Basic Immunology

Lecture 16

Complement system

Why is complement system important?

- 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

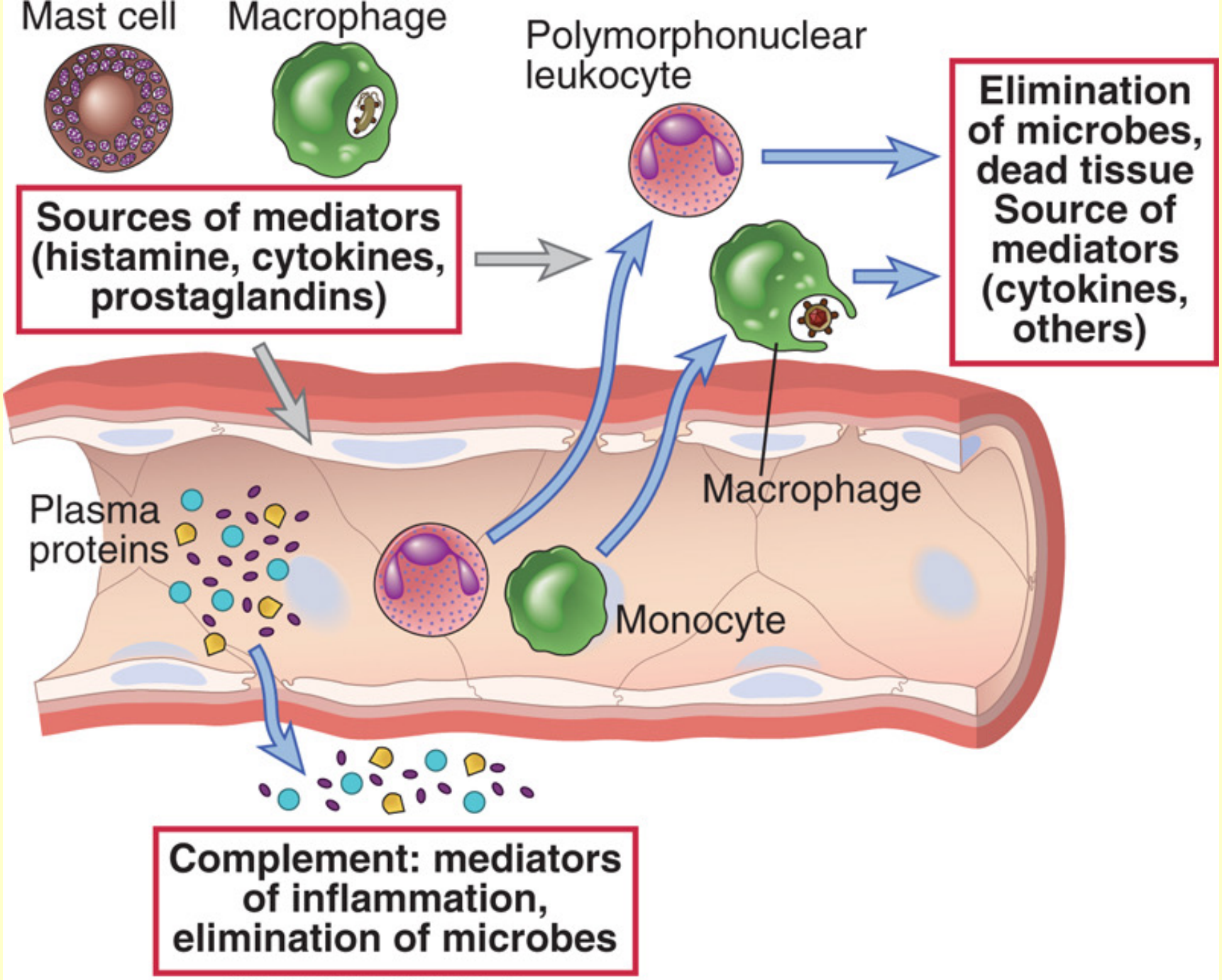
Molecular mediators of inflammation

Plasma enzyme mediators:
- kinin kallikrein system
- Fibrinolytic system
- Complement cascade
- Clotting cascade

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

Lipid mediators:
leukotrienes,
prostaglandins (PGE)

Inflammatory cytokines:
IL-1, IL-6, TNFalpha



Activation of the complement enzyme cascade

Activator: antigen-antibody complex: IgM, IgG1, IgG2, IgG3

Activator: microbial cell wall

Activator: bacterial cell wall components, LPS, viruses, fungi, IgG, IgA and IgE immune complexes

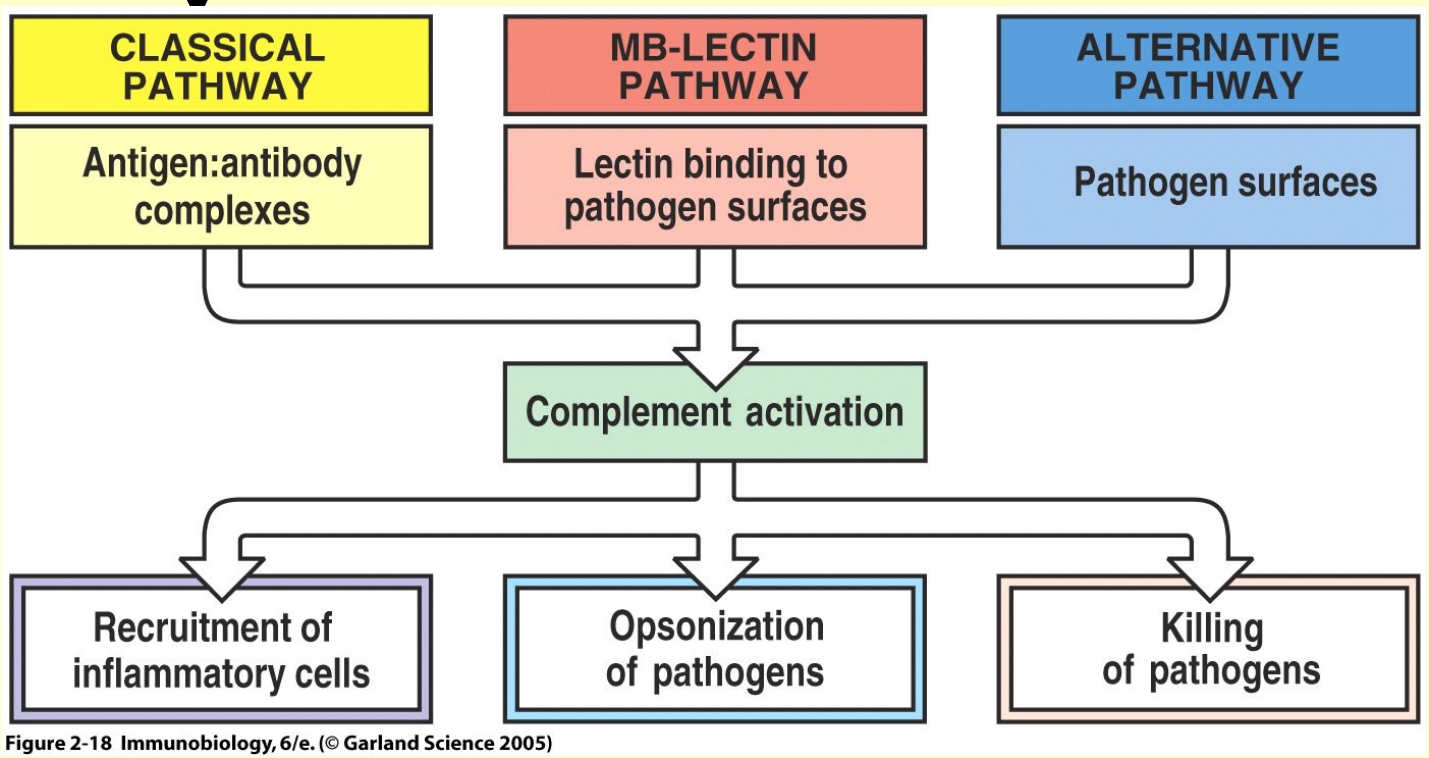
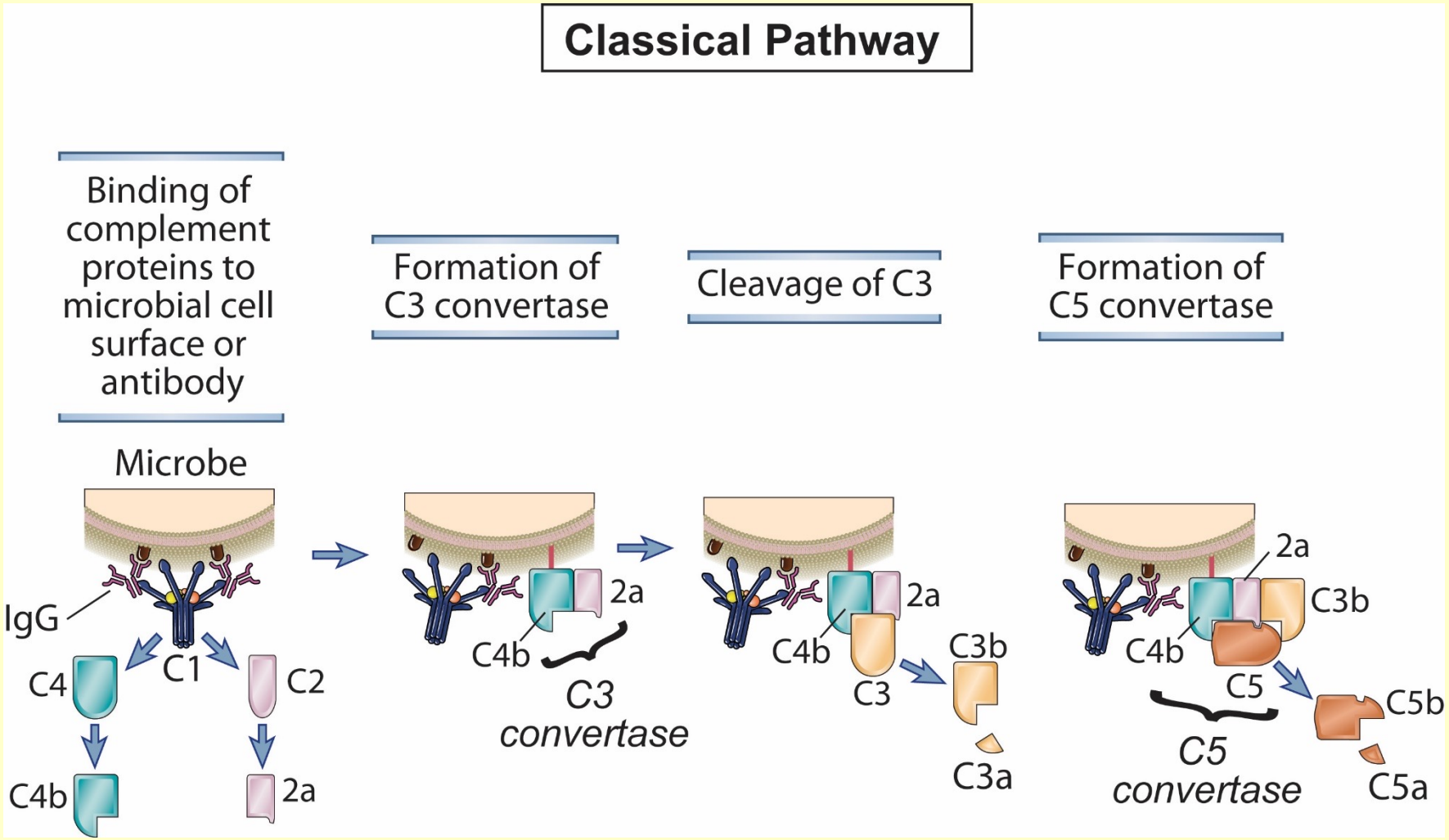
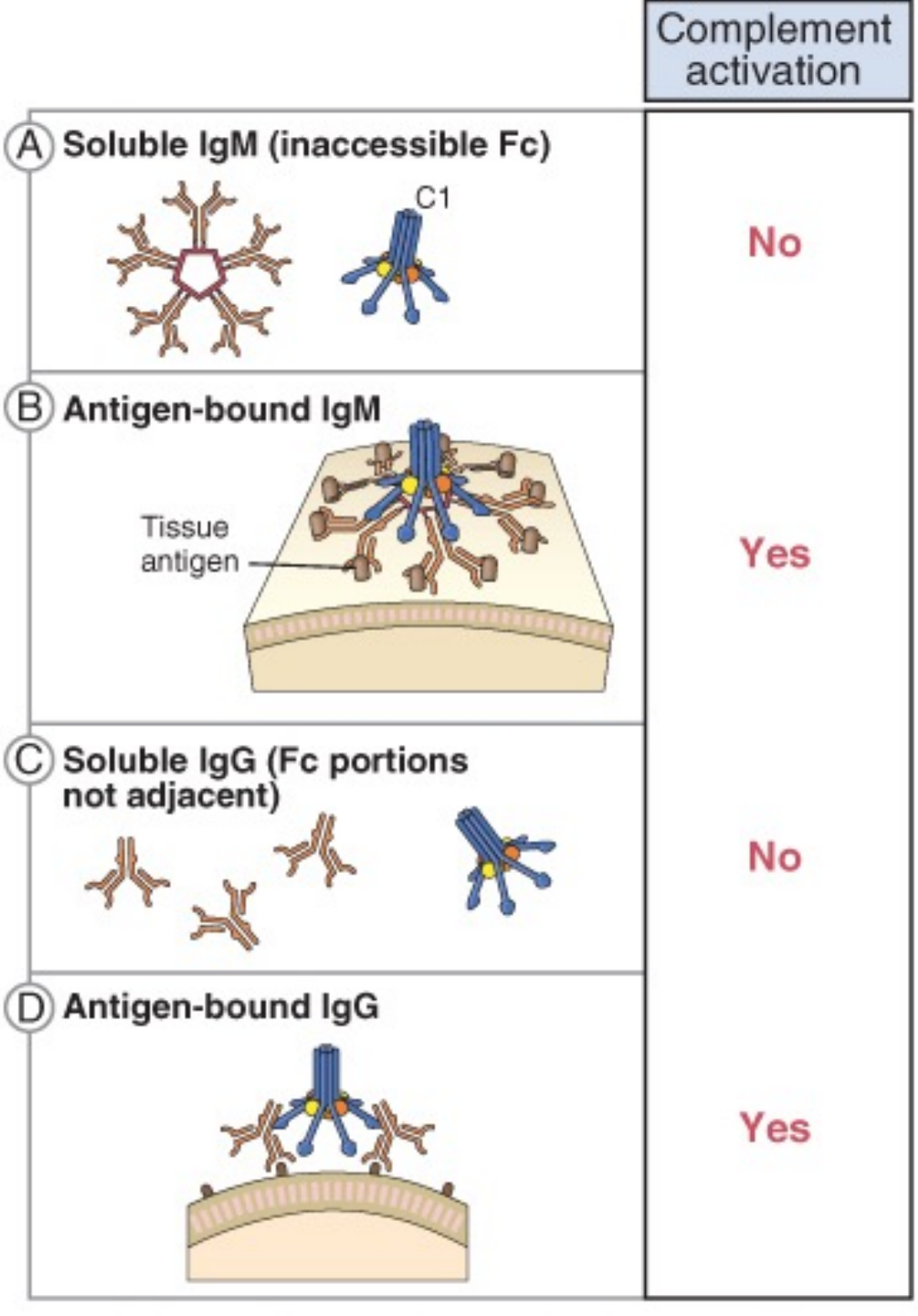


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

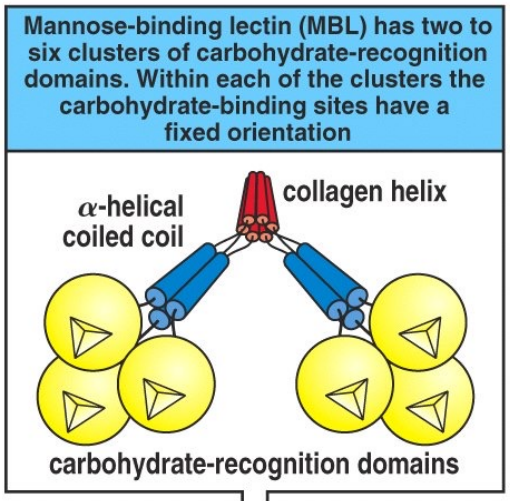
Early steps of classical pathway activation

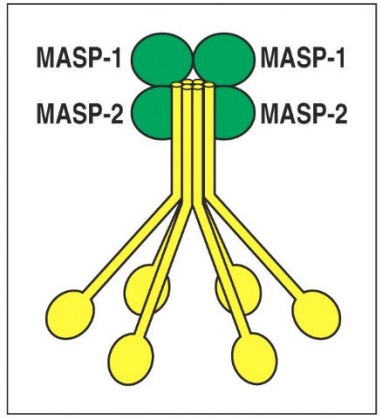



Complement activation
A Soluble IgM (inaccessible Fc)
C1
No
B Antigen-bound IgM
Tissue antigen
Yes
C Soluble IgG (Fc portions not adjacent)
No
D Antigen-bound IgG
Yes

First components of lectin pathway

MBL





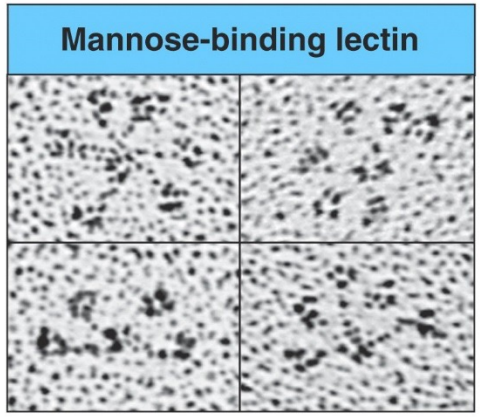


Figure 2-24 Immunobiology, 6/e. (© Garland Science 2005)

MASP

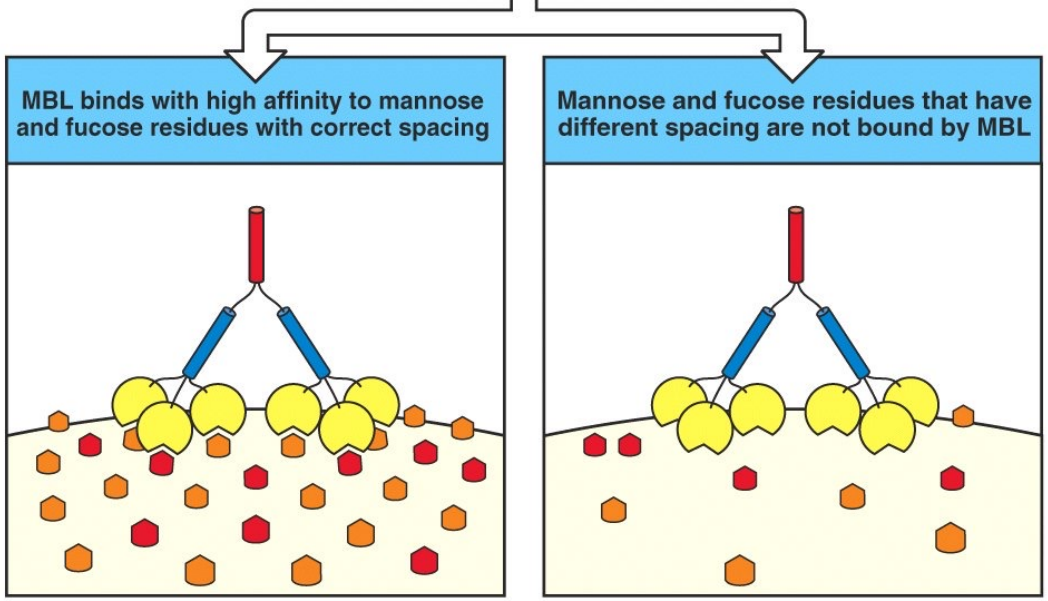


Figure 2-11 Immunobiology, 6/e. (© Garland Science 2005)

MBL: mannose binding lectin

MASP: mannose associated serine protease

Early Steps of Lectin pathway activation

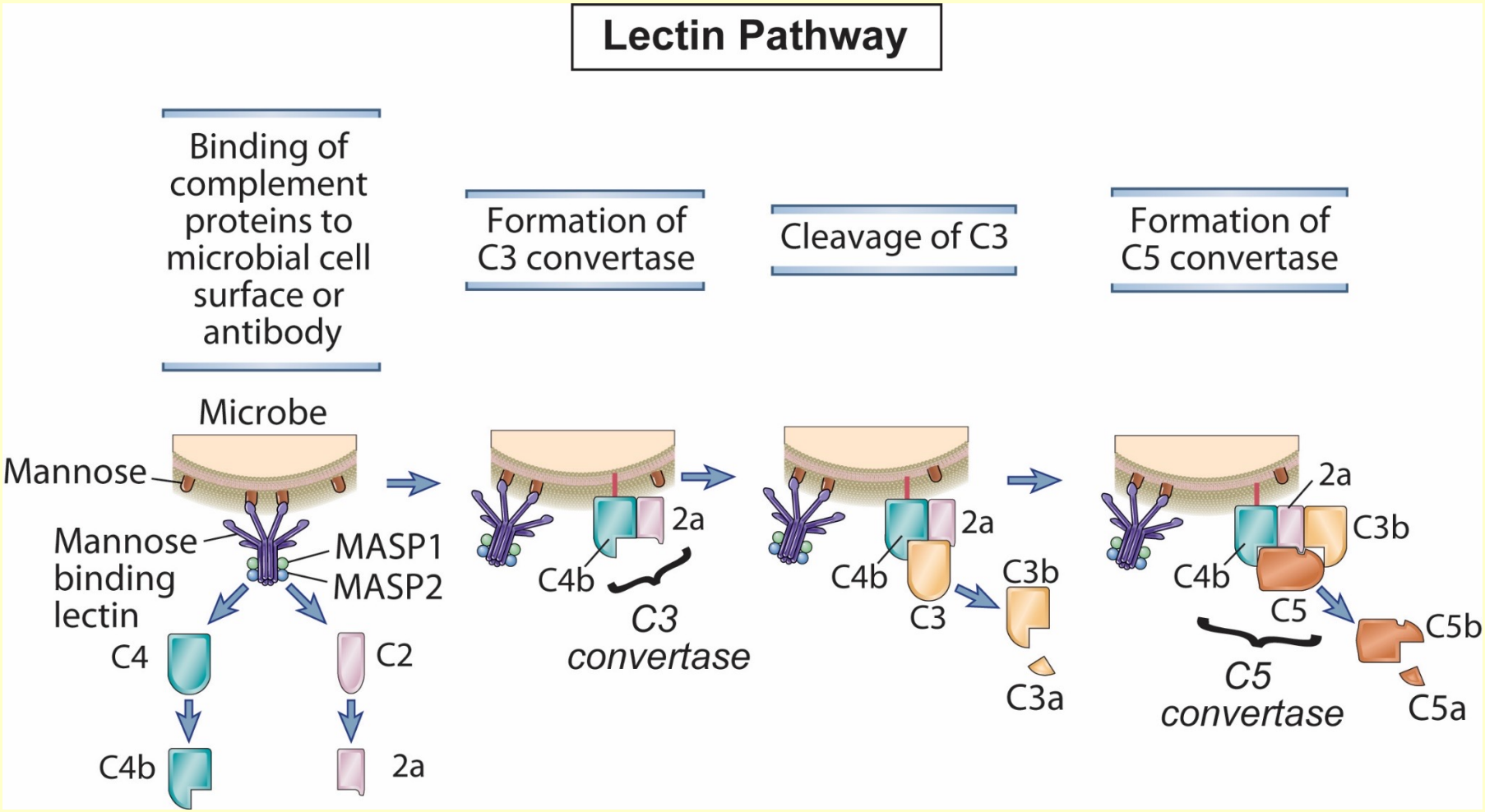
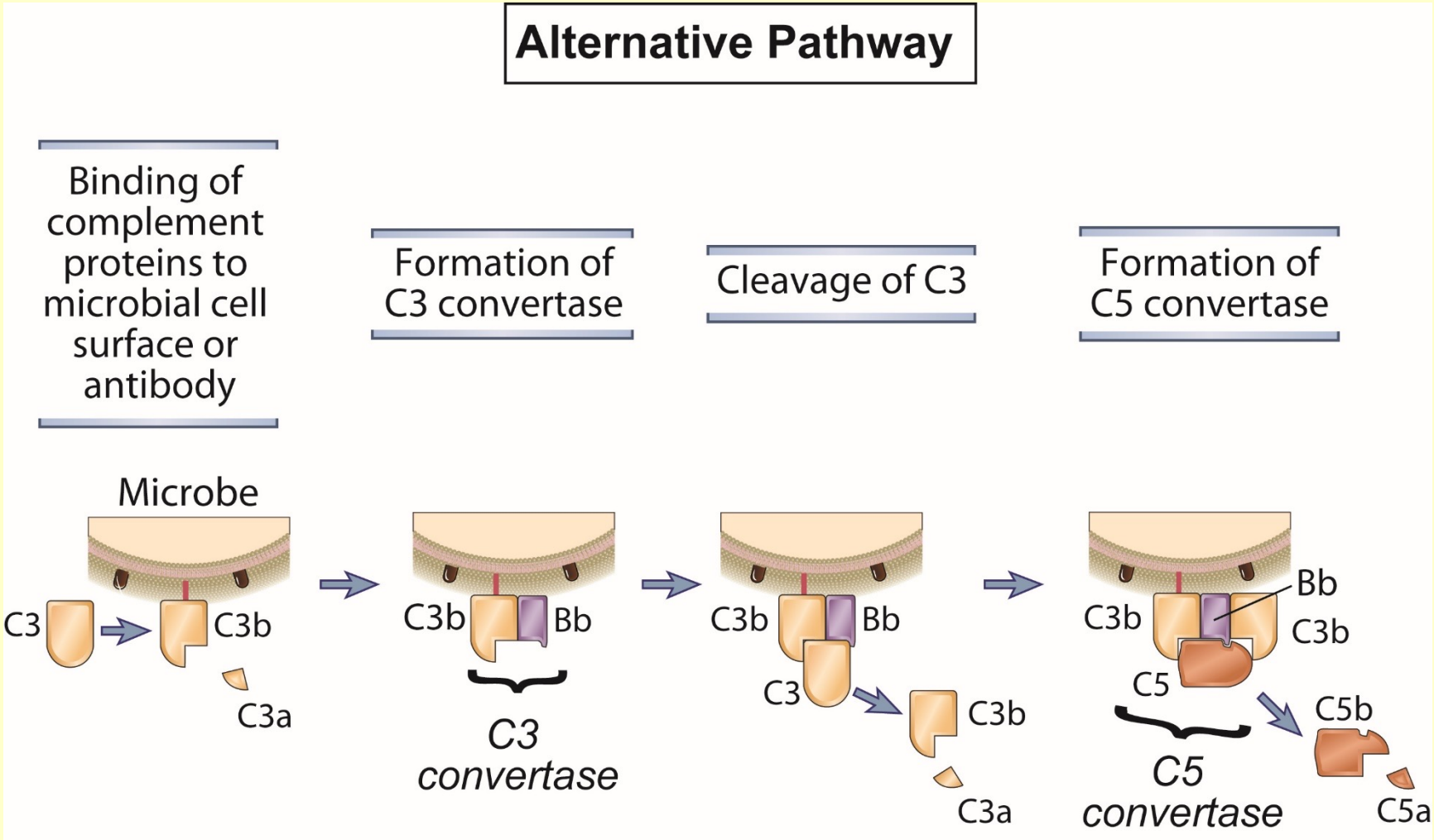
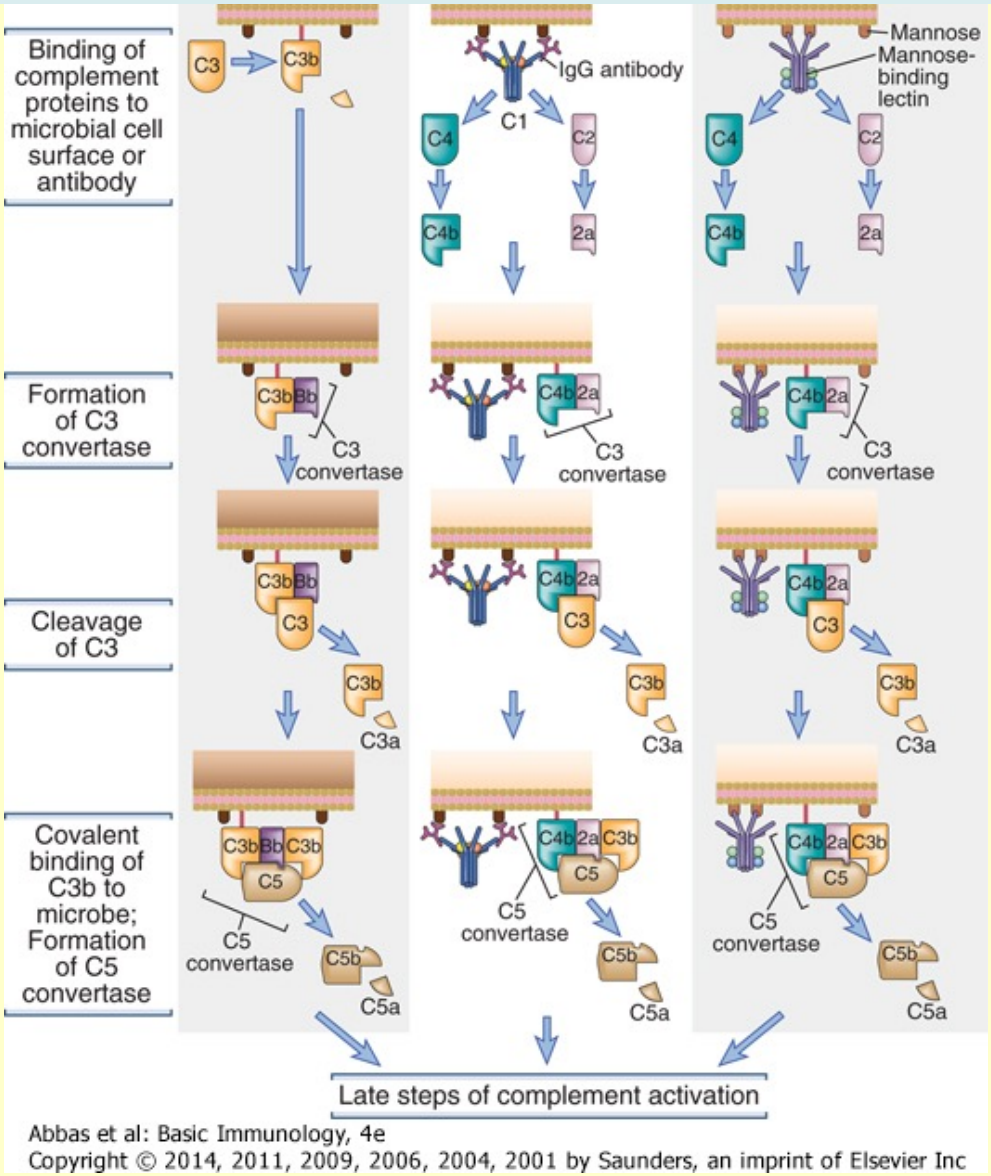


Fig. 12-6C

Early steps of alternative pathway activation



Comparison of pathways activation



Late Steps of Complement Activation:MAC

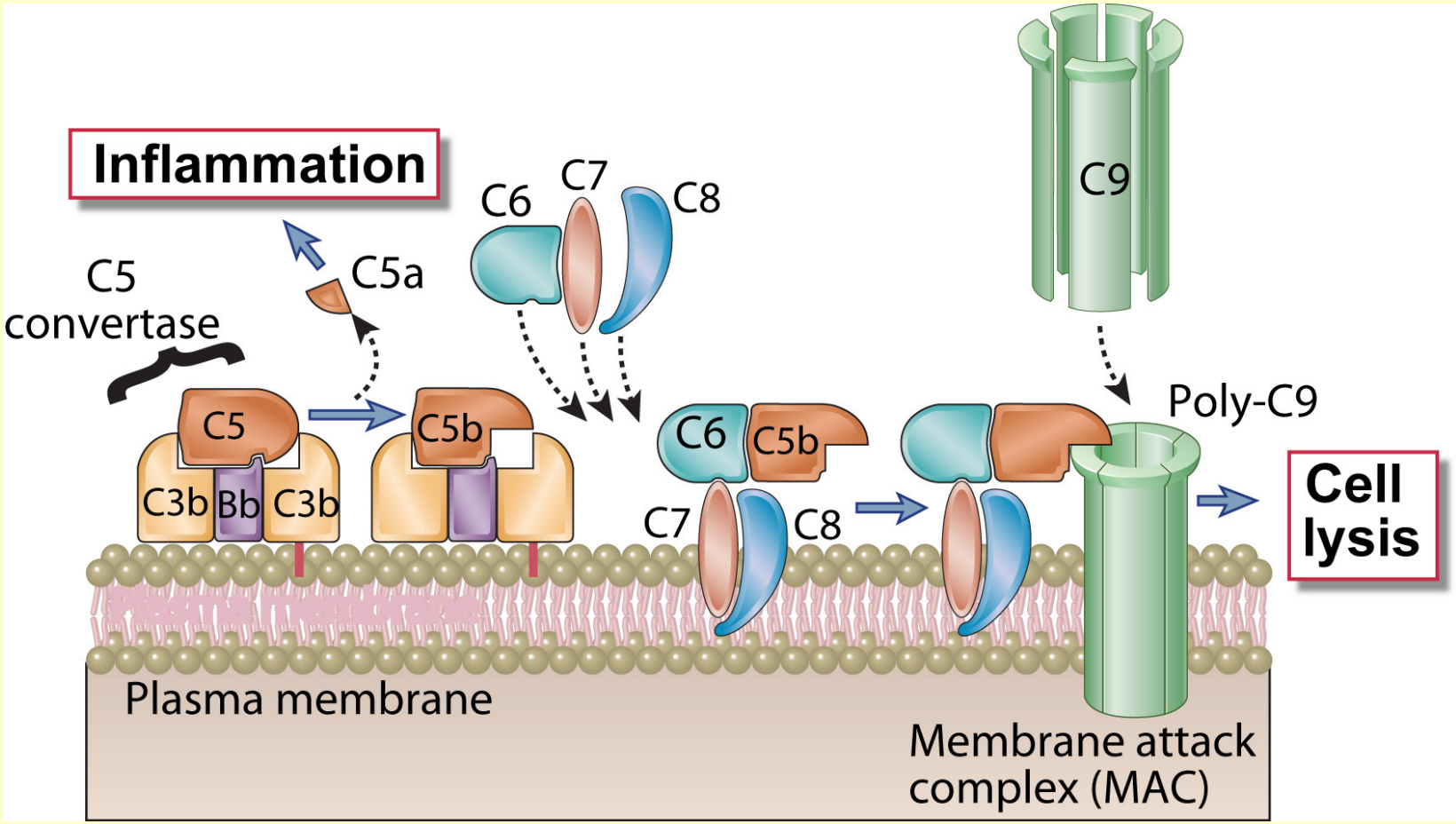
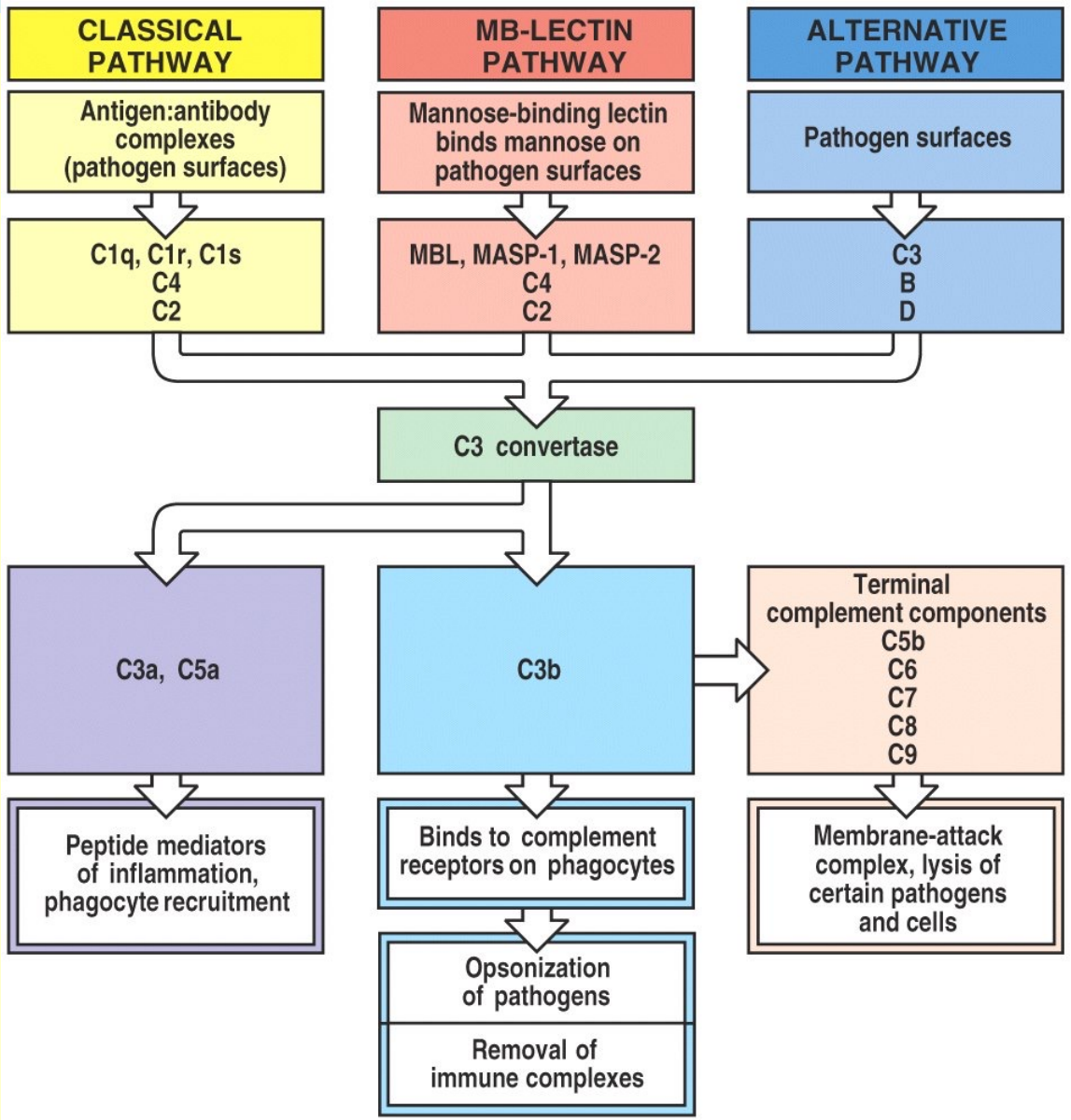


Fig. 12-12

Components and effector actions of complement



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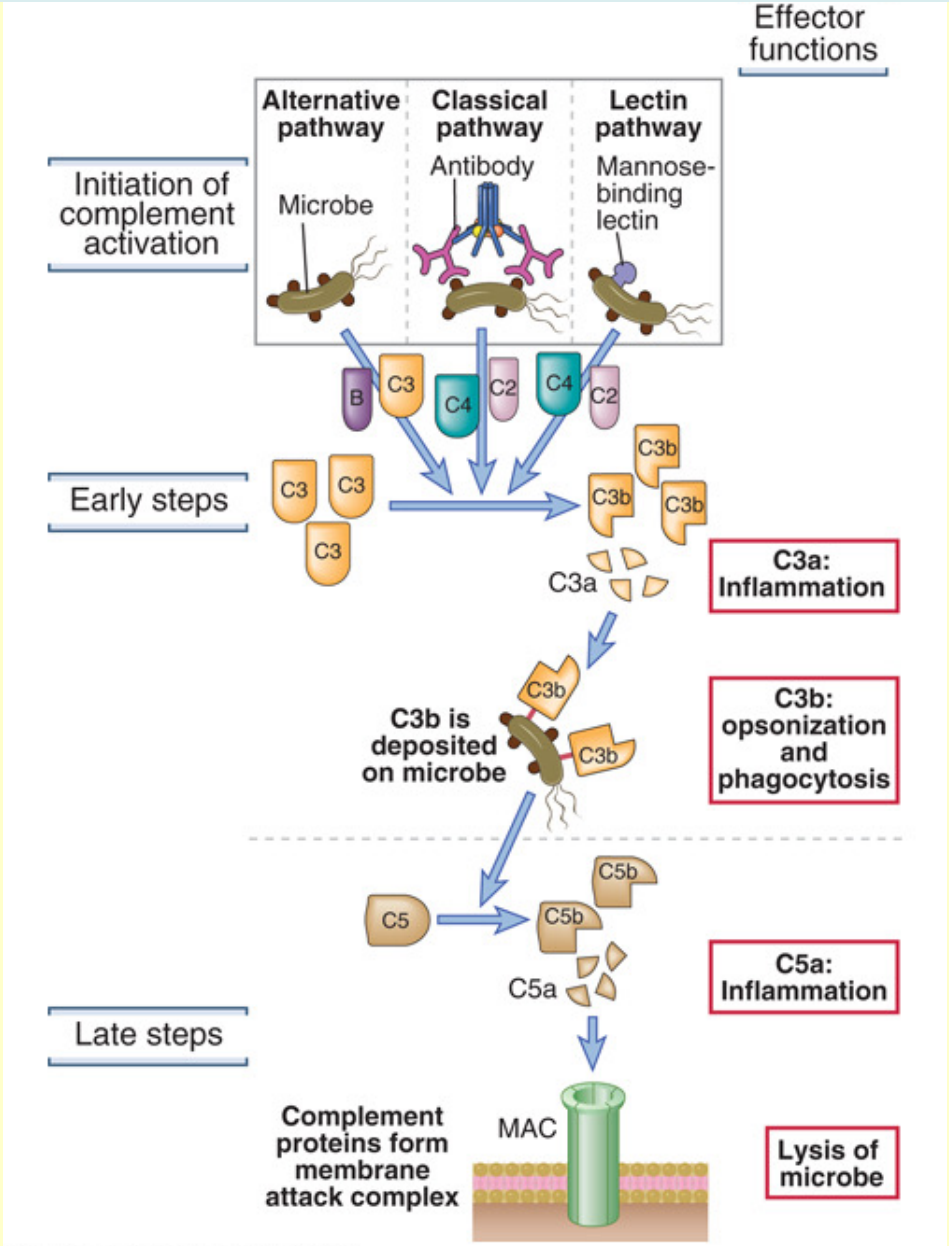
Effector functions of complement



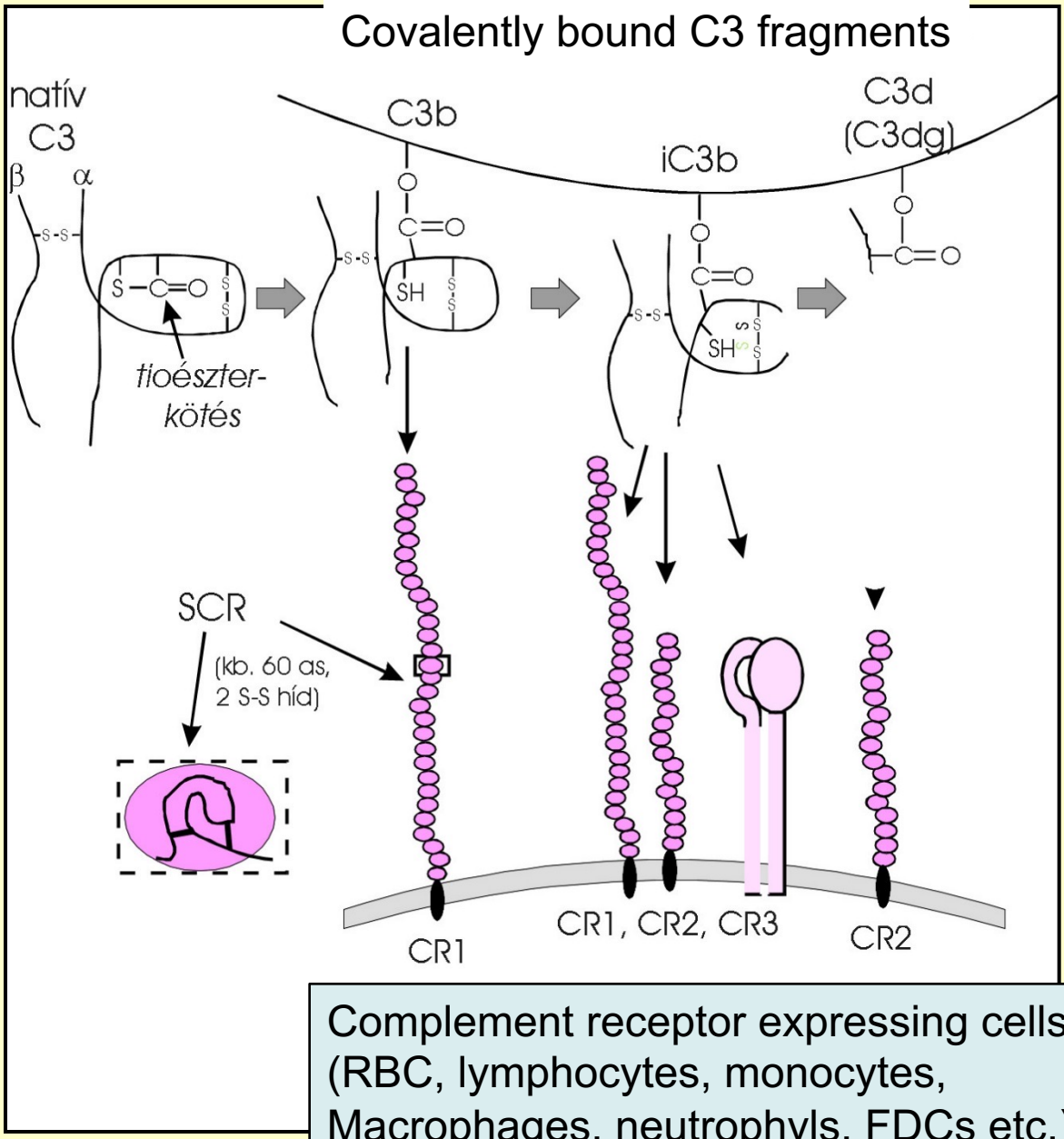
Complement receptors

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–Barrvirus 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

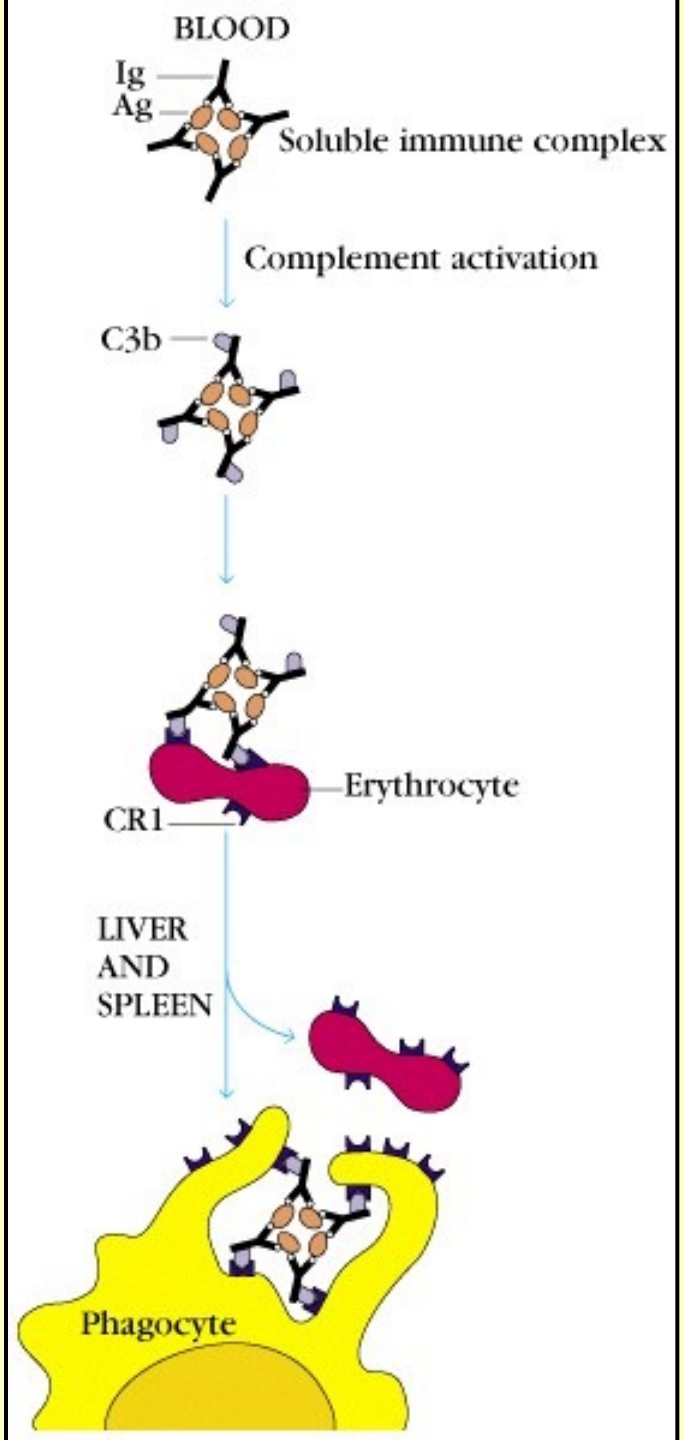
Figure 2-31 Immunobiology, 6/e. (© Garland Science 2005)

C3b-binding receptors

Complement receptors



Complement receptor expressing cells (RBC, lymphocytes, monocytes, Macrophages, neutrophyls, FDCs etc.)

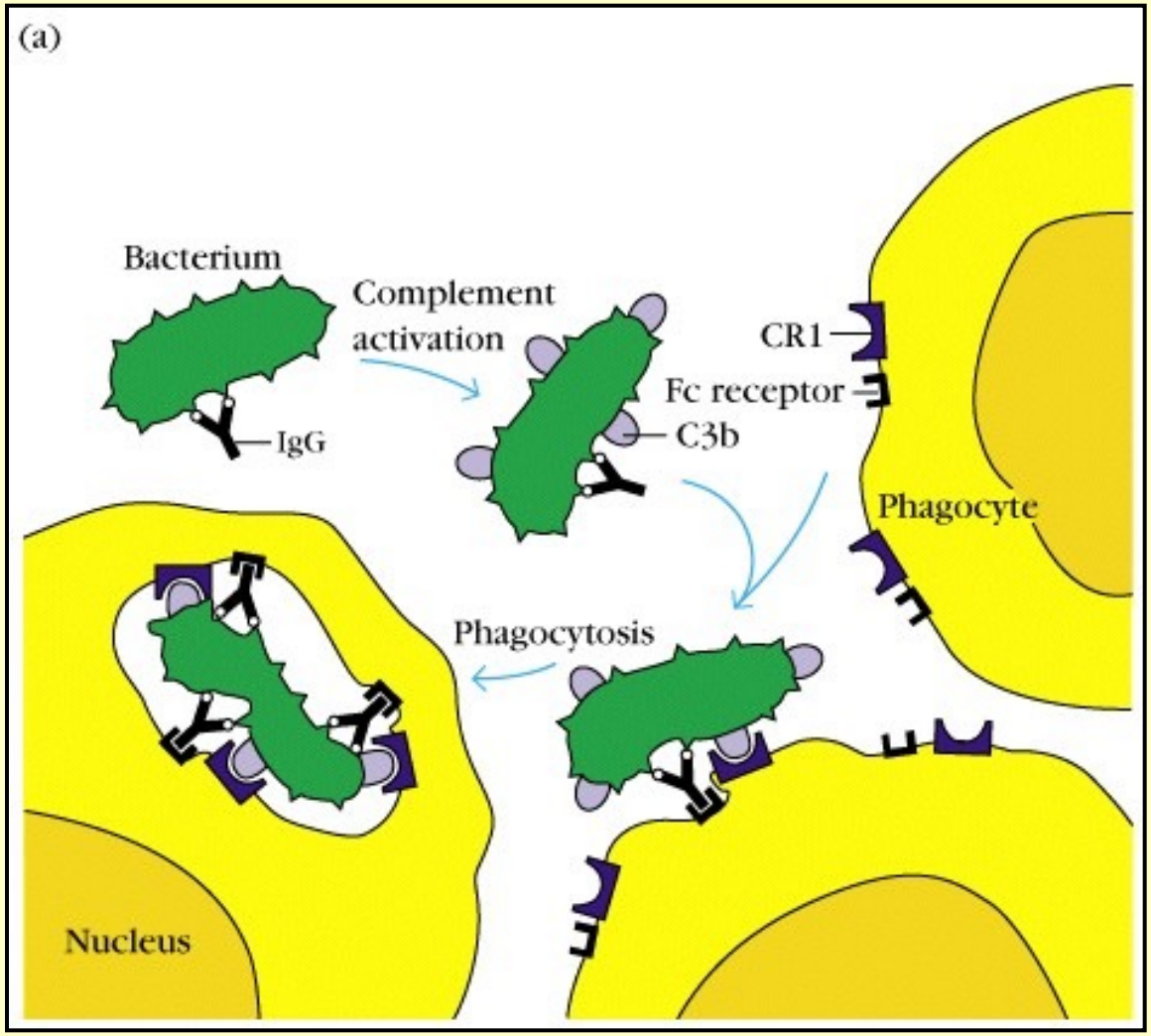


Clearance of immuncomplexes from blood

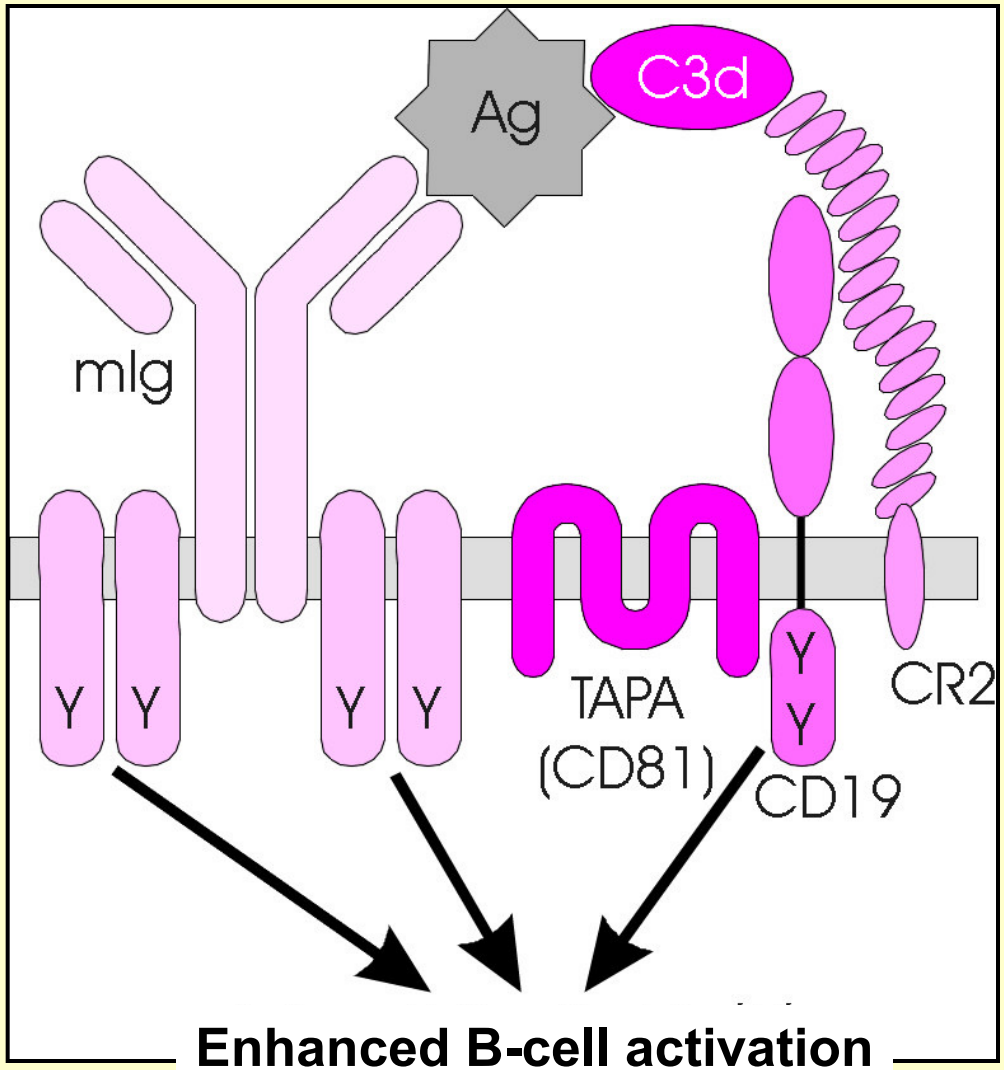
1. Immuncomplex formation
2. Complement activation – C3b binding
3. Binding of IC to CR1 of the RBCs
4. Transport to the spleen and liver
5. Macrophages bind immuncomplexes and take them up by phagocytosis

Inefficient clearance: immuncomplex deposition

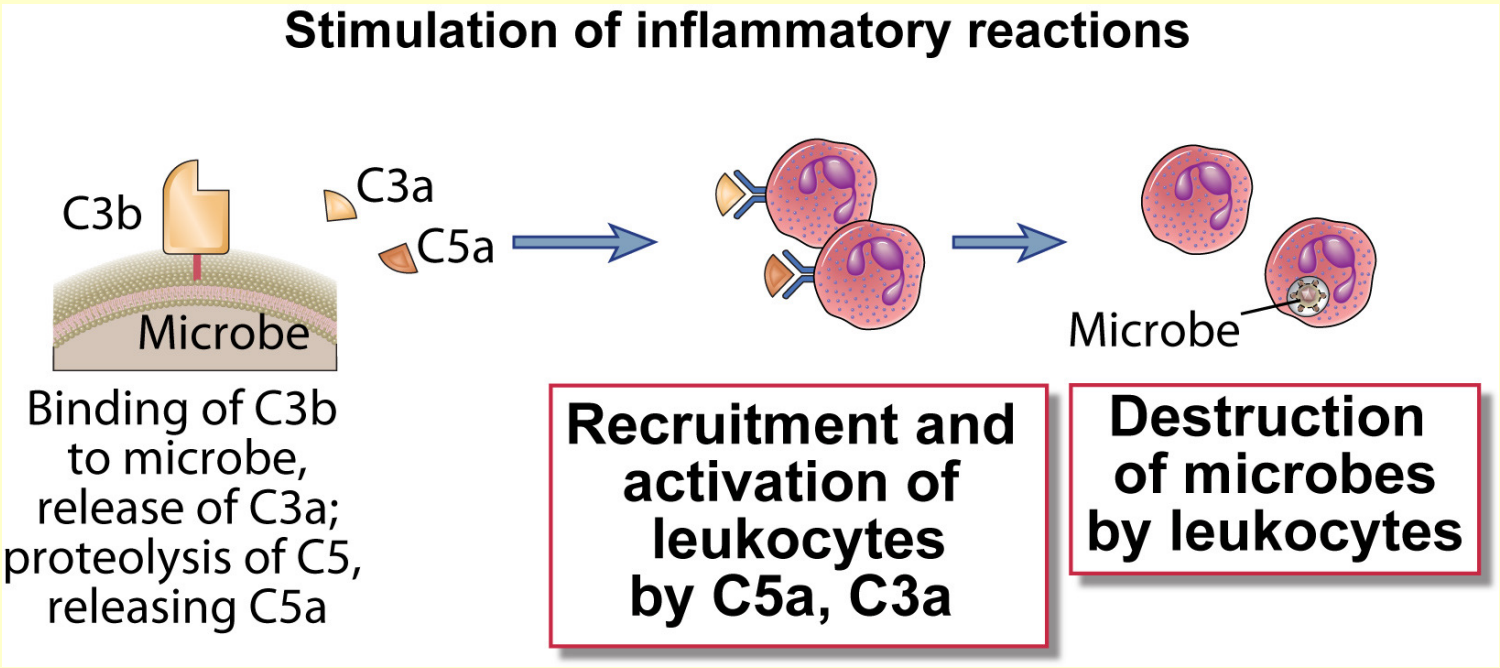
Opsonization with C3b → CR mediated phagocytosis



B-cell co-activation through CR2

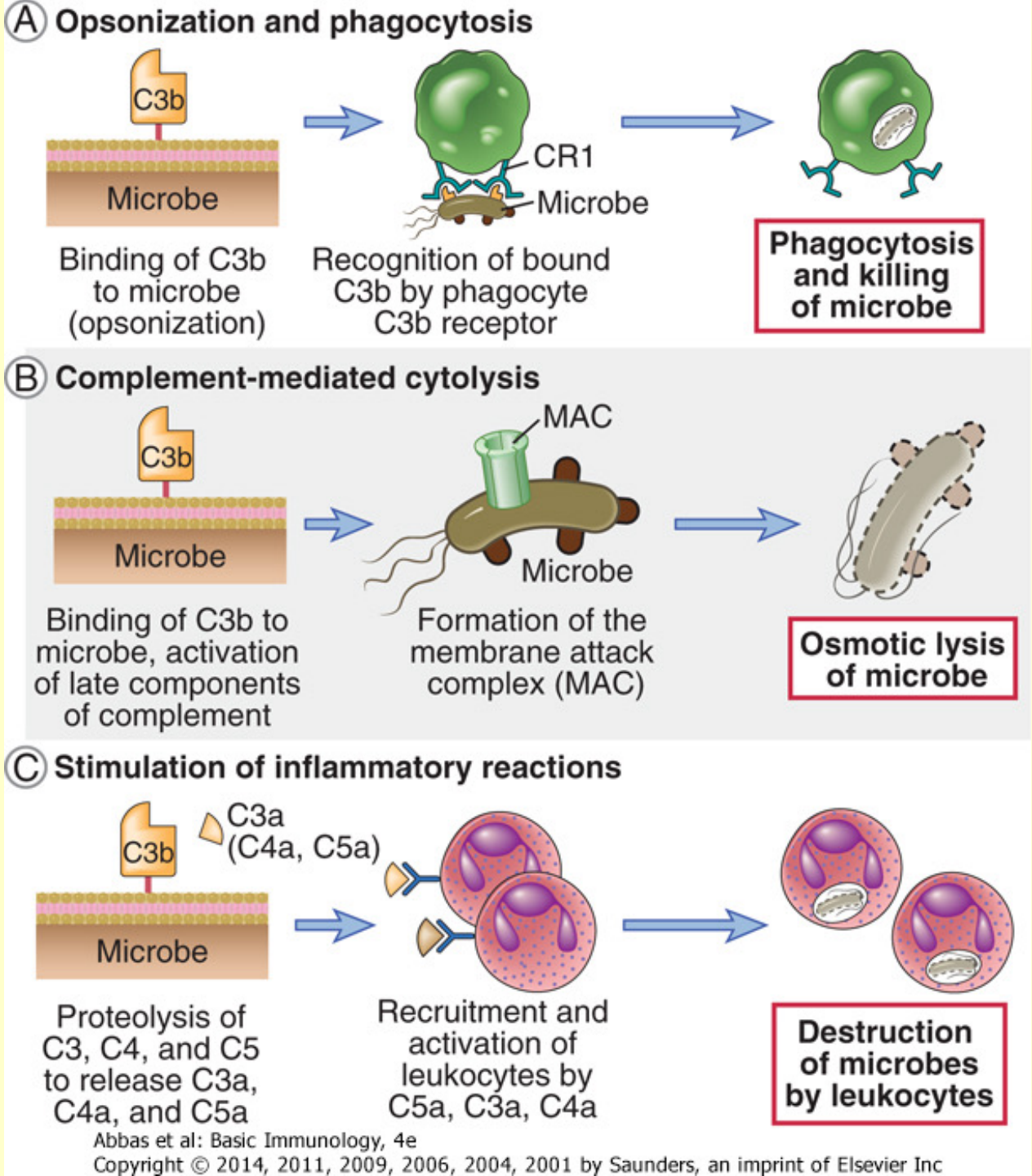


Functions of C3a and C5a



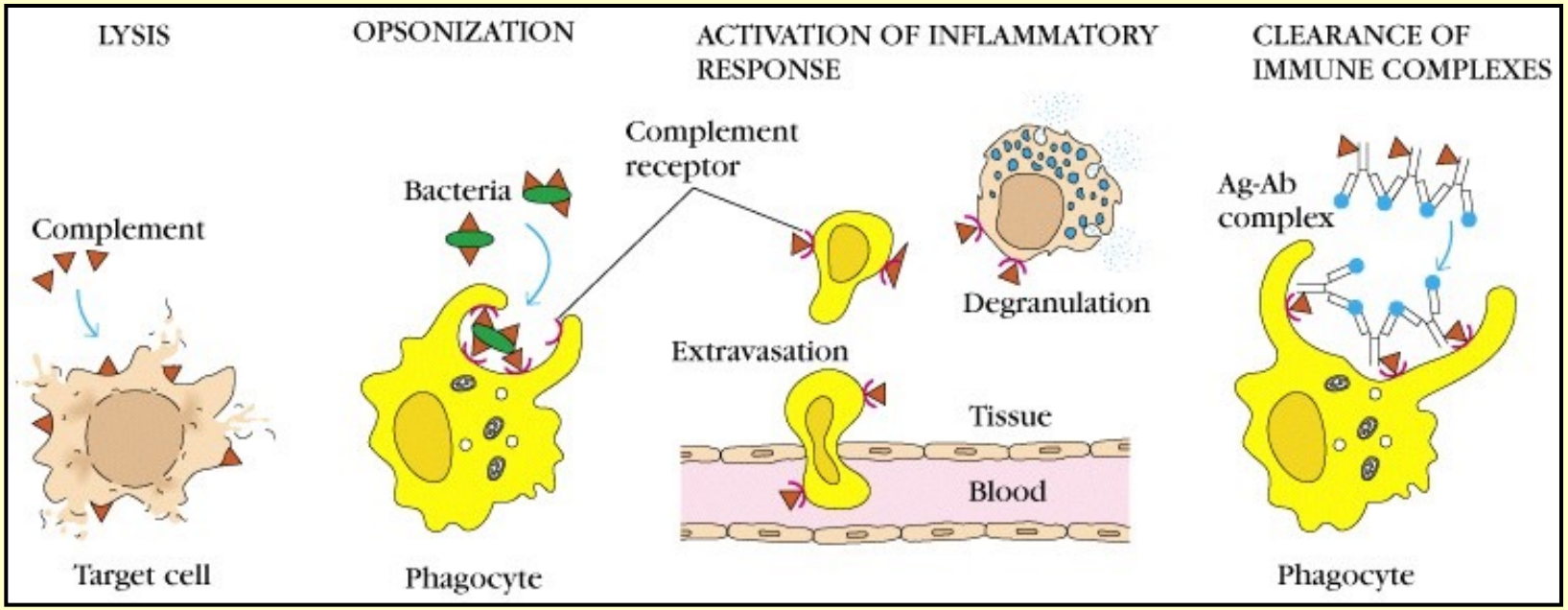
Chemotaxis of granulocytes
Enhancing blood vessel permeability
Mast cell and basophil granulocyte degranulation
Smooth muscle contraction

Fig. 12-17B

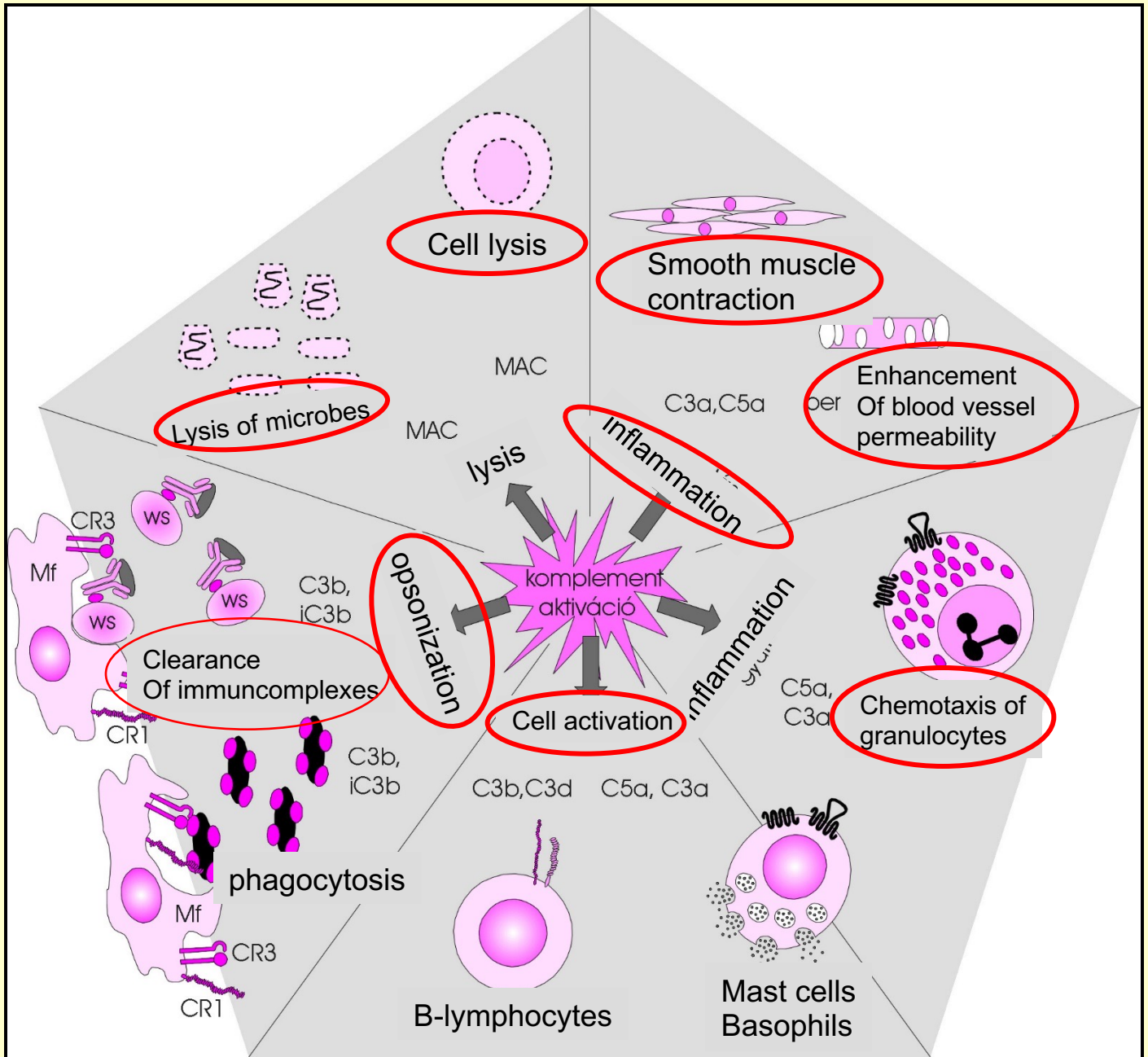


Functions of the complement:

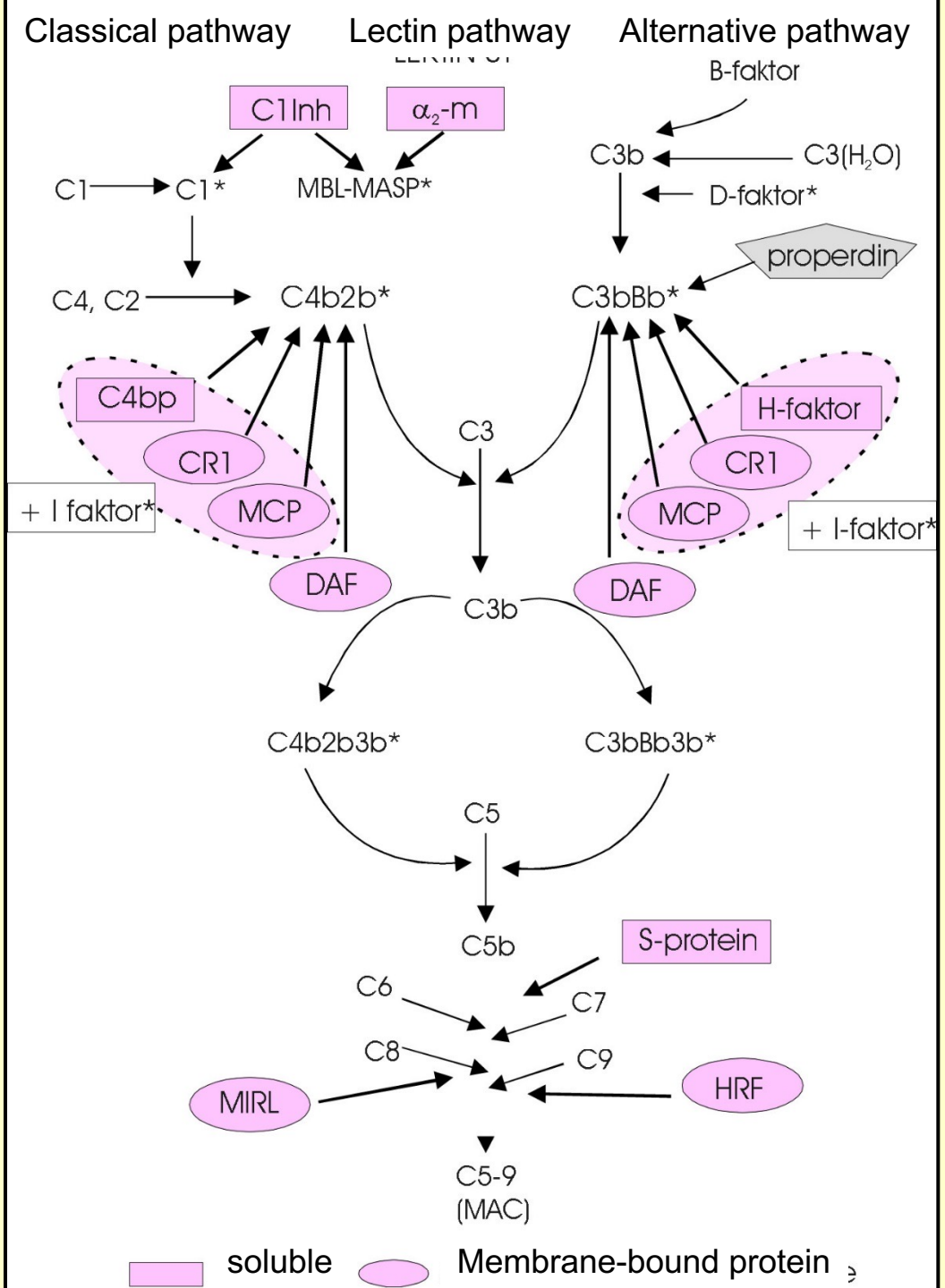
1. Lysis of cells, bacteria, viruses
2. Opsonization, which promotes phagocytosis of particulate antigens
3. Binding to complement receptors results activation of the inflammatory response and specific IR
4. Immune clearance of immune complexes from circulation



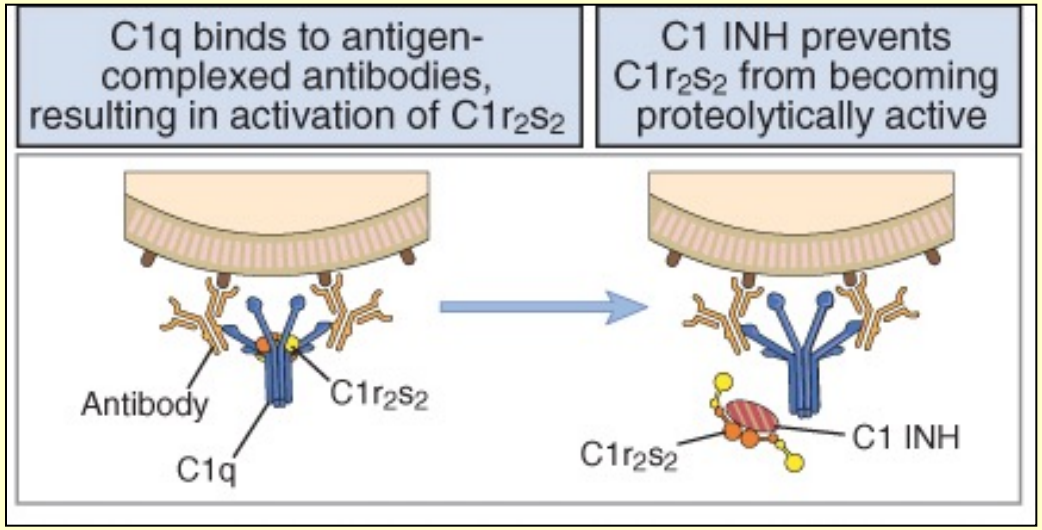
Biological effects, mediated by the complement



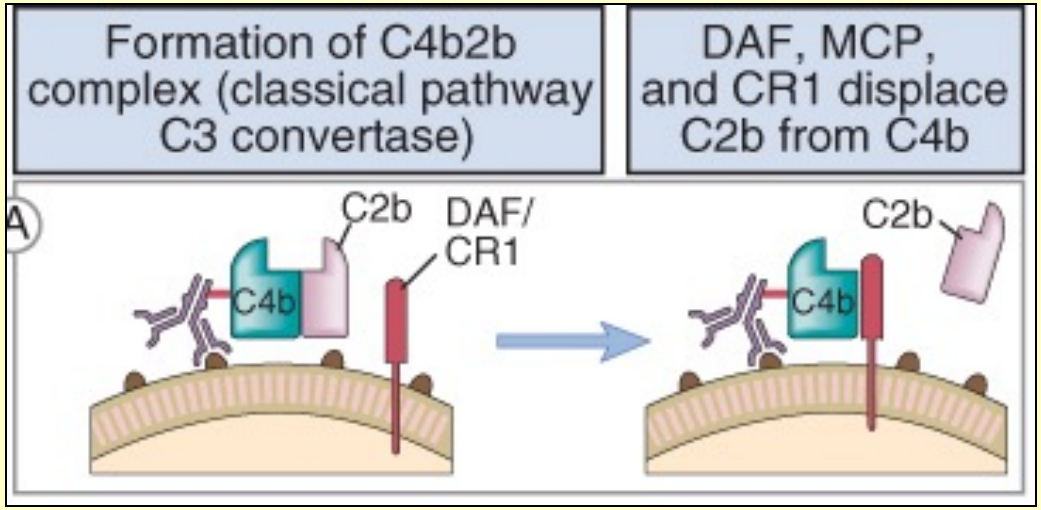
Regulatory proteins



Regulatory proteins of classical pathway

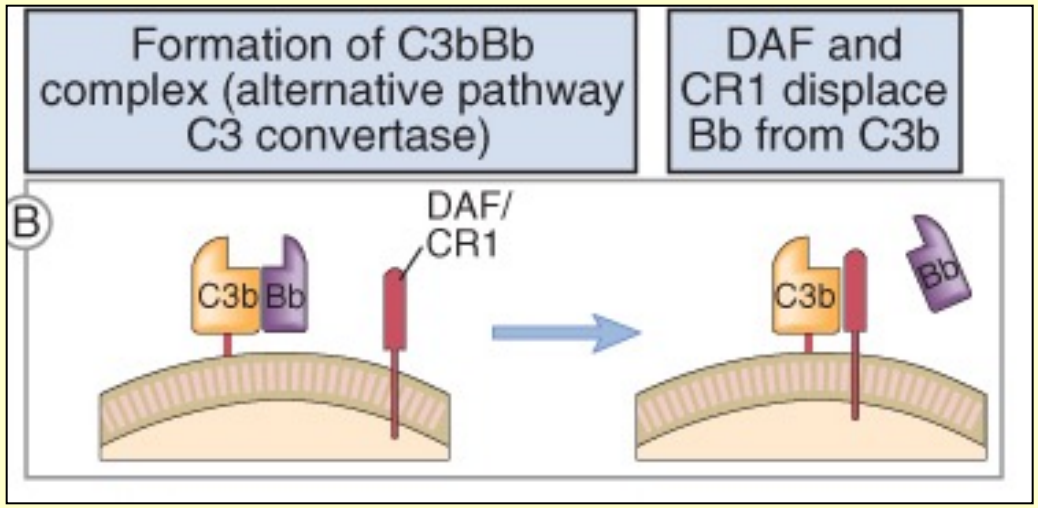


C1 INHIBITOR



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

Regulation of alternative pathway



Regulatory proteins of the classical and alternative pathways

Name (symbol)	Role in the regulation of complement activation
C1 inhibitor (C1INH)	Binds to activated C1r, C1s, removing them from C1q
C4-binding protein (C4BP)	Binds C4b, displacing C2b; cofactor for C4b cleavage by I
Complement receptor 1 (CR1)	Binds C4b, displacing C2b, or C3b displacing Bb; cofactor for I
Factor H (H)	Binds C3b, displacing Bb; cofactor for I
Factor I (I)	Serine protease that cleaves C3b and C4b; aided by H, MCP, C4BP, or CR1
Decay-accelerating factor (DAF)	Membrane protein that displaces Bb from C3b and C2b from C4b
Membrane cofactor protein (MCP)	Membrane protein that promotes C3b and C4b inactivation by I
CD59 (protectin)	Prevents formation of membrane-attack complex on autologous or

There is a close relationship between the factors of the three complement activations pathways

Step in pathway	Protein serving function in pathway			Relationship
	Alternative (innate)	MB-lectin	Classical	
Initiating serine protease	D	MASP	C1s	Homologous (C1s and MASP)
Covalent binding to cell surface	C3b	C4b		Homologous
C3/C5 convertase	Bb	C2b		Homologous
Control of activation	CR1 H	CR1 C4BP		Identical Homologous
Opsonization	C3b			Identical
Initiation of effector pathway	C5b			Identical
Local inflammation	C5a, C3a			Identical
Stabilization	P	None		Unique

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Complement and diseases

- MAC deficiency C8 mutation: → autoimmune diseases
- → Neisseria infections (Gram- bacteria)

- Faktor H és MCP mutation: atypic HUS (haemolytic uremic syndrome)

- C3, B factor, I factor H factor polymorphisms → unregulated complement activation on cell surfaces: macula degeneration

- C1 inhibitor mutation: hereditary angioedema (HAE)

- Diagnostics: CH50 measurement = total complement activity test

Hereditary angioedema (HAE)

- is an autosomal dominant disease caused by either a lack of C1-inhibitor protein or dysfunctional C1-inhibitor protein.
- HAE manifests with symptoms related to angioedema of the upper airway, skin, and/ or gastrointestinal tract.
- Autosomal dominant inheritance or a new mutation
- Deficiency of complement C1-inhibitor (C1-INH), a plasma protein that is an important inhibitor of several serine proteases, specially of the complement system and the contact activation/kallikrein-kinin pathway, but also the fibrinolytic system
- Treatment: C1-inhibitor plasma concentrate or recombinant C1-INH replacement therapy (rhC1INH; conestat alfa) in Europe