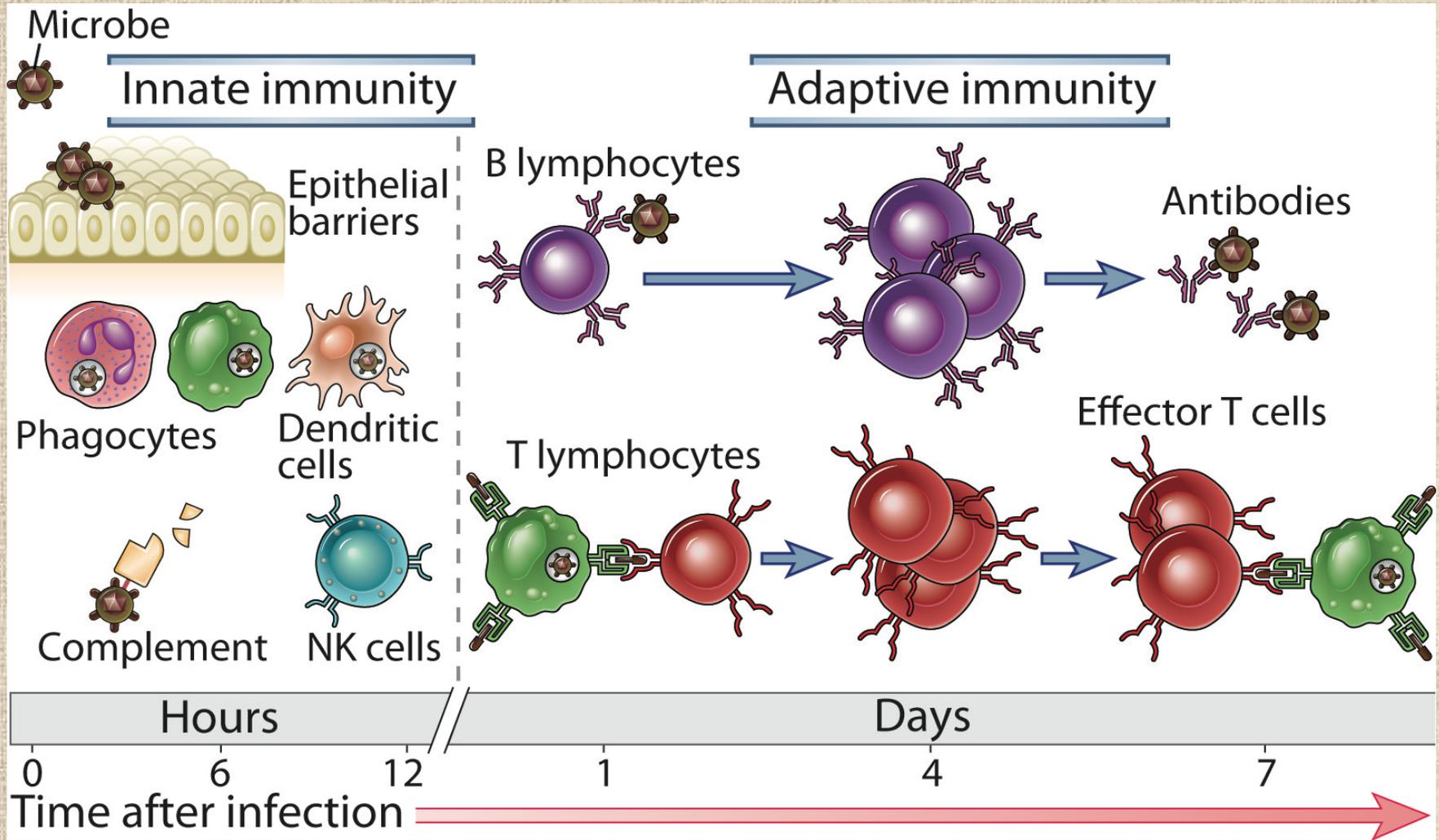
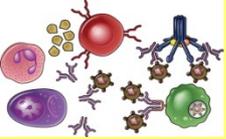


Fig. 1-1



Routes of Antigen Entry

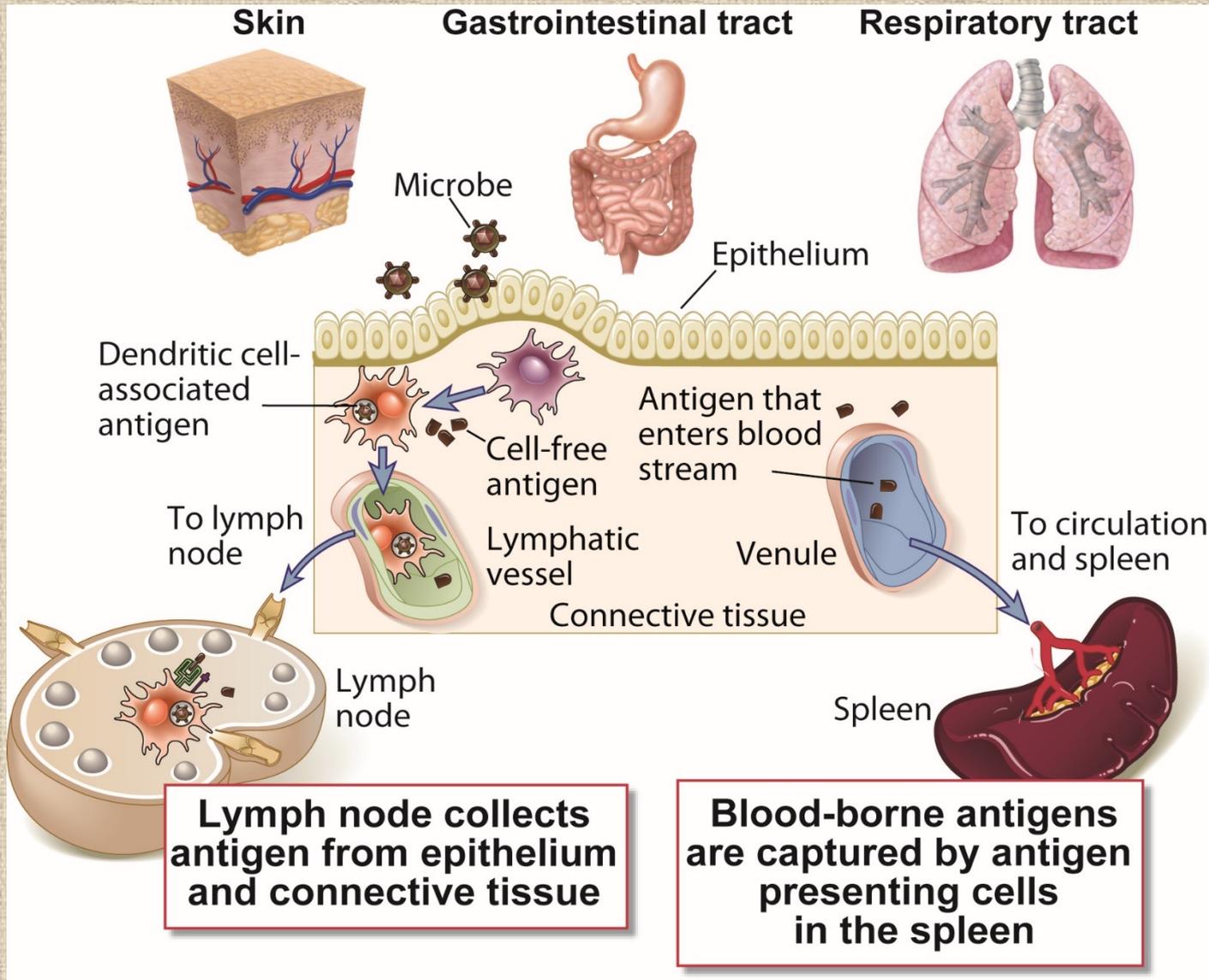
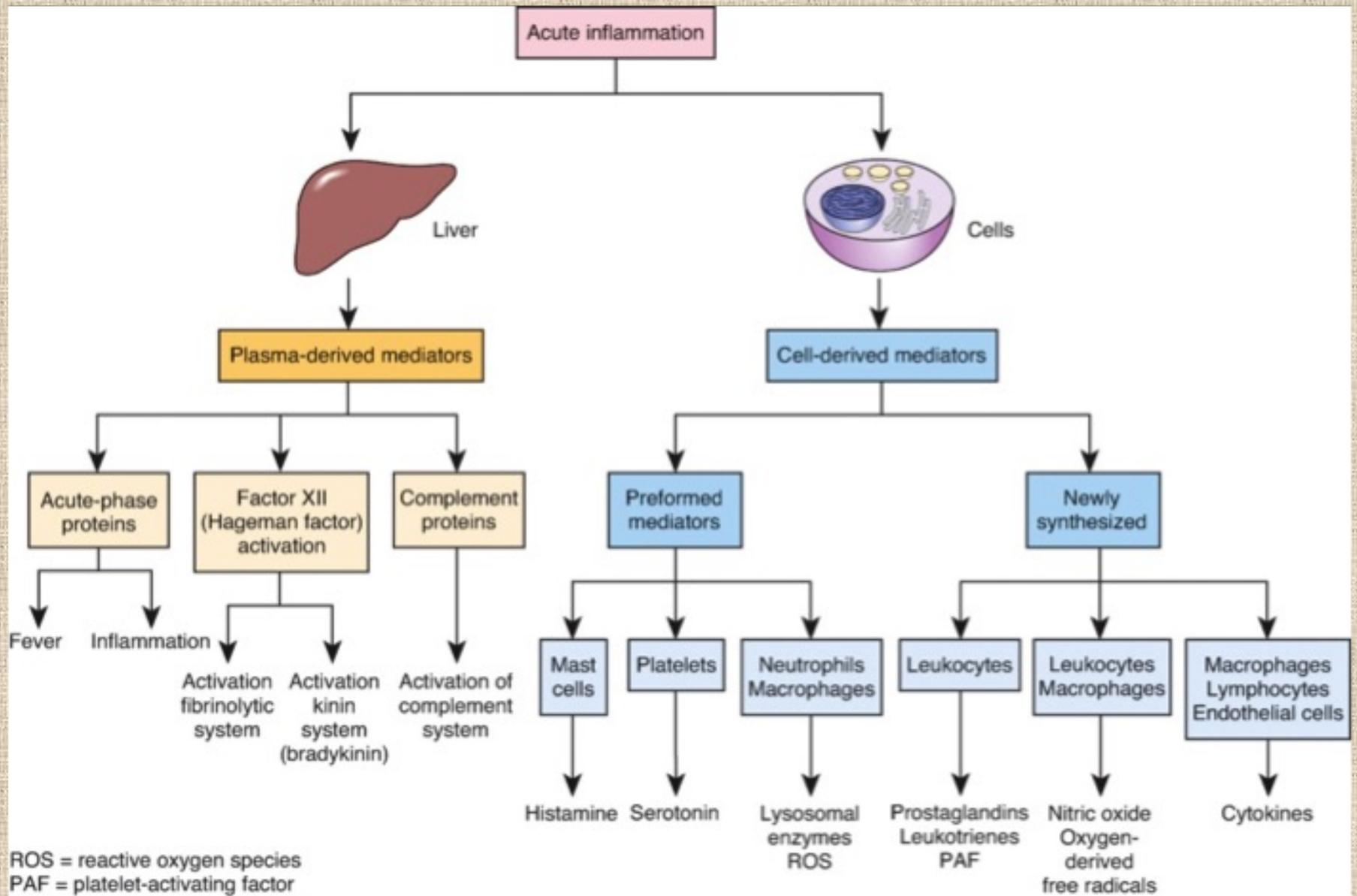


Fig. 6-3

Mediators of inflammation



Molecular mediators of inflammation

Plasma enzyme mediators:

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

Lipid mediators:

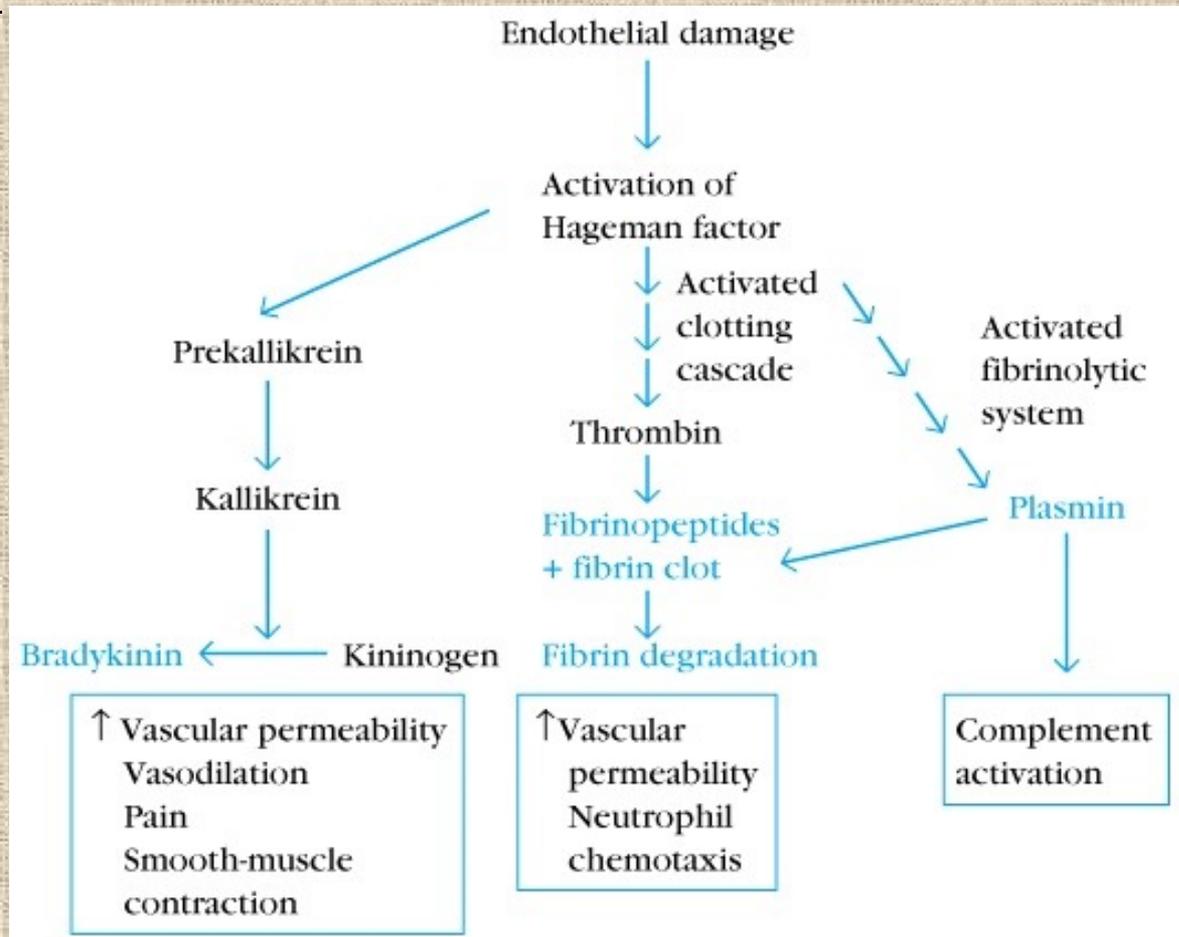
leukotrienes,
prostaglandins (PGE)

Chemoattractants:

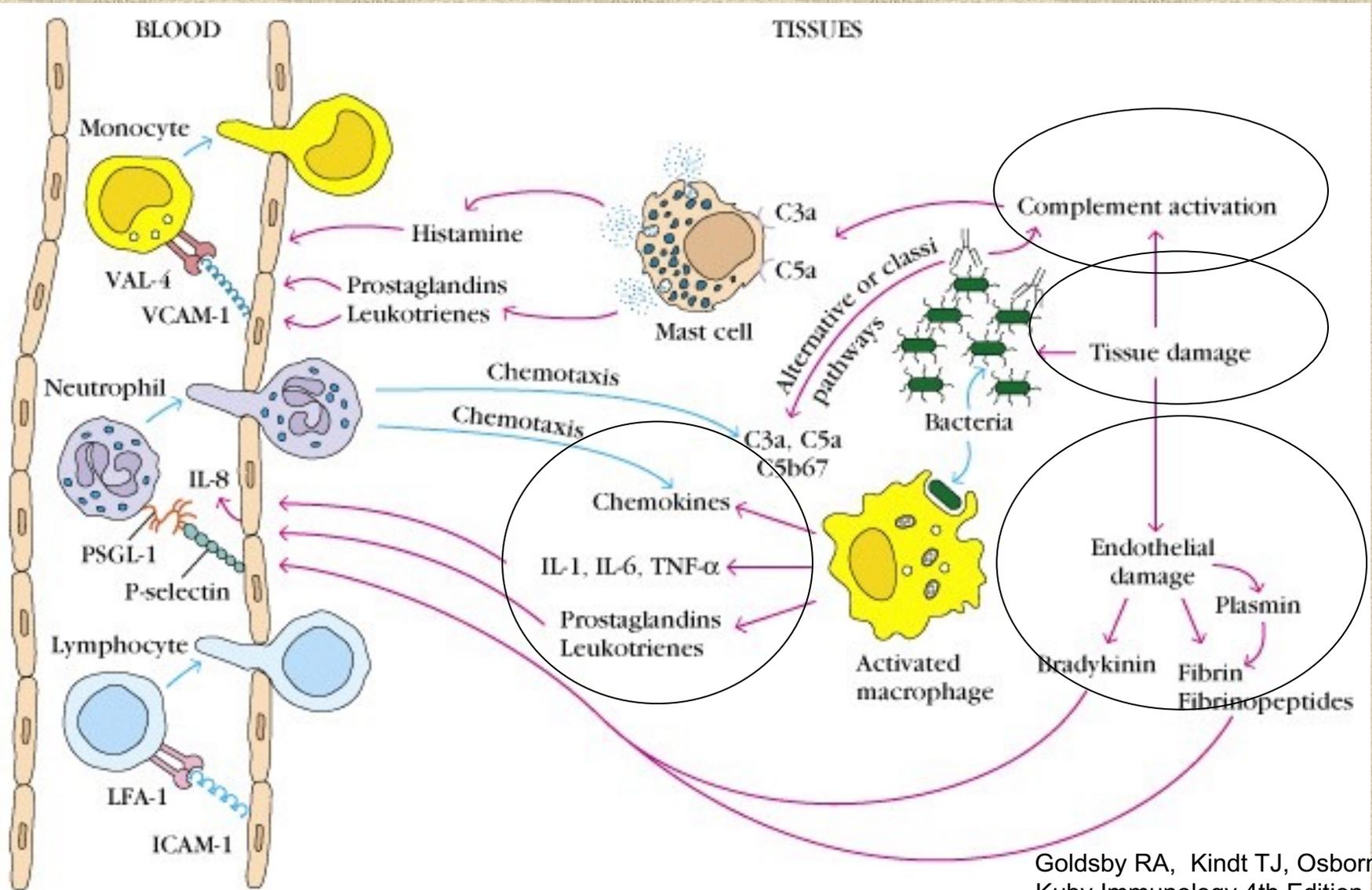
- Chemokines: IL-8
- Complement components
- PAF (platelet activating factor)

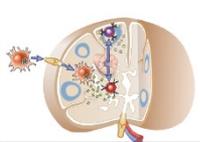
Inflammatory cytokines:

IL-1, IL-6, TNF α



Initiation of acute inflammation





Maturation of Macrophages and DCs

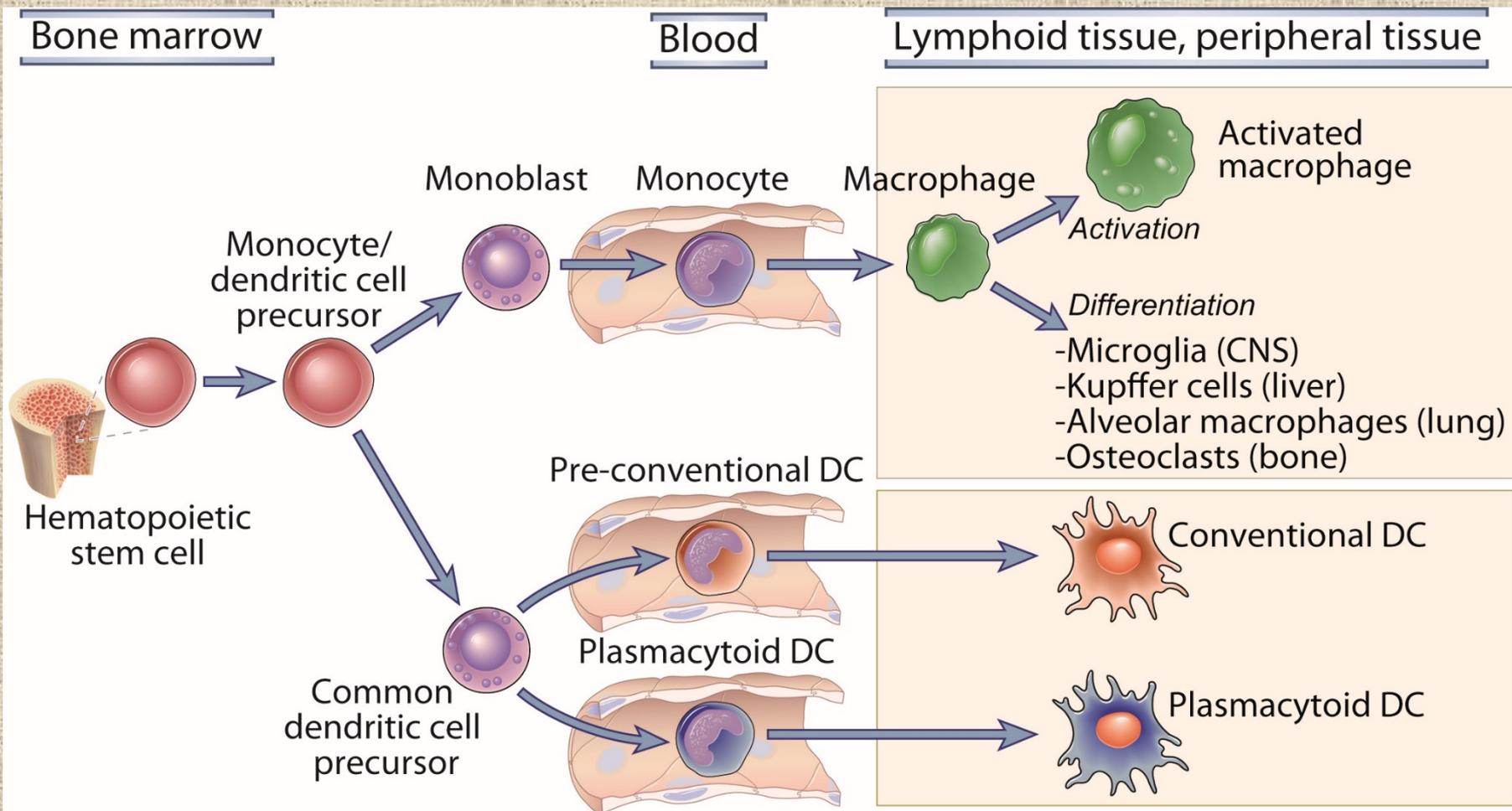
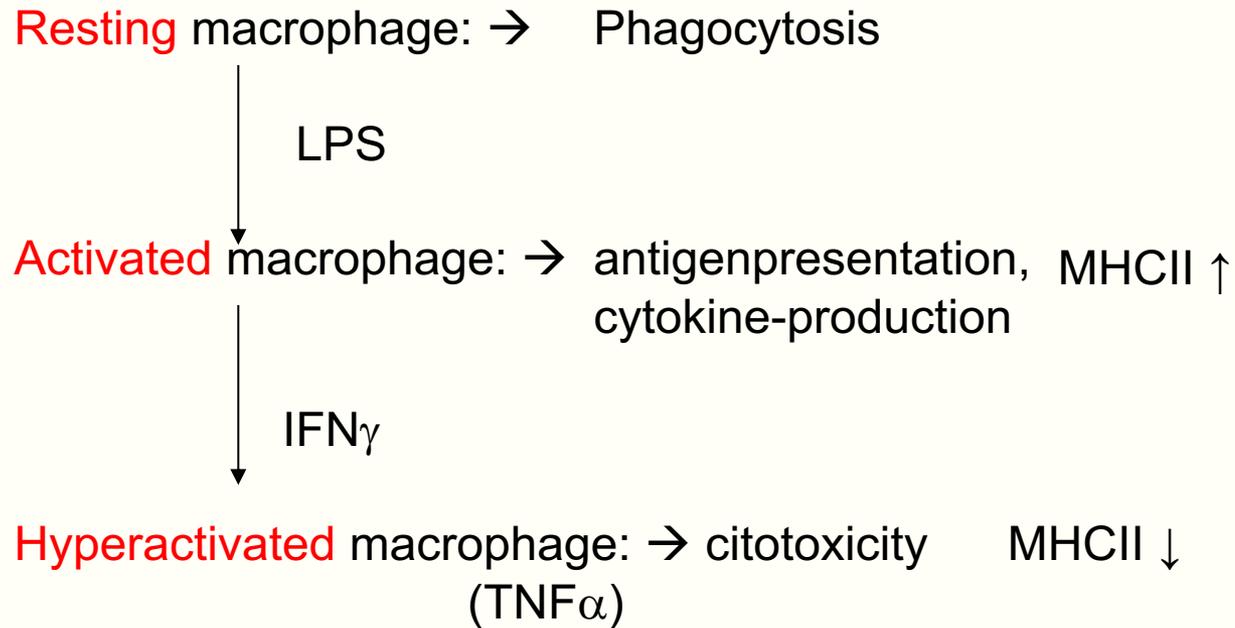
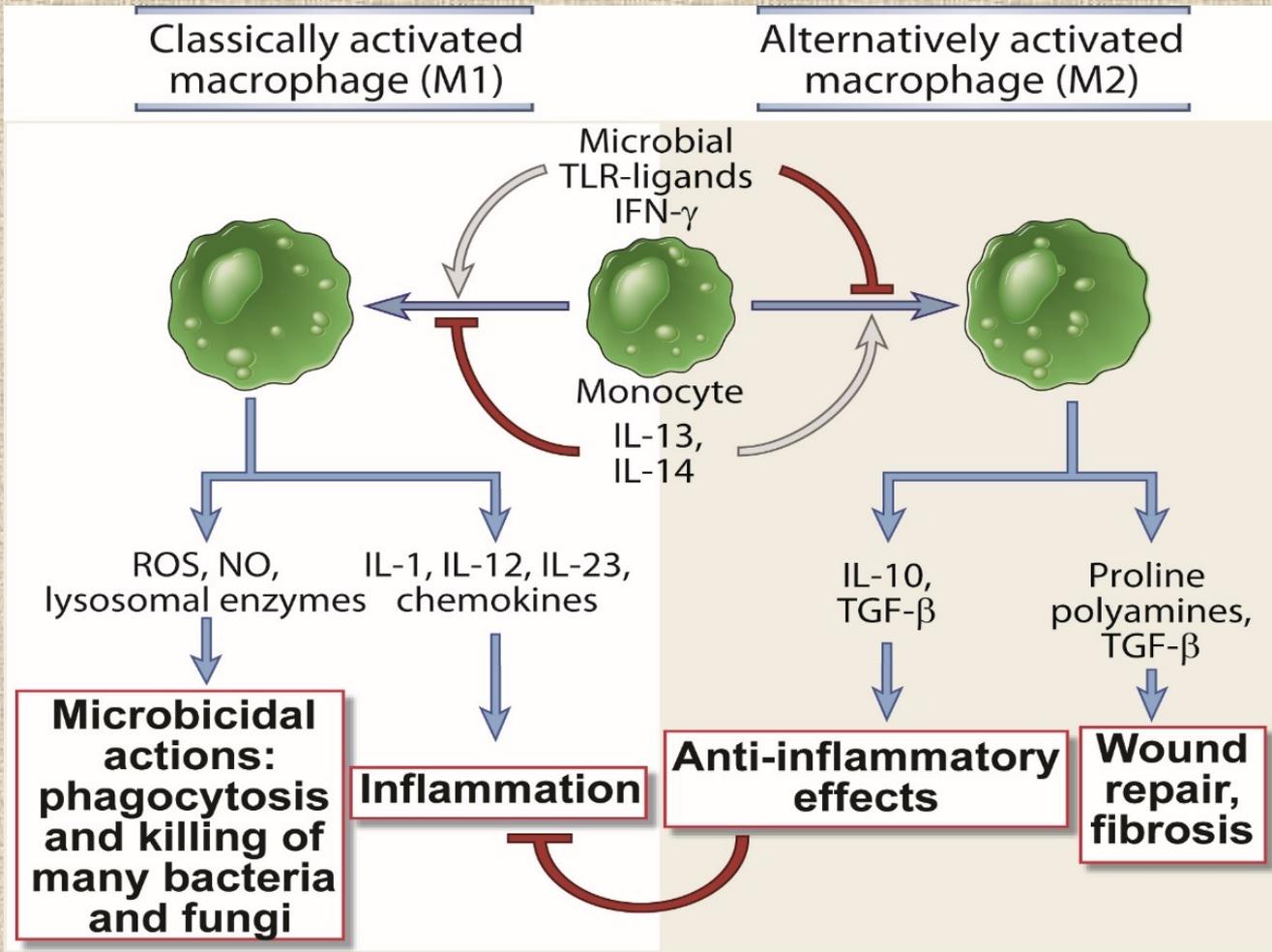


Fig. 2-2

Role of macrophages in acute inflammation: classical activation



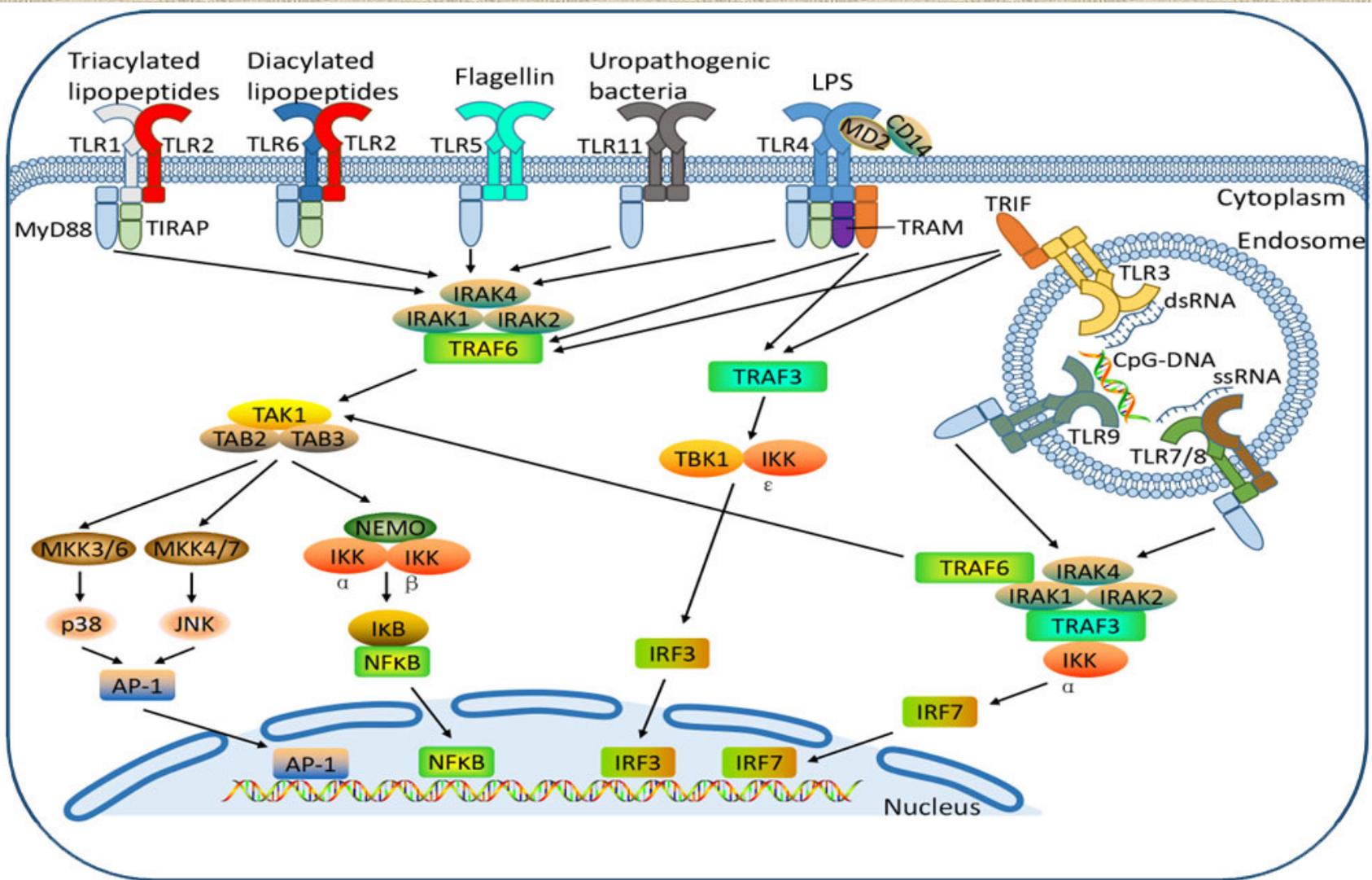
Polarization of macrophages



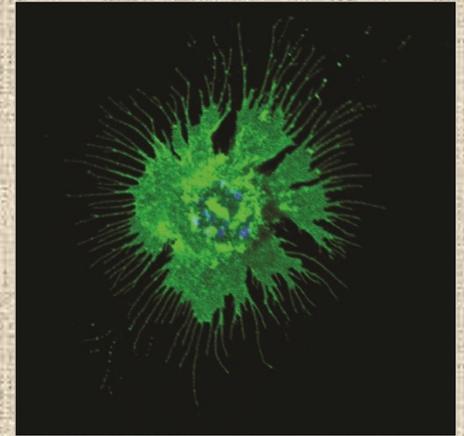
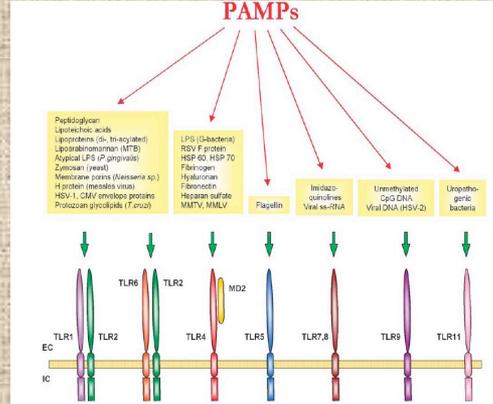
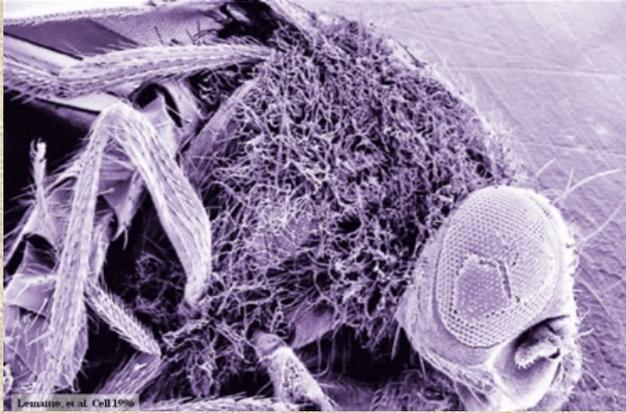
Abbas, Lichtman, Pillai: Cellular and Molecular Immunology 7th Edition, 2012.

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

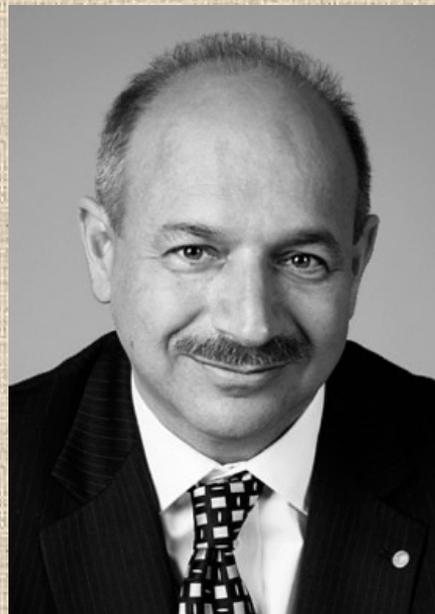
Toll-like Receptors



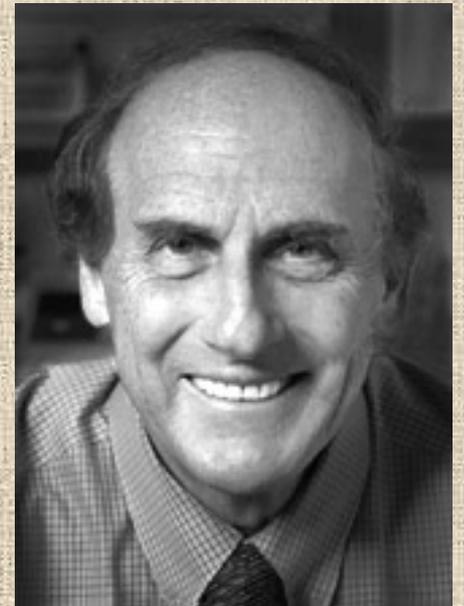
Nobel Laureates in 2011 for medicine and physiology



Jules A. Hoffmann



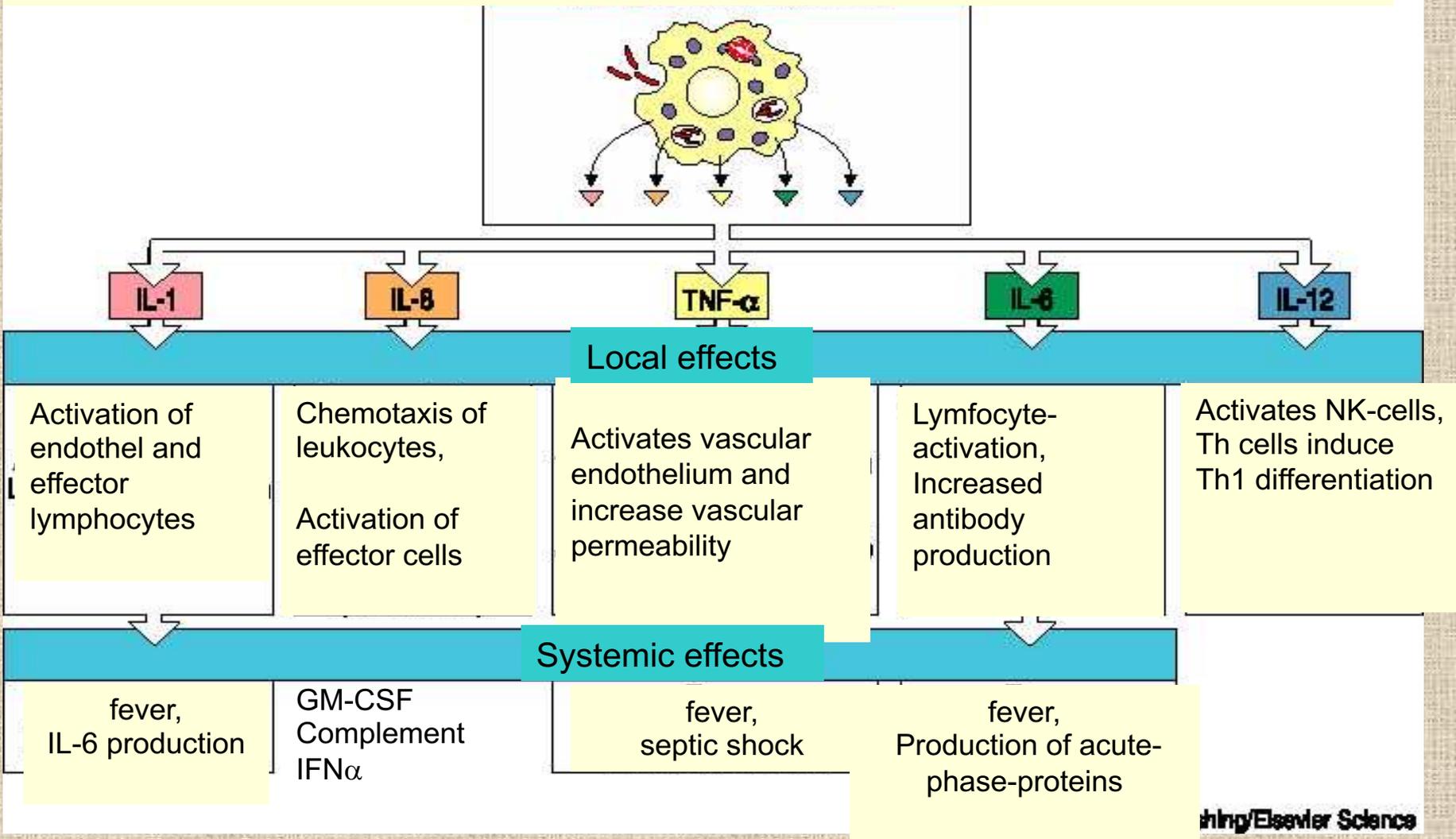
Bruce A. Beutler



Ralph M. Steinmann

Activated macrophages produce inflammatory cytokines

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

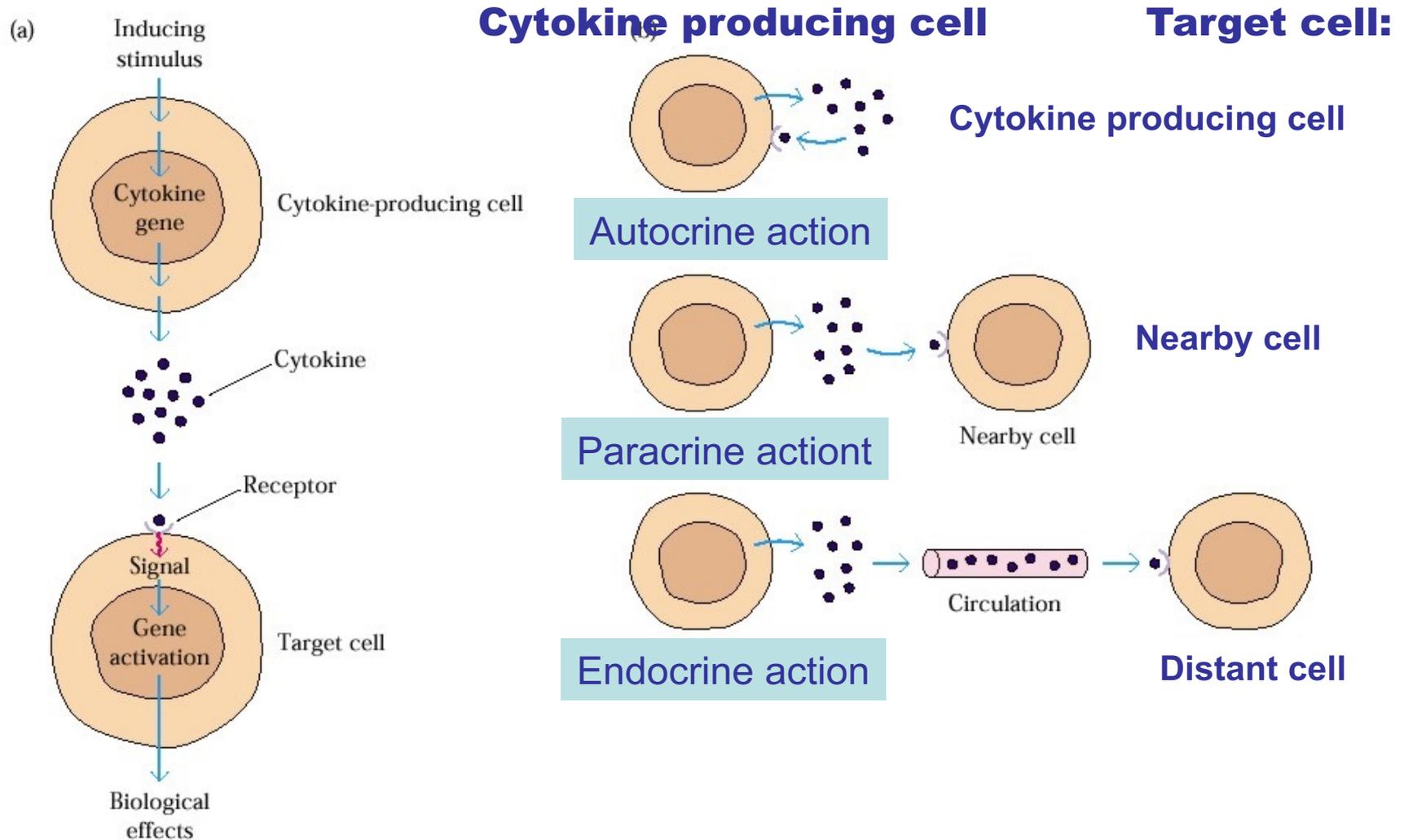


Basic characteristics of cytokines

- Low molecular weight (10-40 kDa) glycoproteins
- Isolated cells secrete them, due to gene activation
- They mediate cell-cell interaction:
 - - sending information
 - - regulation of immune response
- Mechanism of action:
 - produced after transient gene activation
 - act through receptors triggering signal-transduction
 - high affinity
 - picomolar concentration

They act mostly locally.

Mechanism of cytokine action I.:

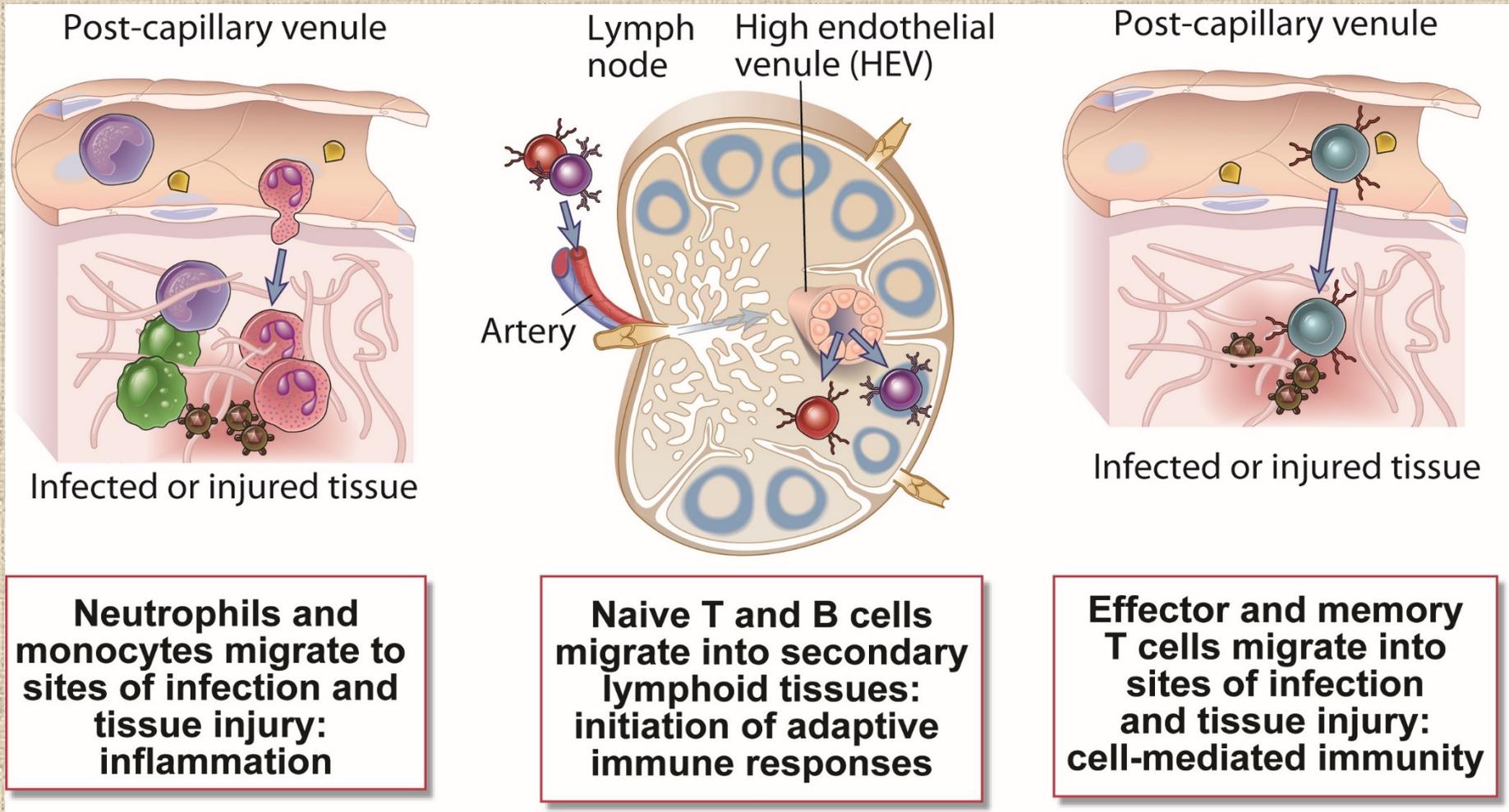


Functional groups of cytokines

I. Regulators of natural immunity and inflammation	IFN α , IFN β , IL-1 α , IL-1 β , IL-6, TNF α IL-12, Chemokines: CXCL8 (IL-8), CCL3,4 (MCP, MIP-1)
II. Regulators of lymphocyte activation and differentiation	TH1: IL-2, INF γ , TNF β (LT) TH2: , IL-4, IL-5, IL-6, IL-13, IL-15 Treg: IL-10 and TGF β
III. Regulators of haematopoiesis	IL-3, IL-7, GM-CSF, SCF

- **Extravasation, homing (leukocyte migration)**

Functions Served by Leukocyte Migration



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

Fig. 3-1

Leukocyte Recruitment Into Tissues

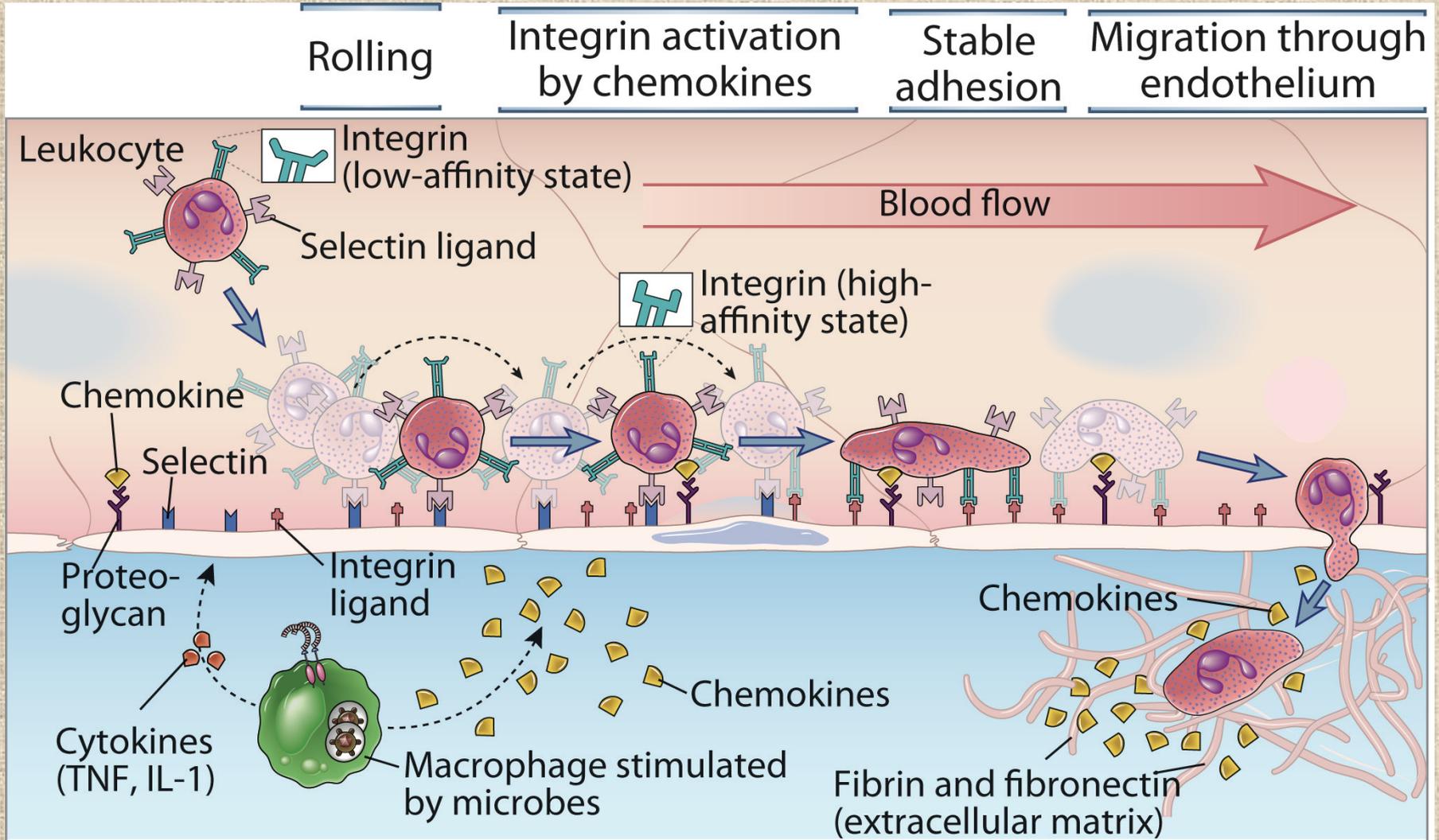
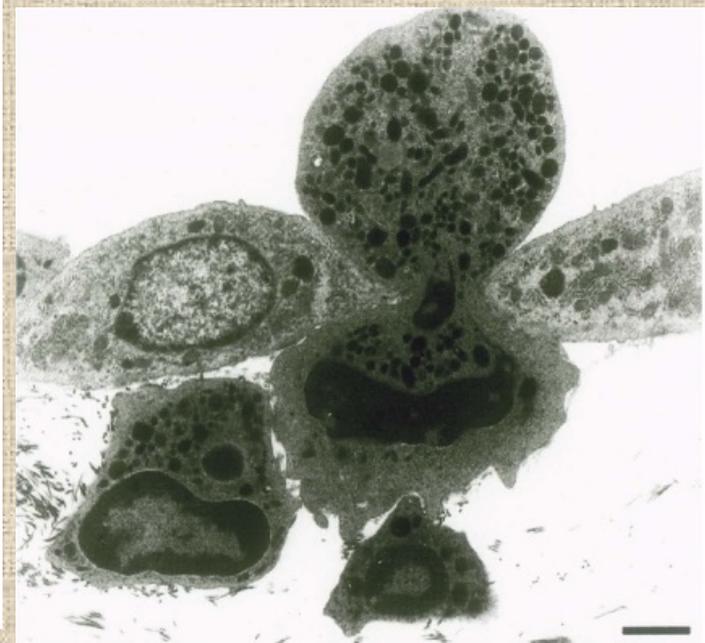
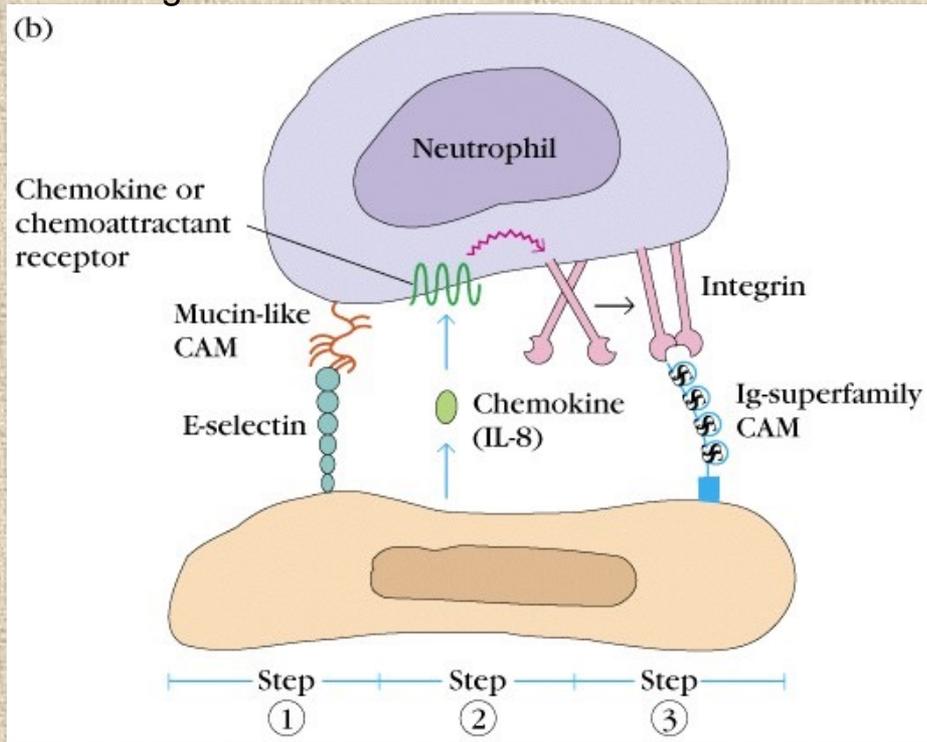
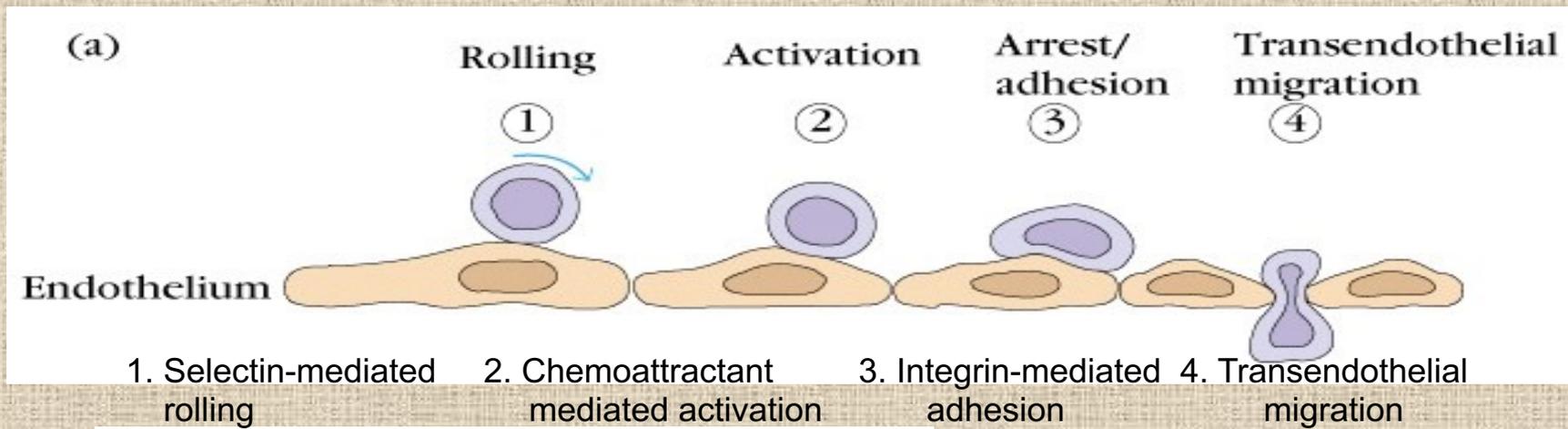


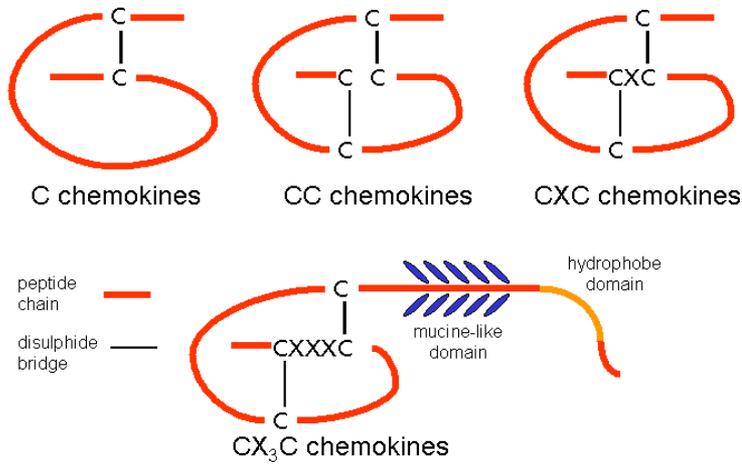
Fig. 3-3

Neutrophil extravasation through the inflamed endothelium

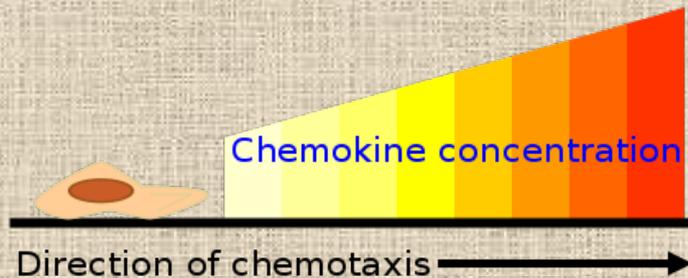
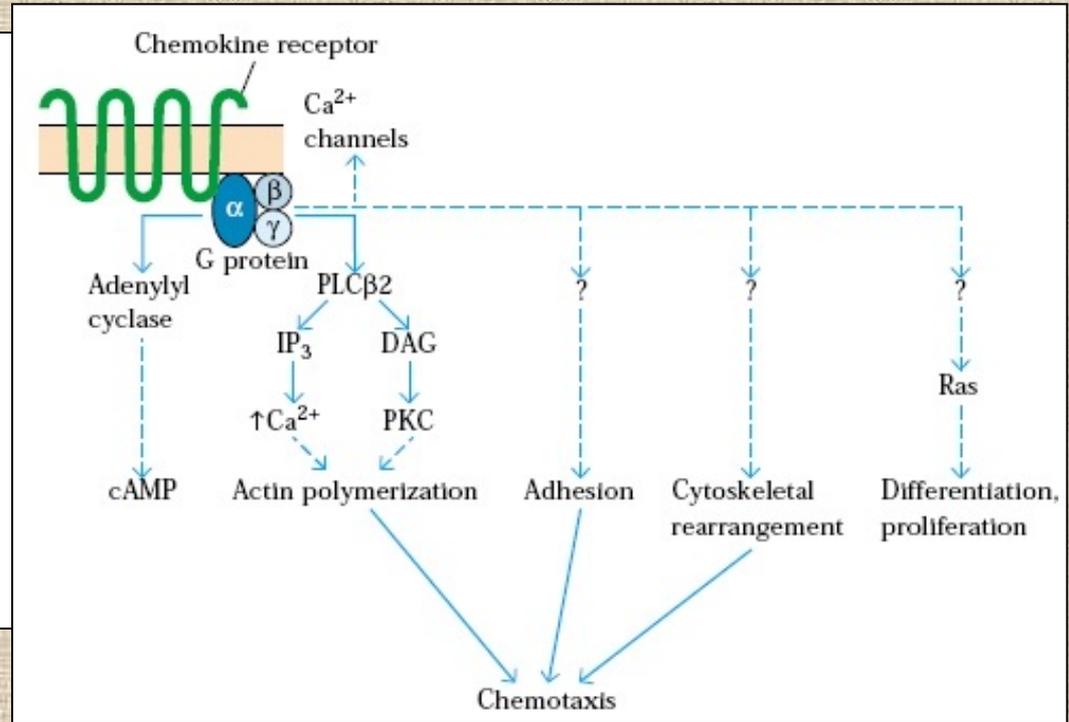


Chemokine action

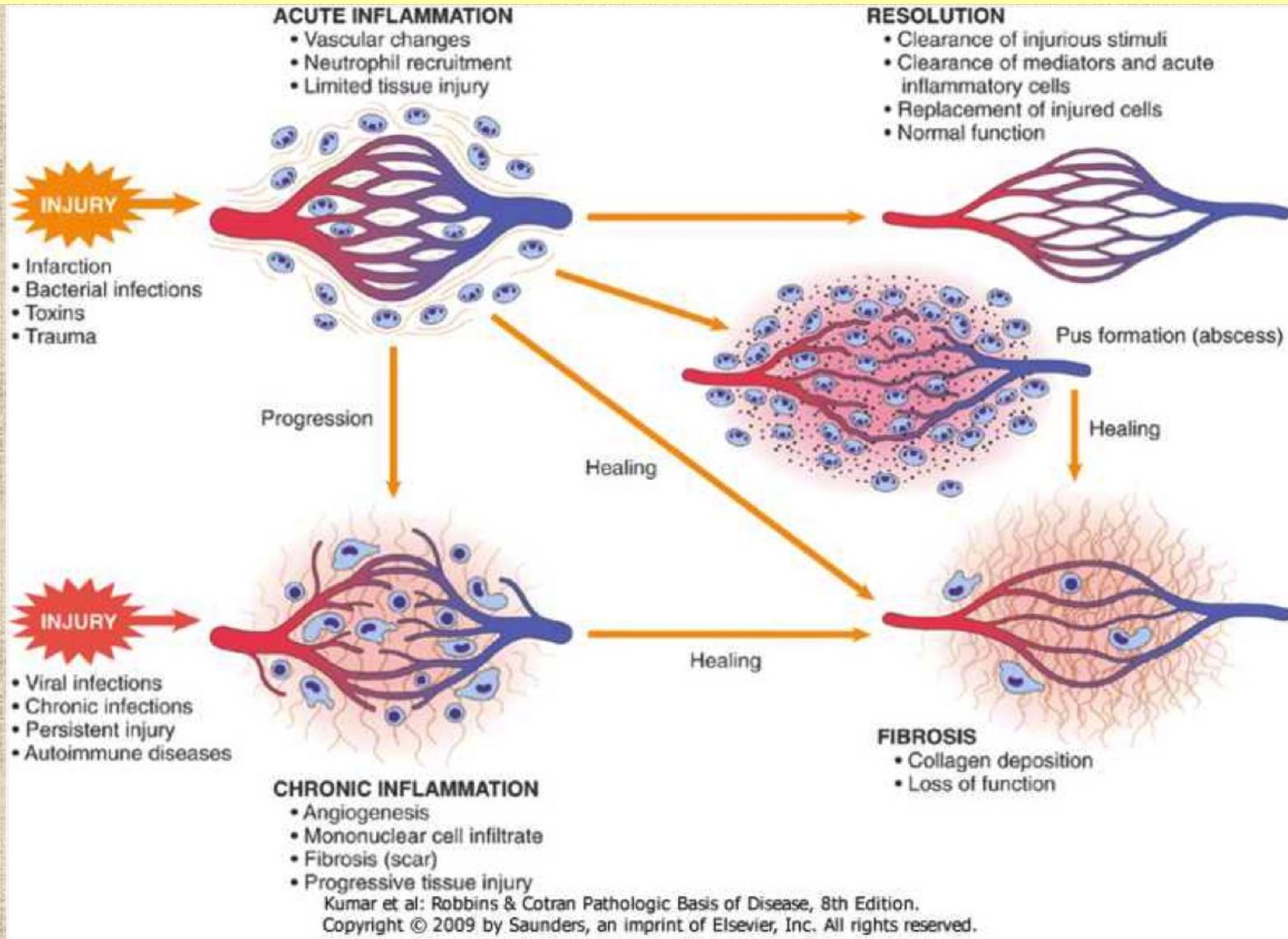
Structure of chemokine classes



© Kohidai, L.



Outcomes of acute inflammation



Causes of Chronic Inflammation

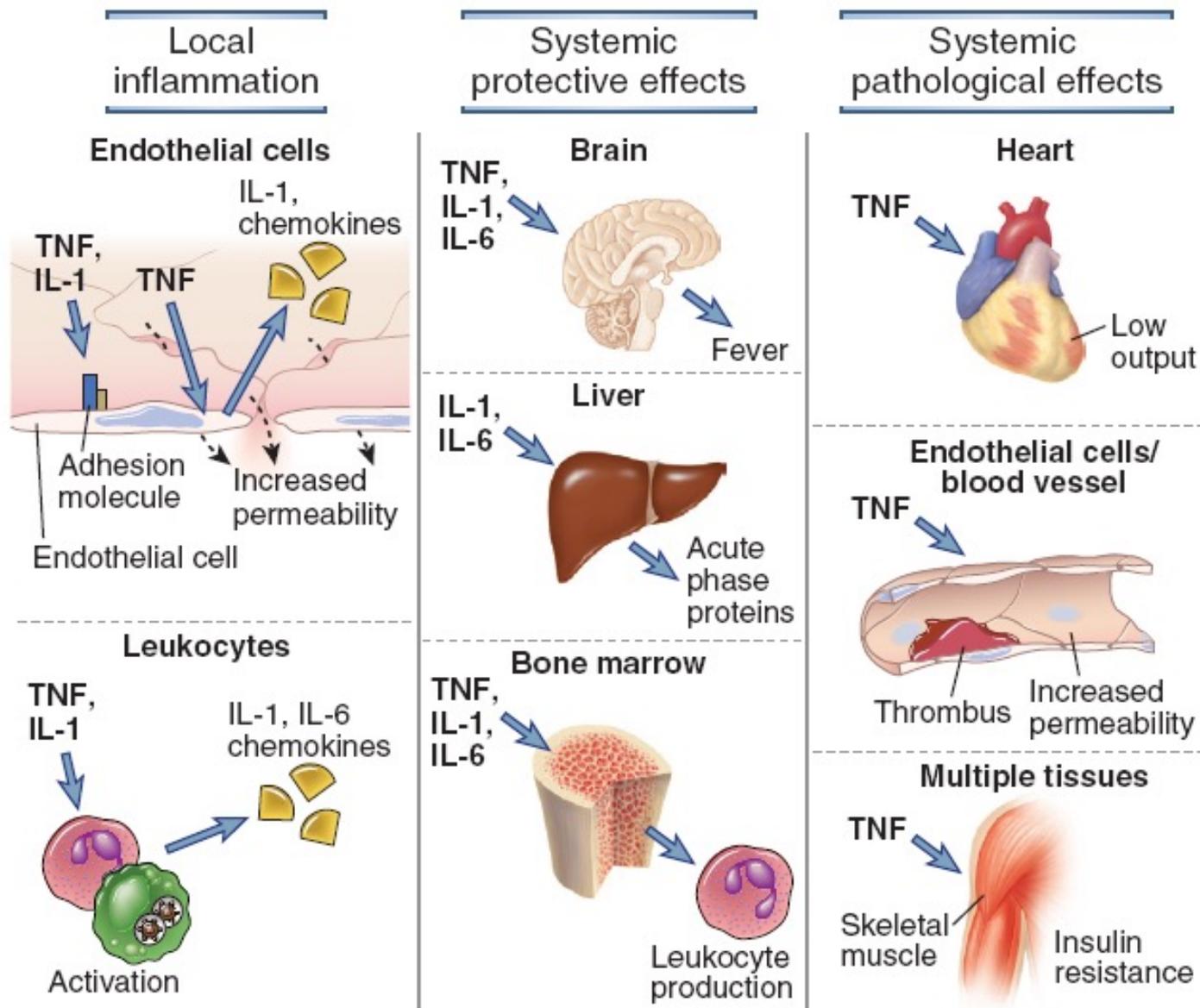
Unlike acute inflammation showing redness, swelling and pain, chronic inflammation can be invisible

Causes

- Autoimmune diseases e.g. such as rheumatoid arthritis, lupus
- Infectious agents e.g. H. pylori, viruses
- Atherosclerosis
- Environmental e.g. smoking
- Allergens
- Central adiposity: more macrophages localised in fat will thus produce more inflammatory mediators

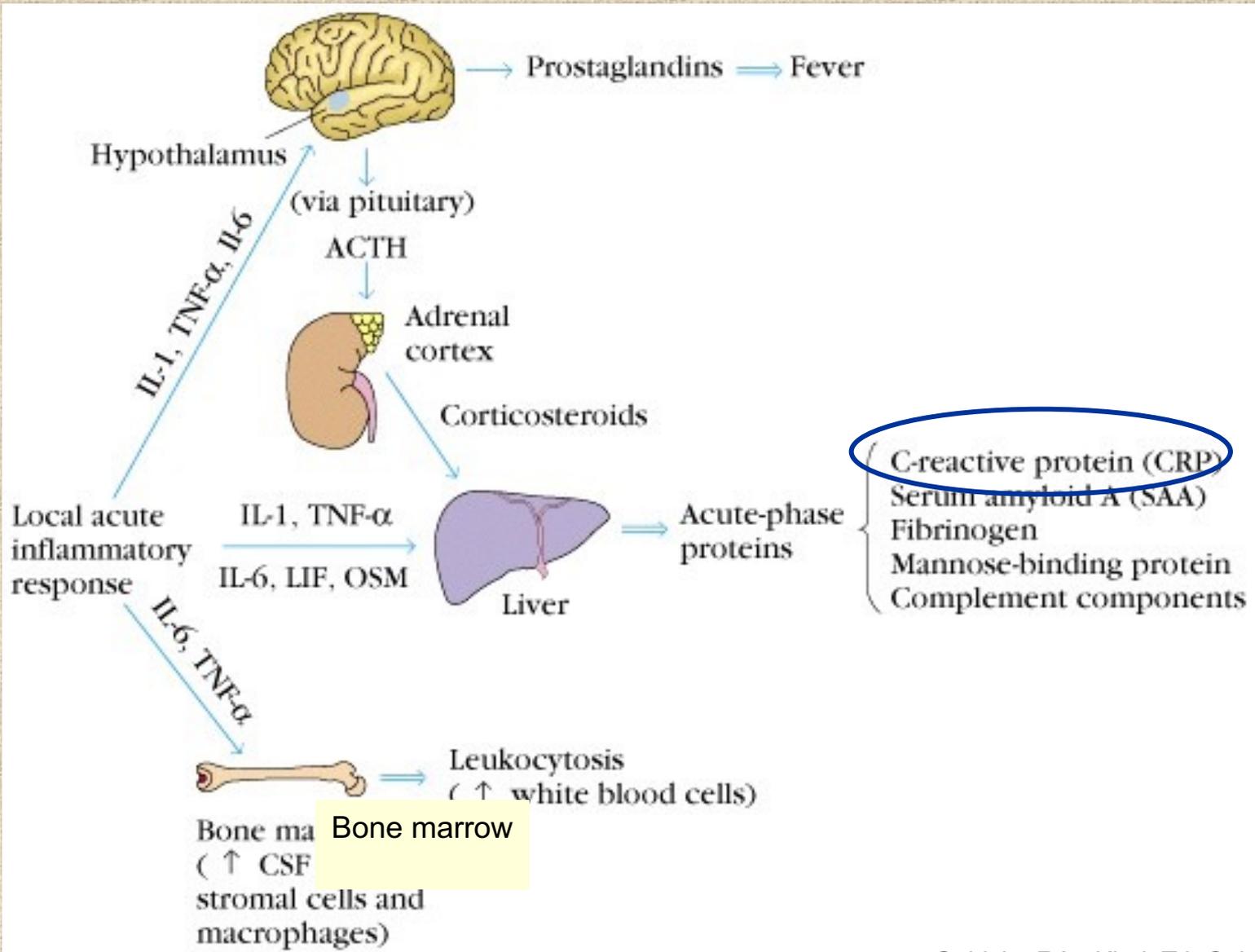
- **Systemic inflammation**

Local and systemic effects of TNF

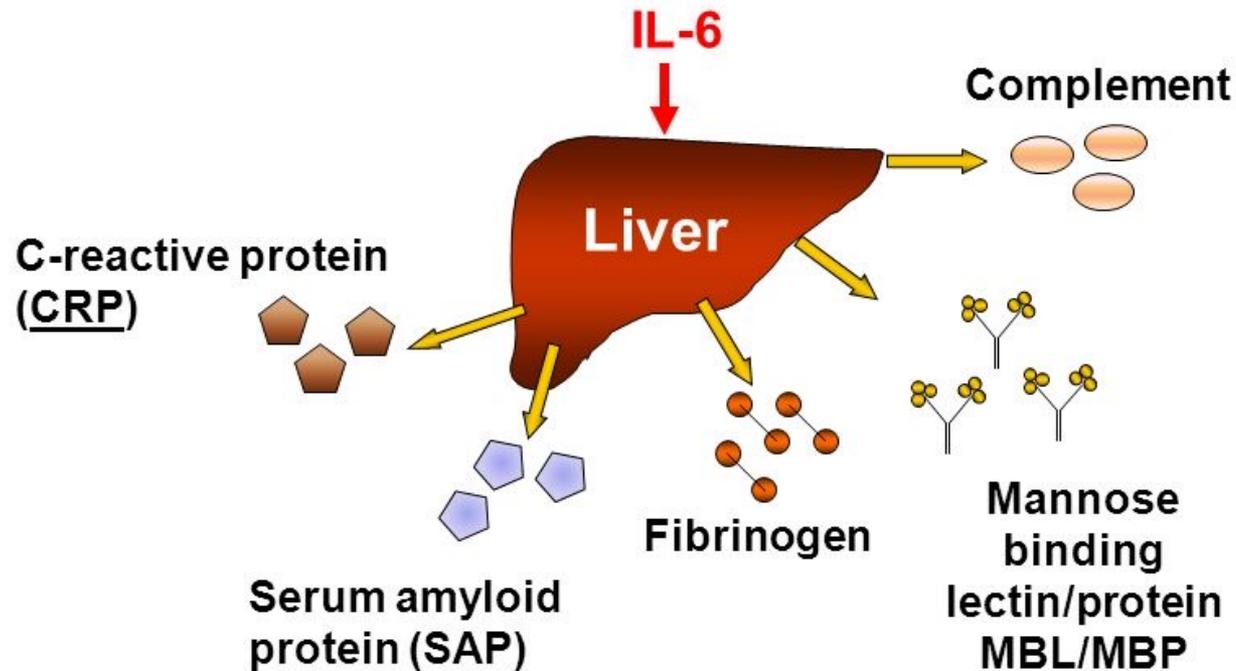


TNF inhibitors,
Steroids

Systemic acute inflammation = acute phase reaction



ACUTE PHASE REACTION

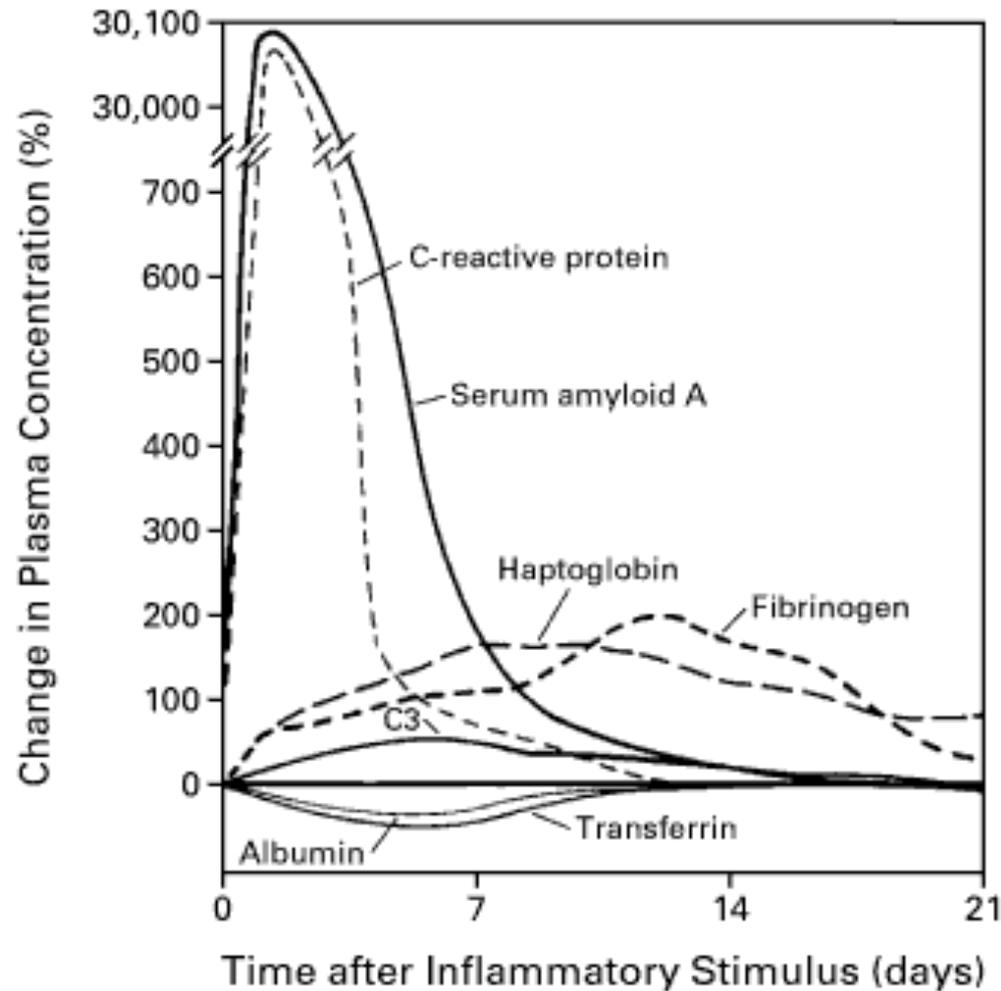


UNDER THE INFLUENCE OF IL-6 THE LIVER PRODUCES A BUNCH OF ACUTE-PHASE PROTEINS

Systemic effects of acute inflammation *acute phase response*

- Fever (temperature $> 37.8^{\circ}\text{C}$ or $>100\text{ F}$)
 - Increased pulse, blood pressure
 - Chills
 - Anorexia
- Leukocytosis
 - neutrophilia and left shift of neutrophils points to bacterial infection
 - Lymphocytosis points to viral infection
 - Eosinophilia point to allergy or parasitic infection
- Acute phase protein production in liver
 - fibrinogen, CRP, SAA leads to increased ESR

Acute phase proteins in serum



Complement system

- Major effector system of the humoral IR
- Component of the innate (non-specific) immune IR
- Results immediate response
- Connection to the specific IR

Discovery:

1890: **Jules Bordet's** experiment:

- Immune serum against *Vibrio cholerae* caused lysis of the bacteria
- Heating the antiserum destroyed this activity
- Addition of a fresh serum to the antiserum restored its killing ability

Paul Ehrlich:

2 components of the ANTISERUM:

- heat stable: specific antibody
- heat sensitive: responsible for the lytic activity →

COMPLEMENT

Components:

- **Inactive factors** in the serum and body fluids which can activate each other in an enzyme cascade
- **Cell surface receptors** (CR) for binding the activated complement components
- **Regulatory proteins**: soluble and cell surface bound – to prevent uncontrolled complement activation

Activation of the complement enzyme cascade

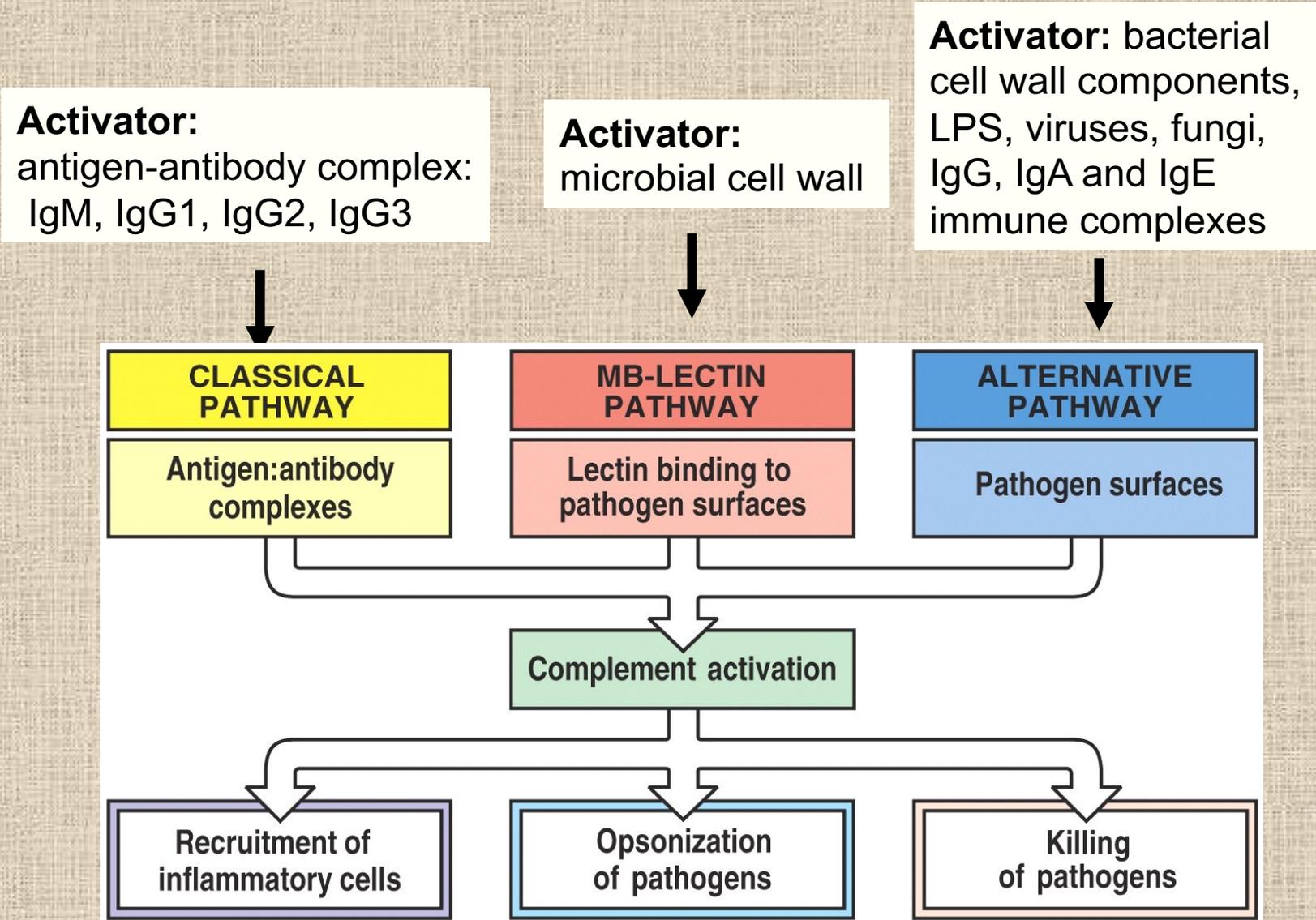
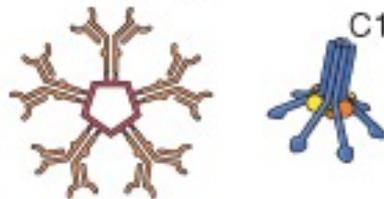


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

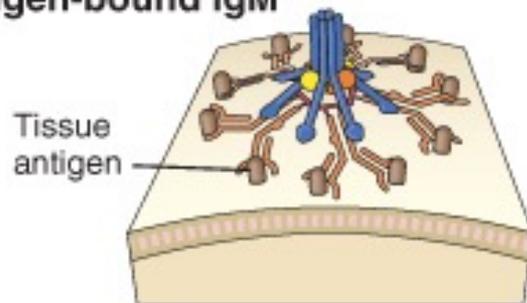
Complement activation

(A) Soluble IgM (inaccessible Fc)



No

(B) Antigen-bound IgM



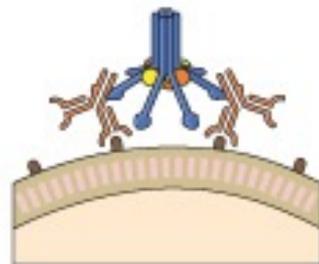
Yes

(C) Soluble IgG (Fc portions not adjacent)



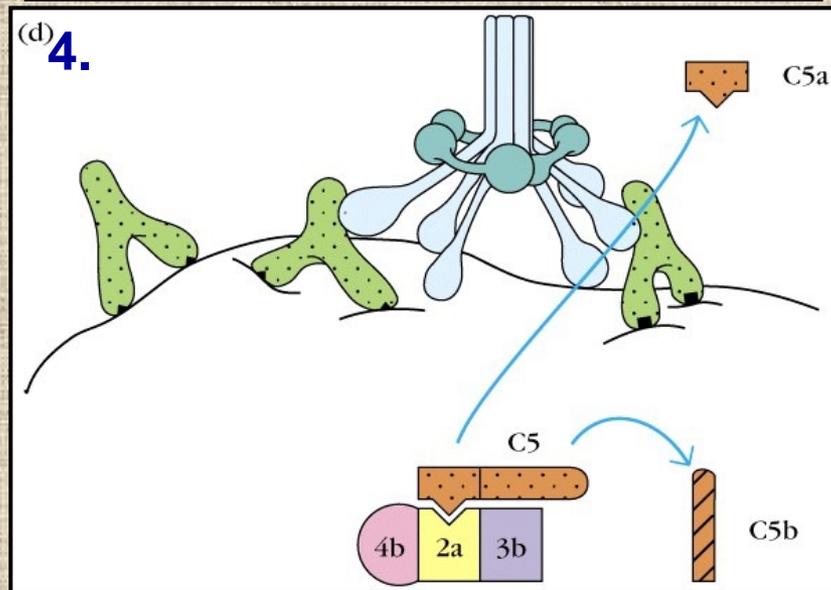
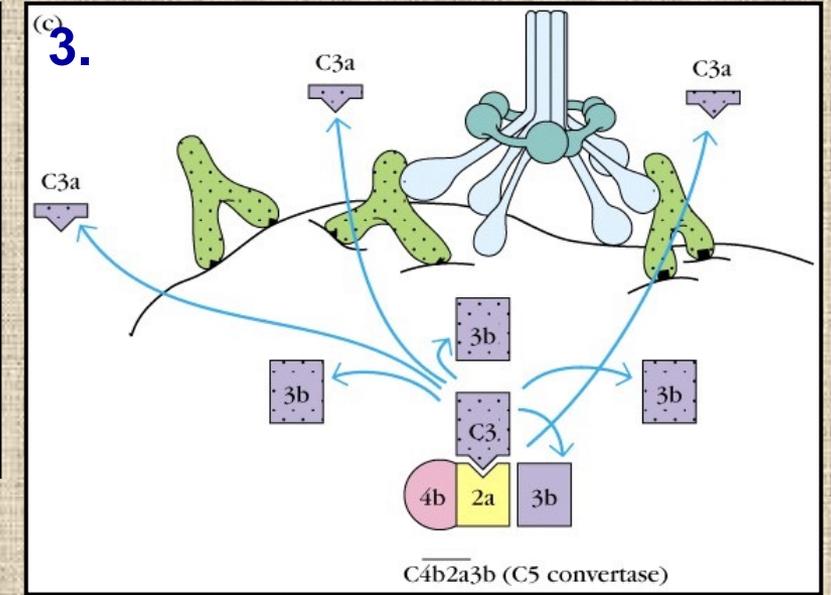
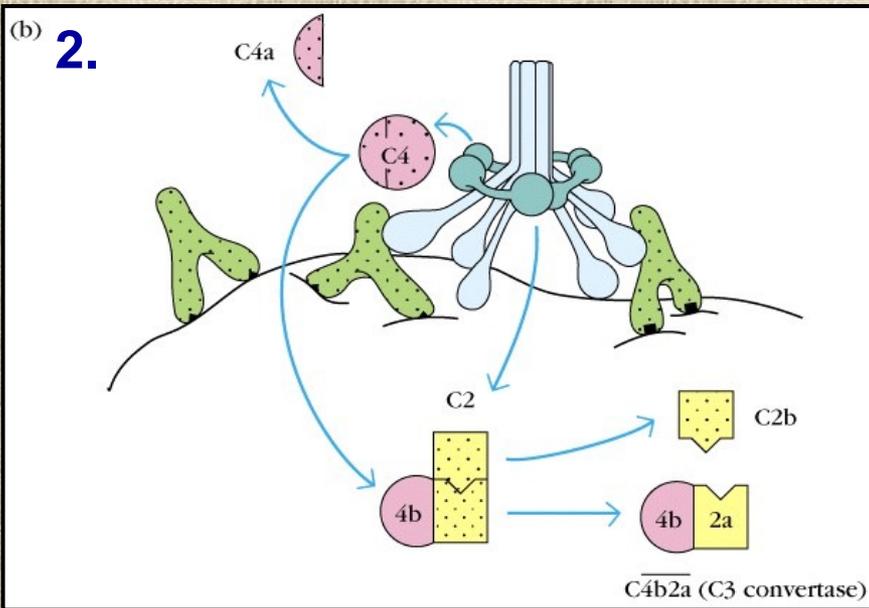
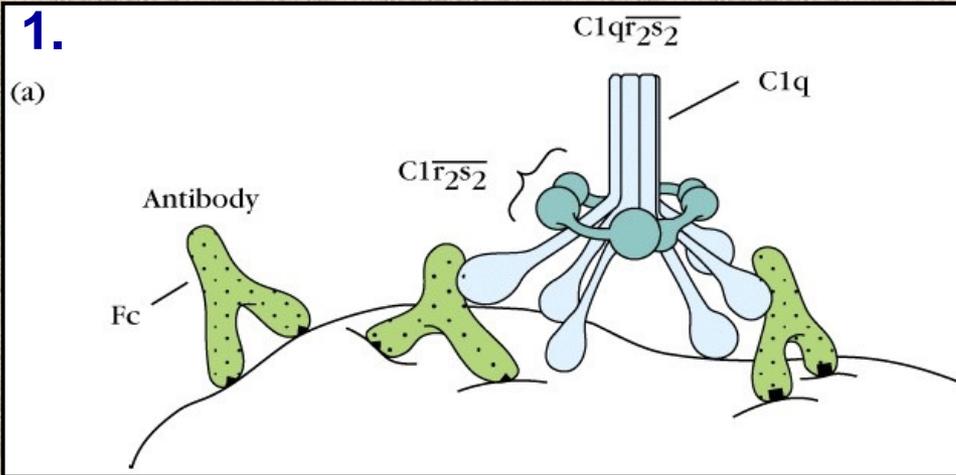
No

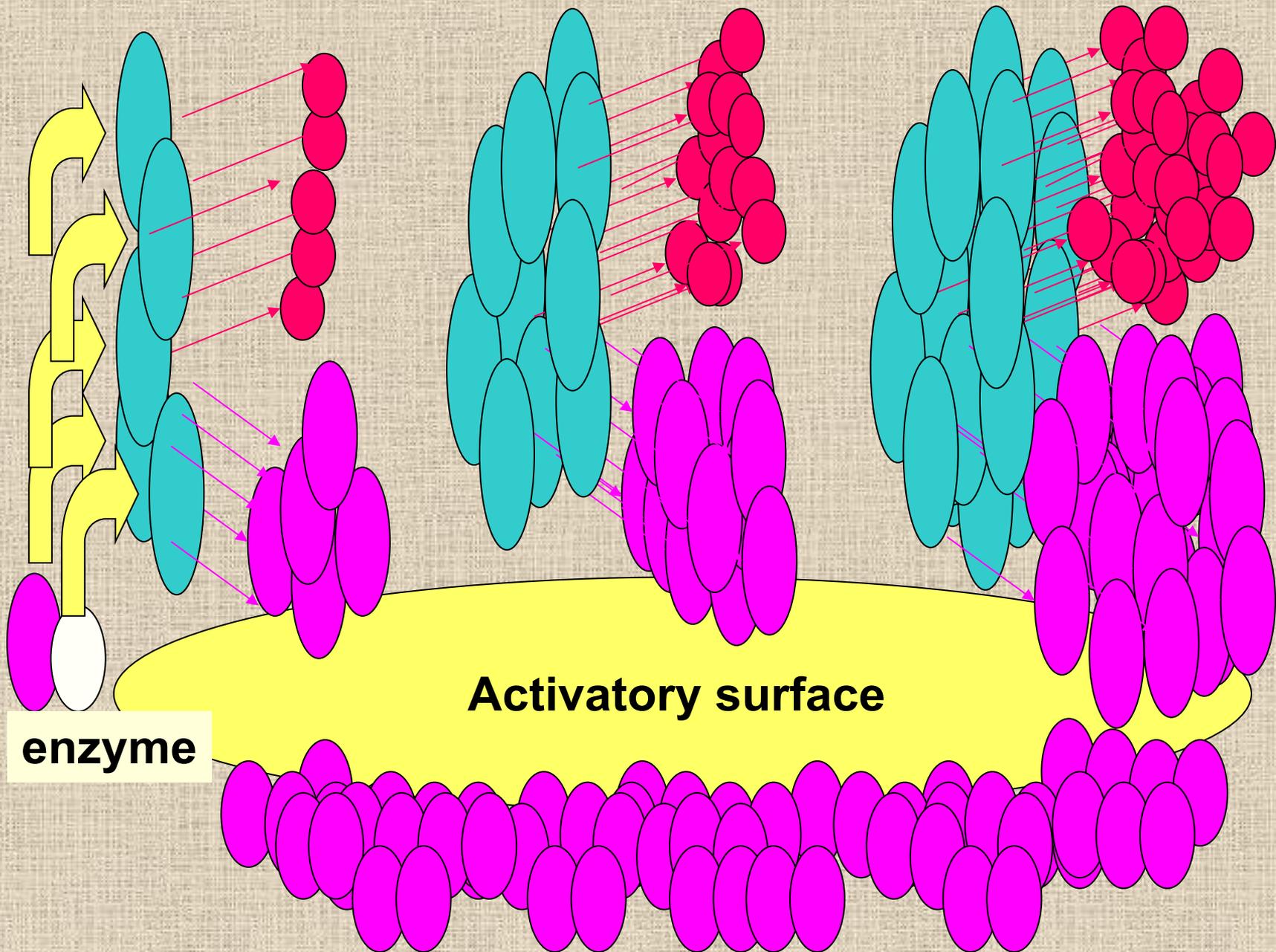
(D) Antigen-bound IgG



Yes

Components of the classical pathway





MBL forms a complex with serin proteases that resembles the C1qrs complex

MBL

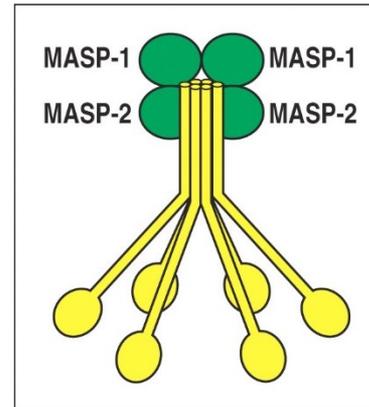
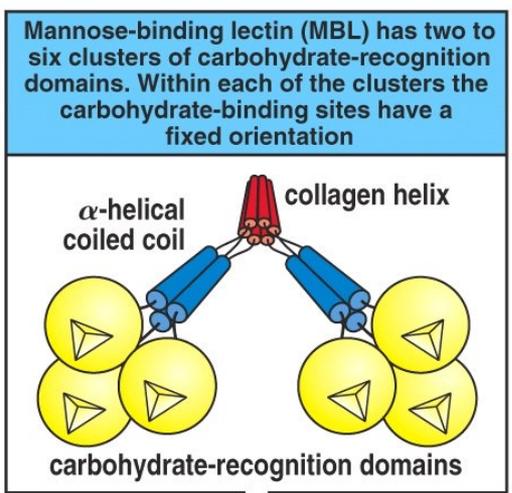


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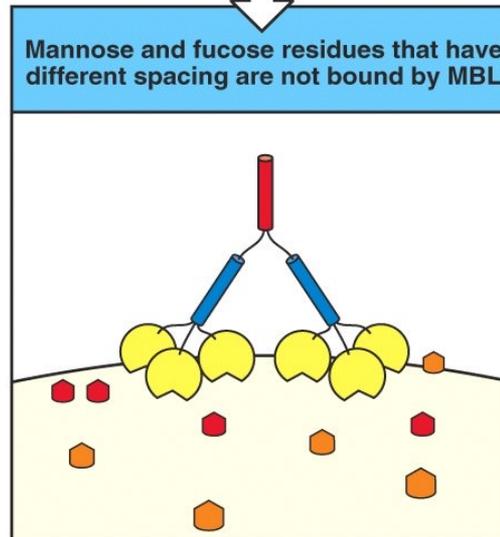
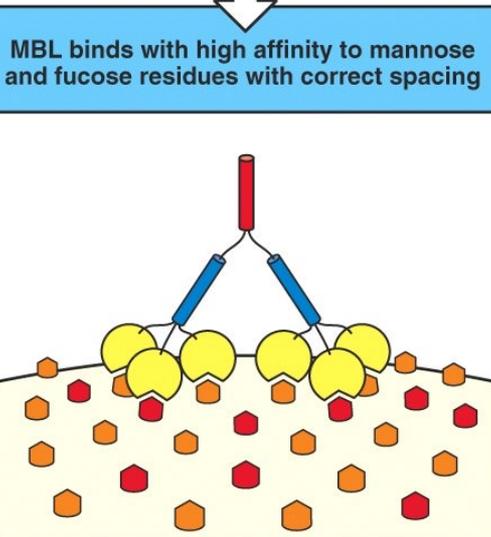
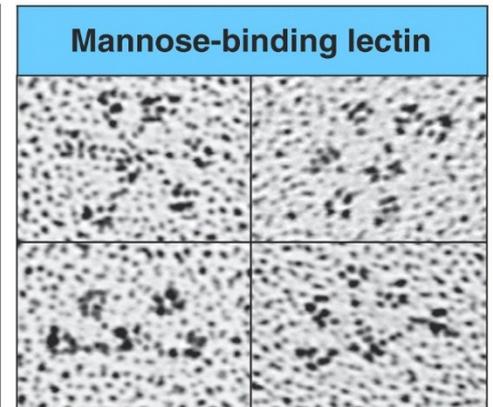


Figure 2-11 Immunobiology, 6/e. (© Garland Science 2005)

MASP

MBL: mannose binding lectin

MASP: mannose associated serine protease

Main components and effector actions of complement

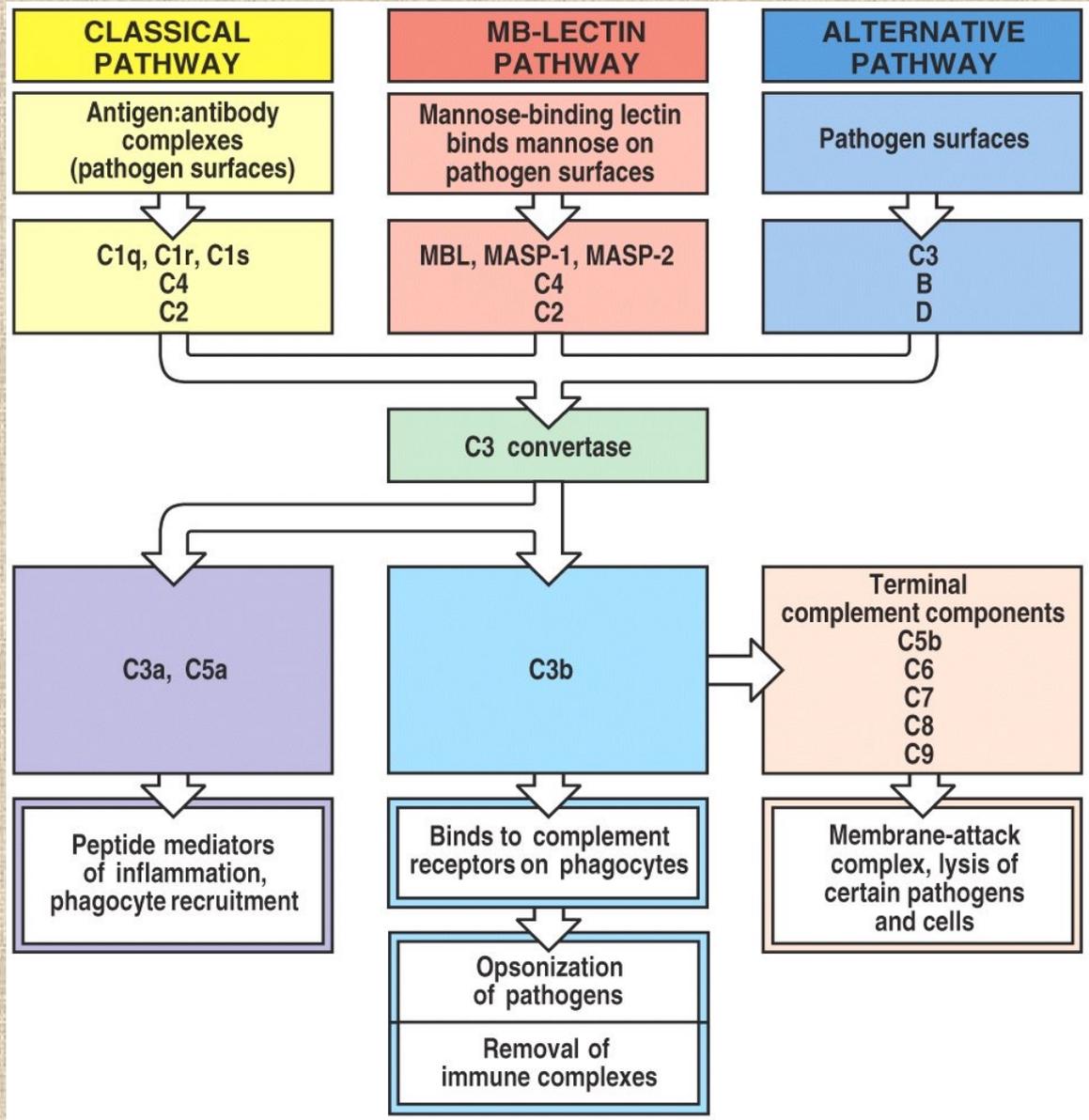
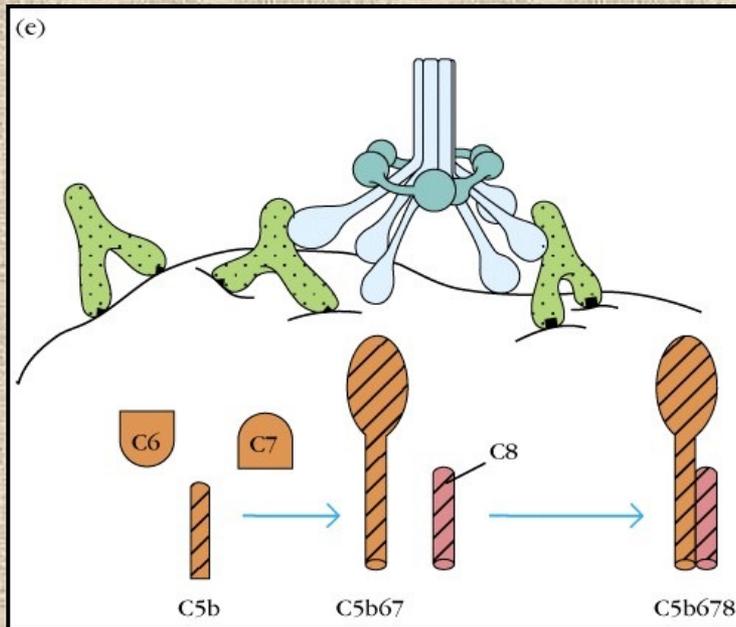
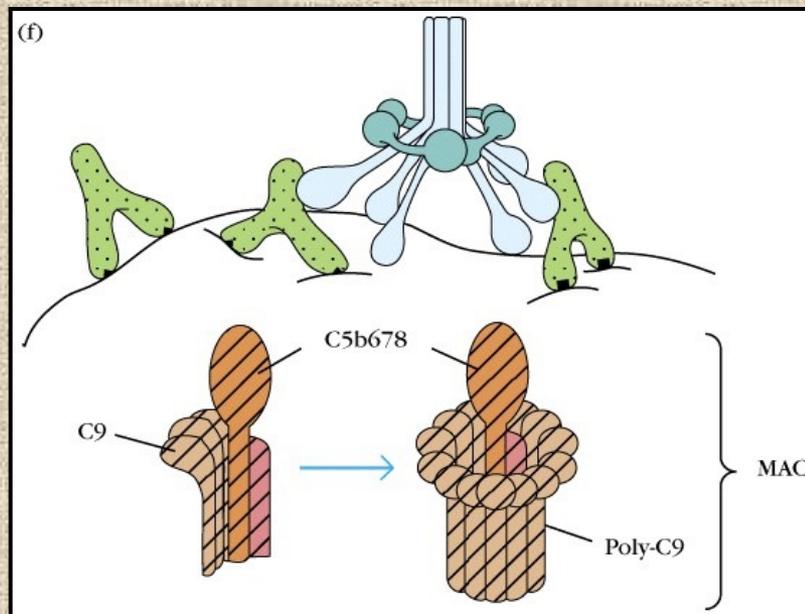


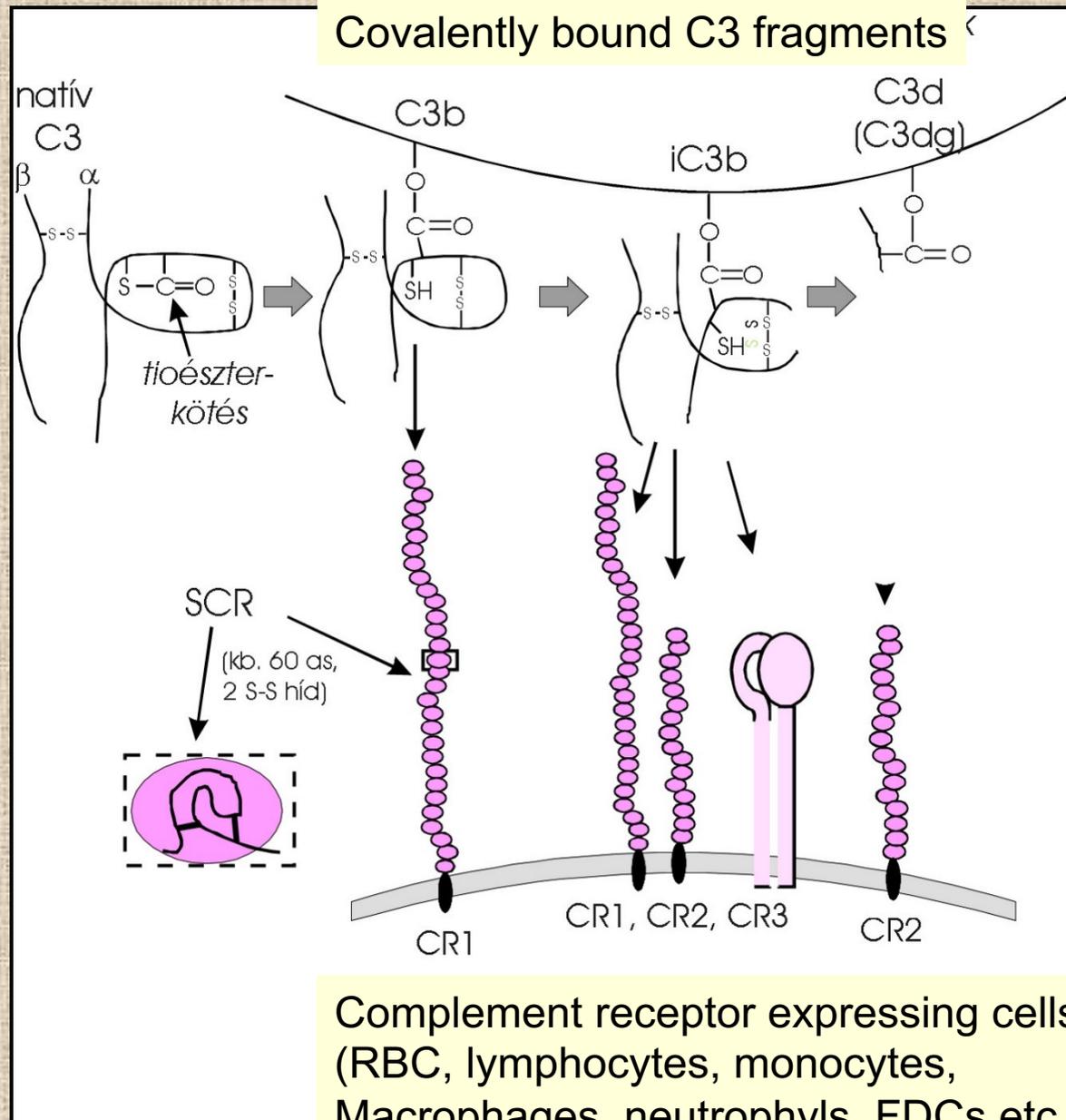
Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)



Membrane Attack Complex (MAC)



C3b-binding receptors



Complement receptors

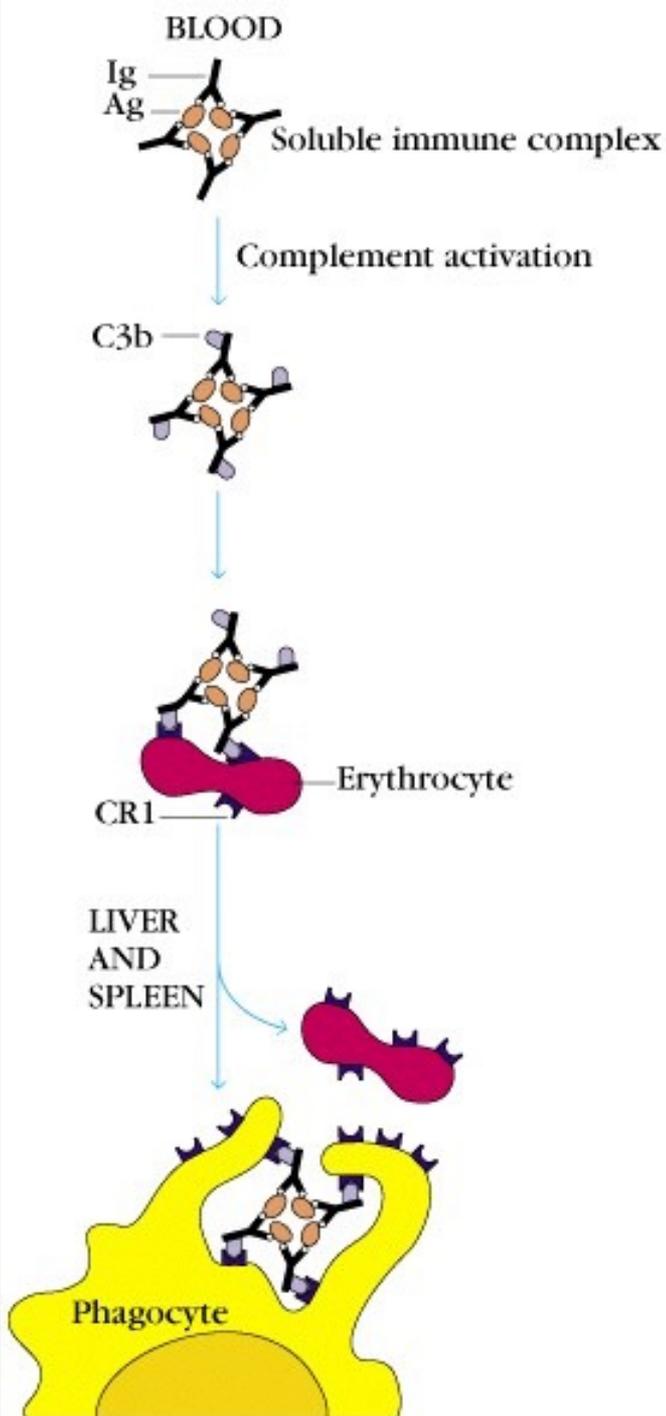
Receptor	Specificity	Functions	Cell types
CR1 (CD35)	C3b, C4b iC3b	Promotes C3b and C4b decay Stimulates phagocytosis Erythrocyte transport of immune complexes	Erythrocytes, macrophages, monocytes, polymorphonuclear leukocytes, B cells, FDC
CR2 (CD21)	C3d, iC3b, C3dg Epstein– Barr virus	Part of B-cell co-receptor Epstein–Barr virus receptor	B cells, FDC
CR3 (Mac-1) (CD11b/ CD18)	iC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, FDC
CR4 (gp150,95) (CD11c/ CD18)	iC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, dendritic cells
C5a receptor	C5a	Binding of C5a activates G protein	Endothelial cells, mast cells, phagocytes
C3a receptor	C3a	Binding of C3a activates G protein	Endothelial cells, mast cells, phagocytes

Figure 2-31 Immunobiology, 6/e. (© Garland Science 2005)

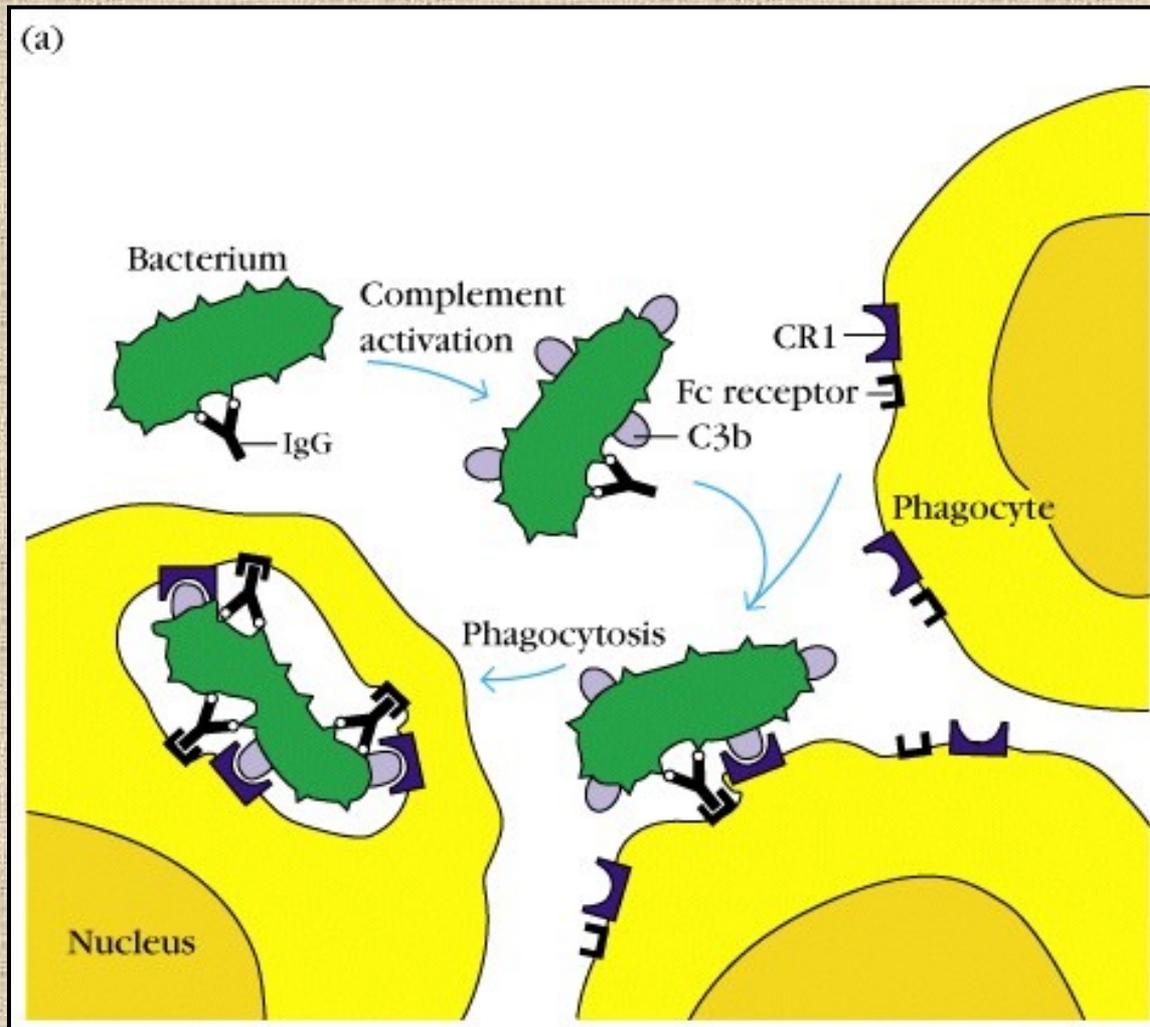
Clearance of immunocomplexes from blood

1. Immunocomplex formation
2. Complement activation – C3b binding
3. Binding of IC to CR1 of the RBCs
4. Transport to the spleen and liver
5. Macrophages bind immunocomplexes and take them up by phagocytosis

Inefficient clearance: immunocomplex deposition

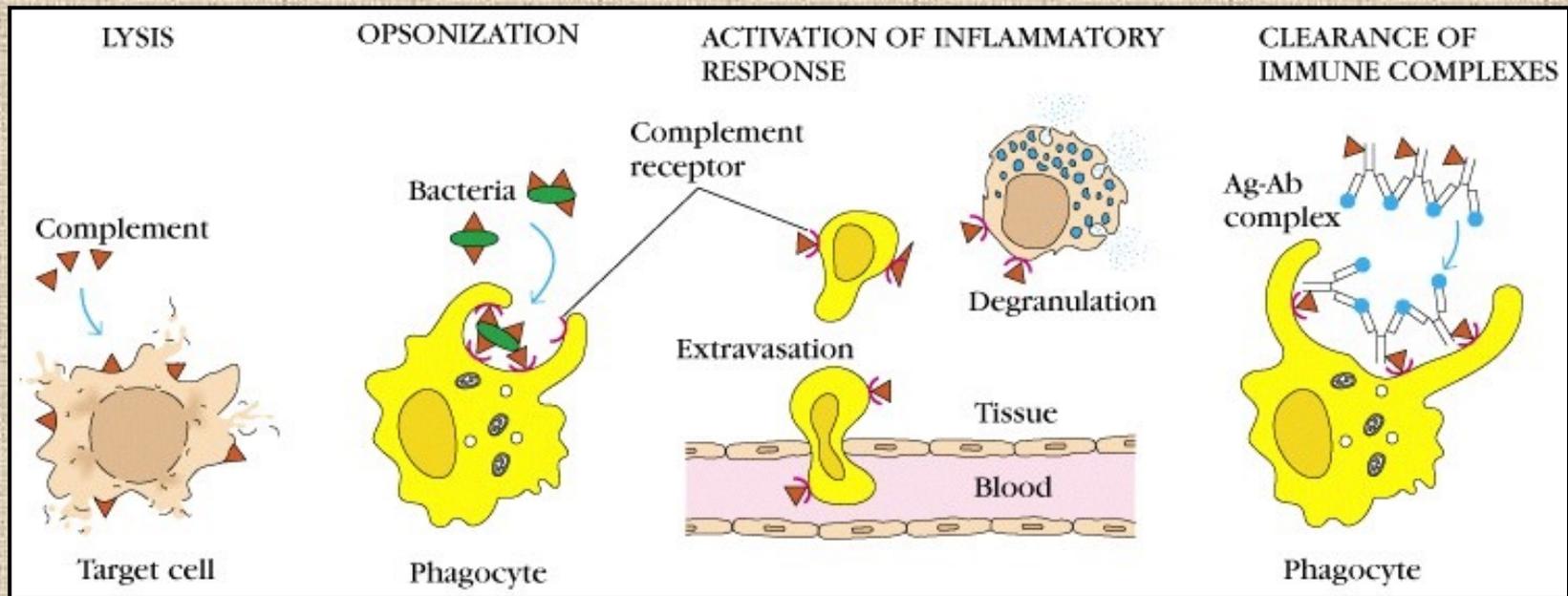


OPSONIZATION: C3b and IgG serve as opsonins

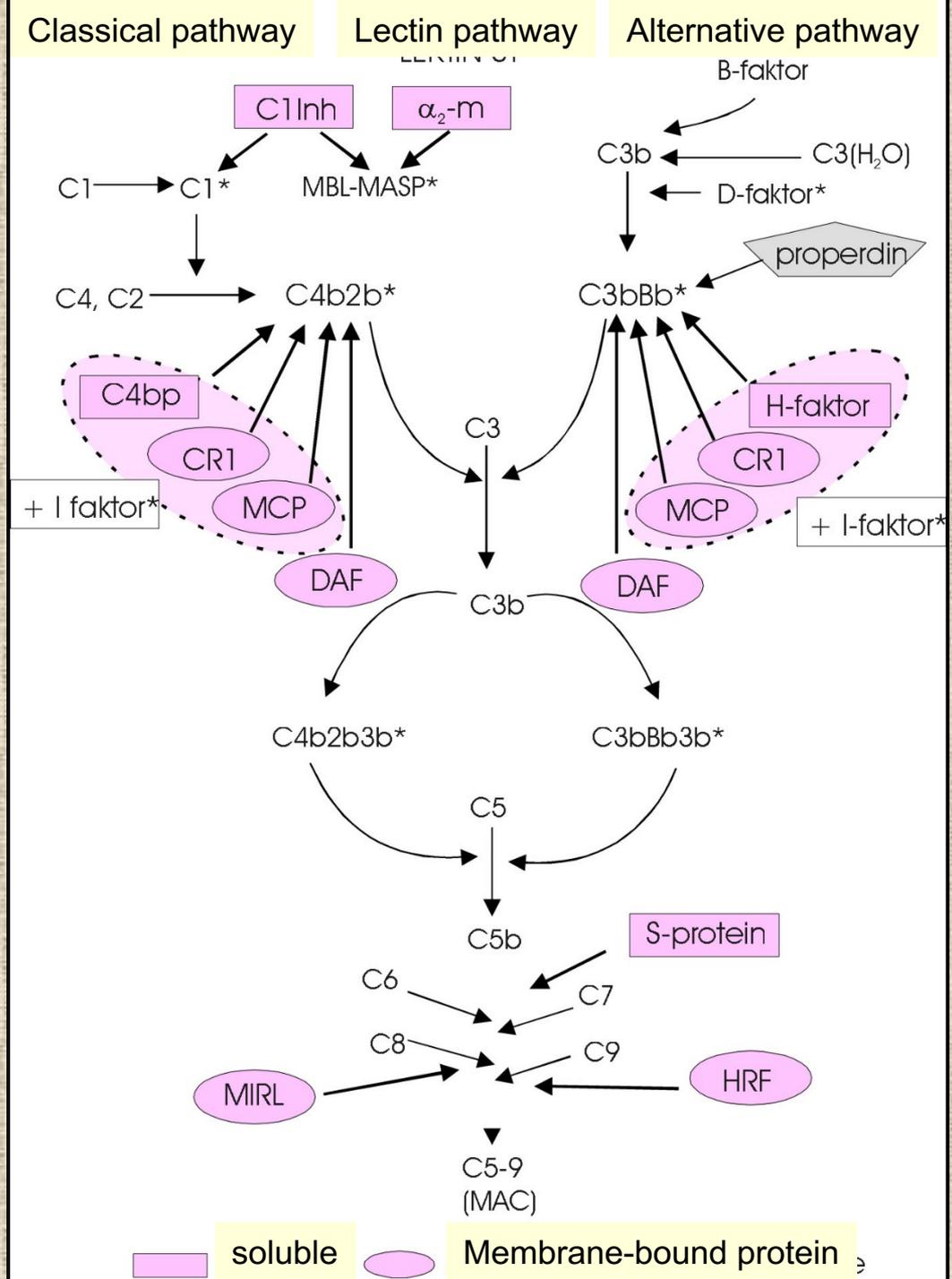


Functions of the complement:

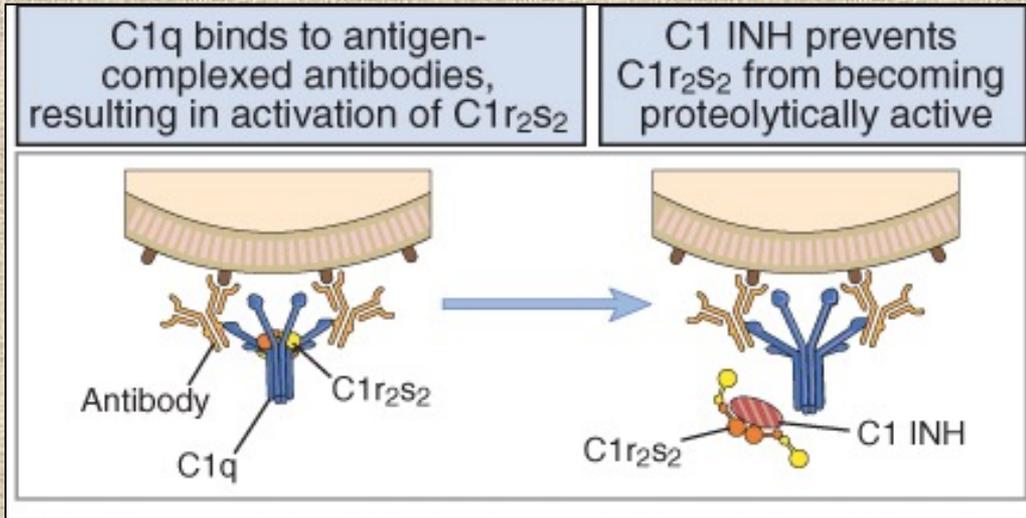
1. Lysis of cells, bacteria, viruses
2. Opsonization, which promotes phagocytosis of particulate antigens
3. Binding to complement receptors results activation of the inflammatory response and specific IR
4. Immune clearance of immune complexes from circulation



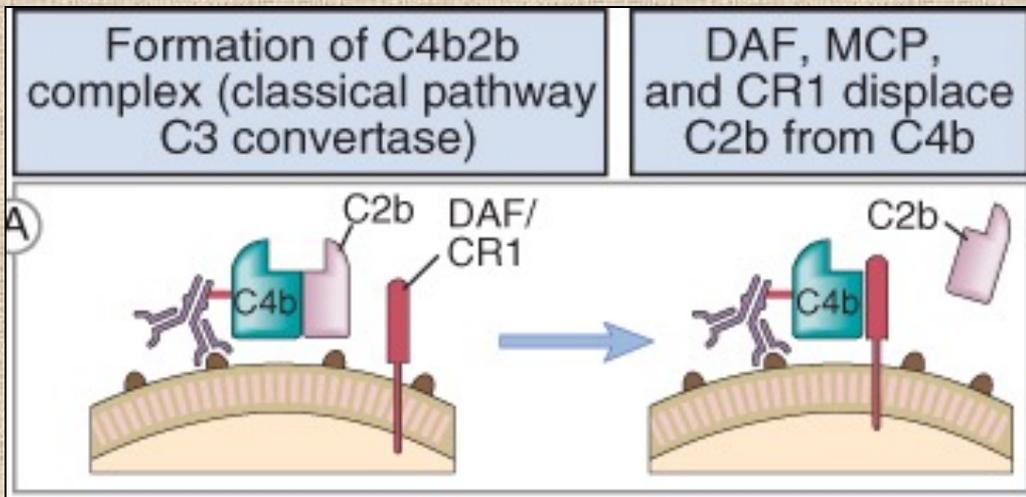
Regulatory proteins



Regulatory proteins of classical pathway



C1 INHIBITOR



DAF: Decay accelerating factor
MCP: Membrane cofactor Protein
CR1: complement receptor-1

Regulation of alternative pathway

