Basic immunology

Humoral effector mechanisms II: complement

Lecture structure

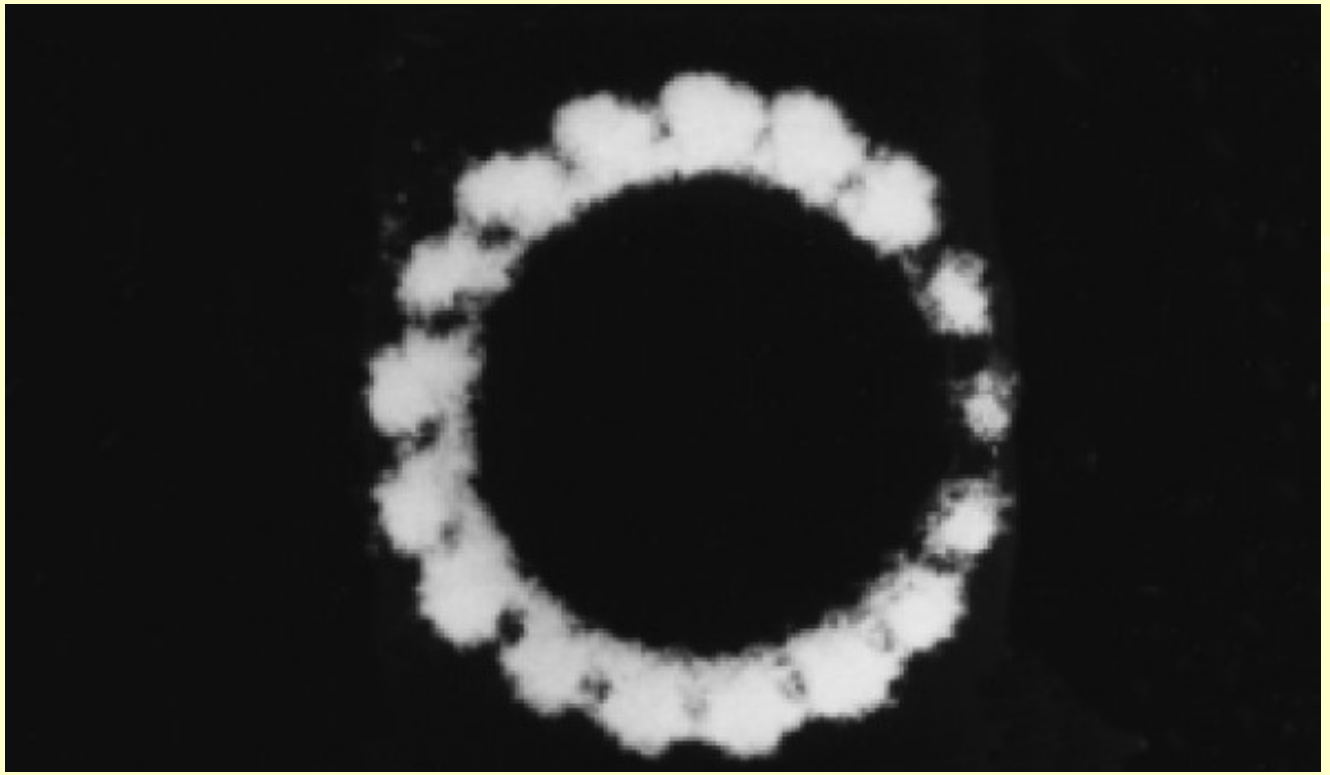
- Complement: general facts
- Complement activation routes
- Complement functions

Humoral effector functions

- Complementsystem – innate immunity

- Immunglobulin mediated – adaptive immunity

Complement system



Why is the complement system important?

- Main effector system of the humoral immune response
- Part of innate immunity
- Immediate response
- Interaction with adaptive immune response

Discovery:

1890: Experiment of **Jules Bordet**:

- Immunized serum raised against *Vibrio cholerae* cause bacteriolysis in vitro
- Heating of this serum damages this capability.
- Complementation with non-immunised serum can re-establish the bacteriolysis capacity

Paul Ehrlich:

ANTISERUM contains two components:

→ **heat-stable**: specific antibody → mediates recognition

→ **heat-sensible**: responsible for lysis →

COMPLEMENT

Constitutents:

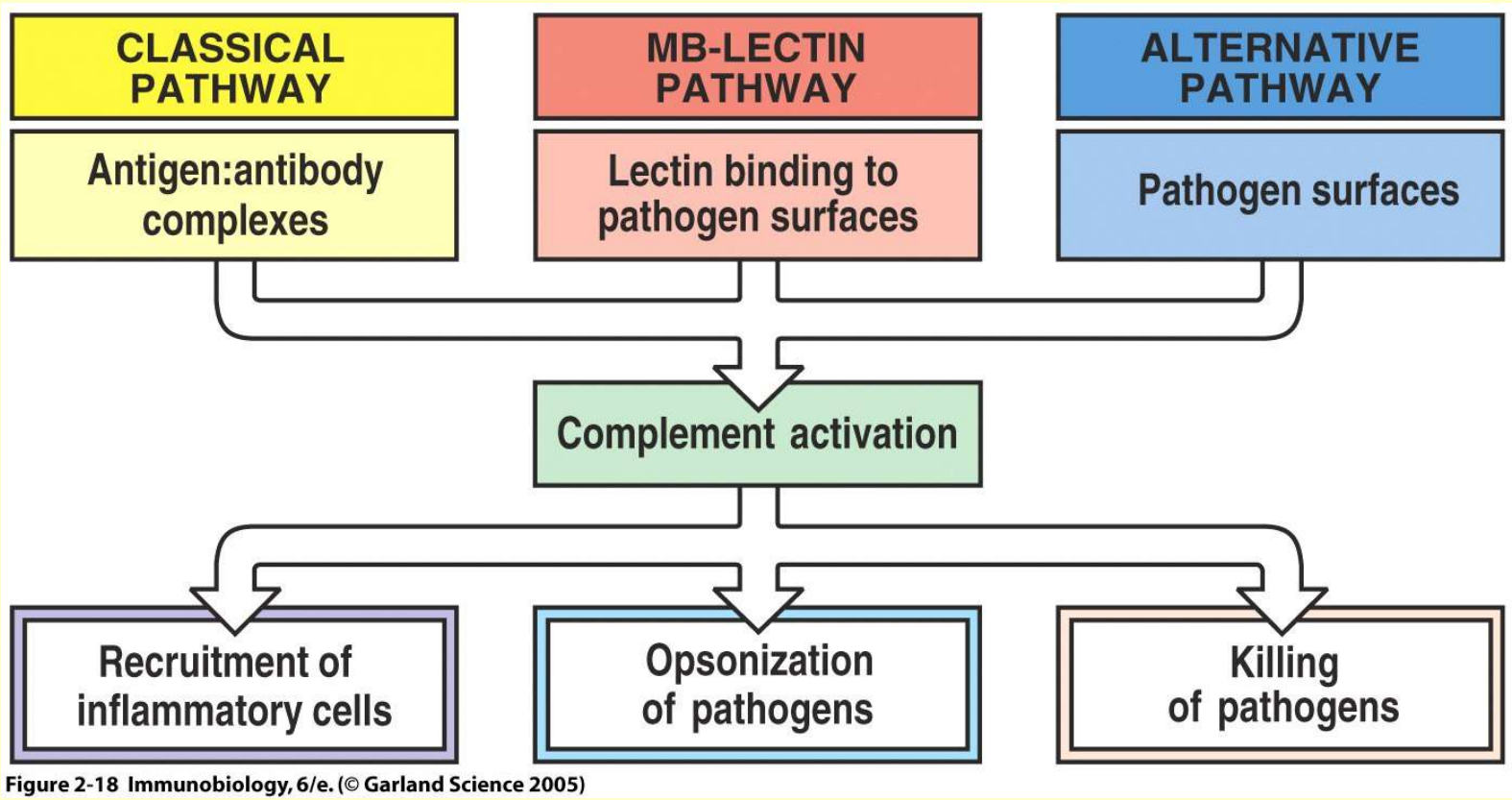
- Inactive factors in the serum and other body fluids, that activate each other: enzyme cascade
- Cell surface receptors (CR) to bind the activated complement components
- Regulatory proteins: soluble and cell surface molecules

Activation routes of complement cascade

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

Activator:
Microbial cell wall
(mannose-rich)

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



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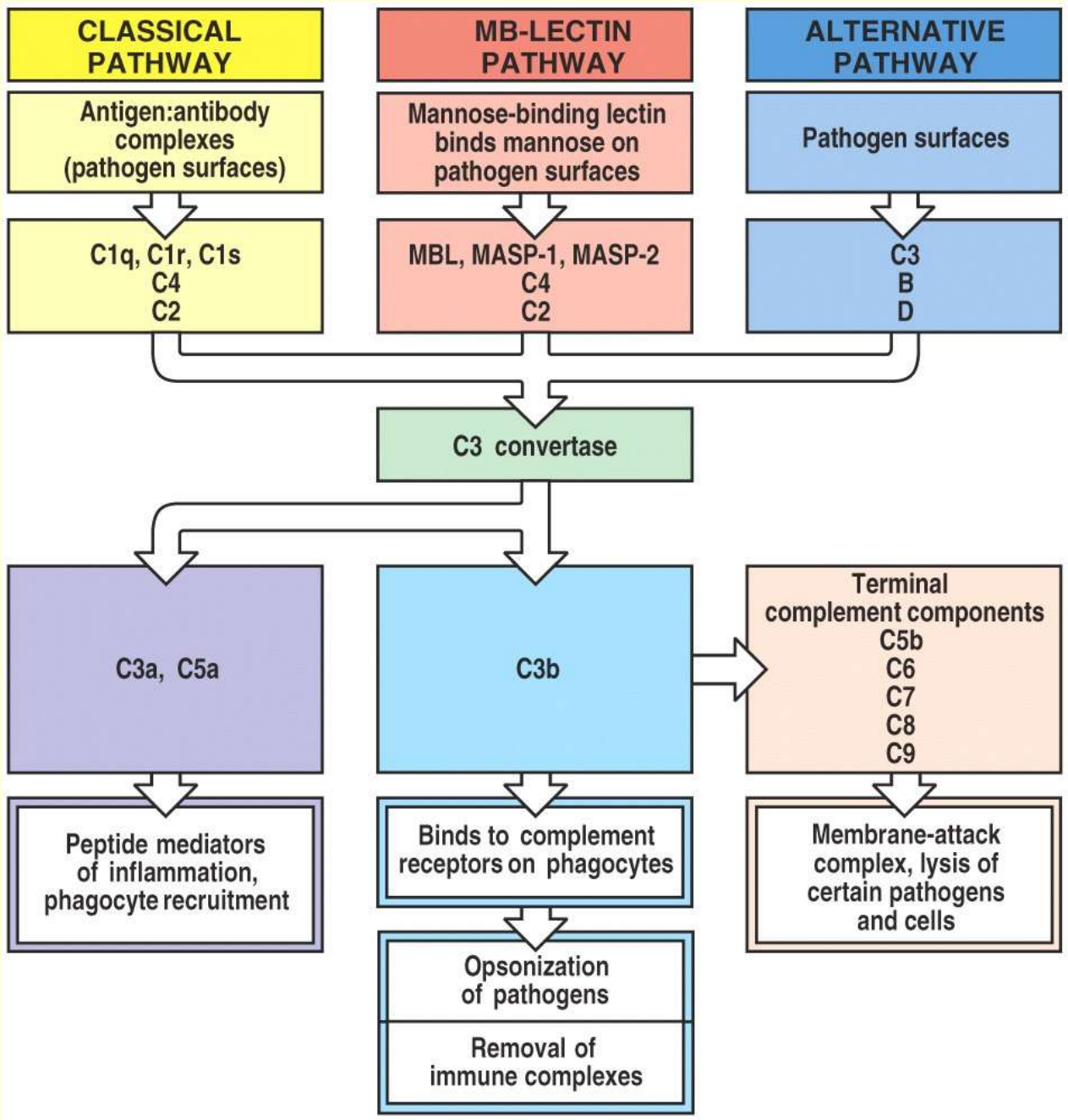
Main components and their effects



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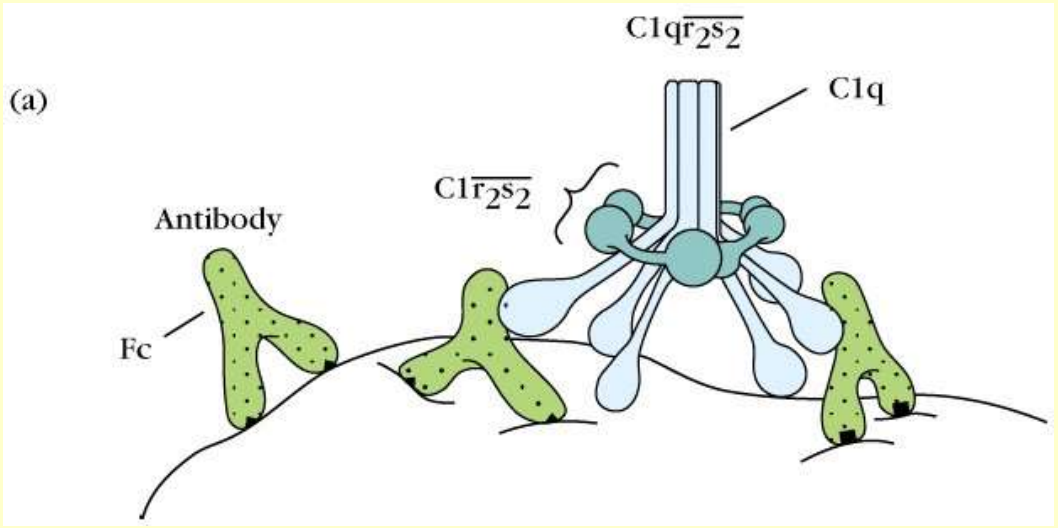
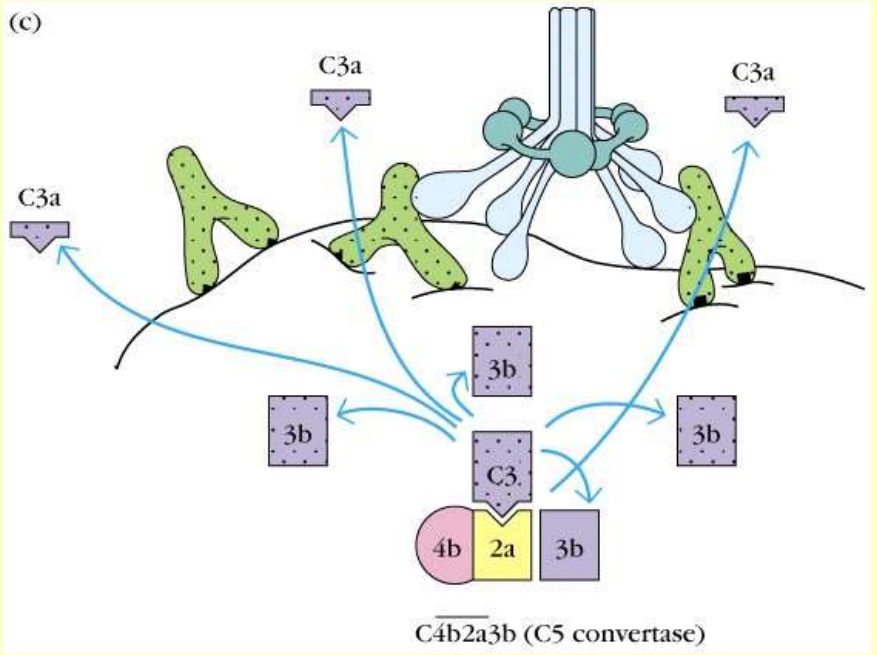
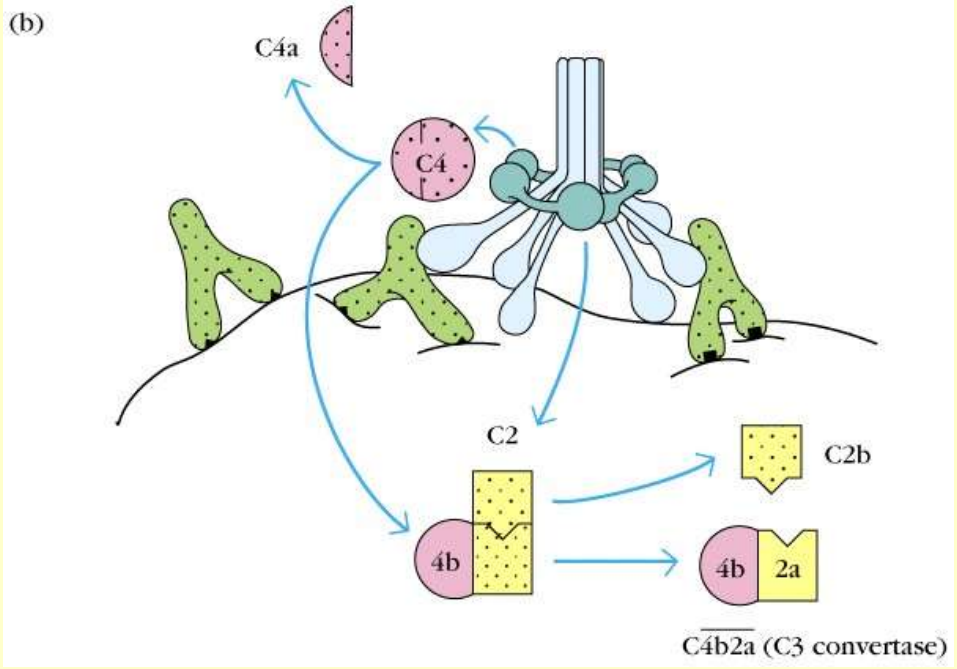
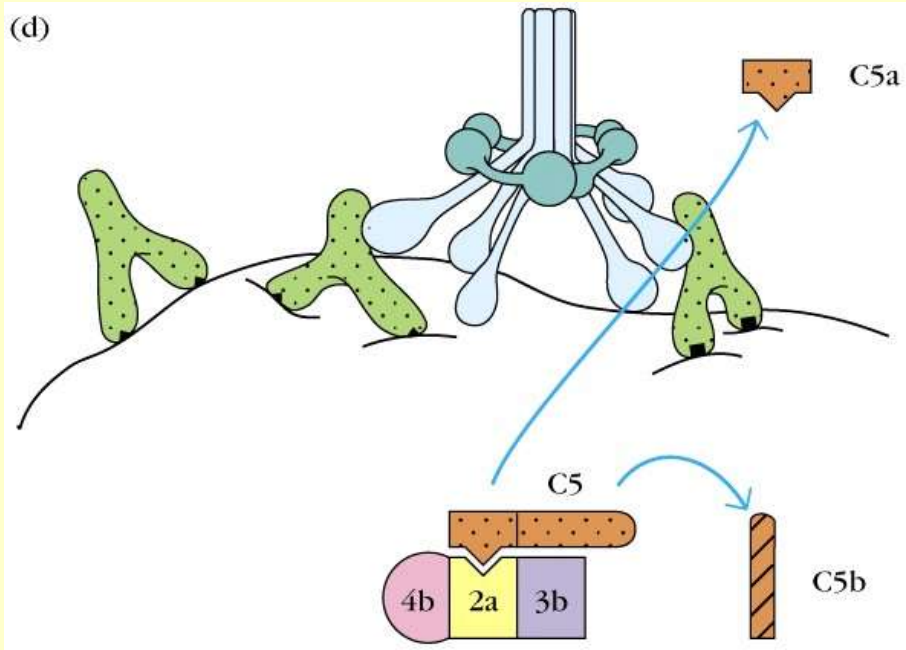
Components of the classical pathway

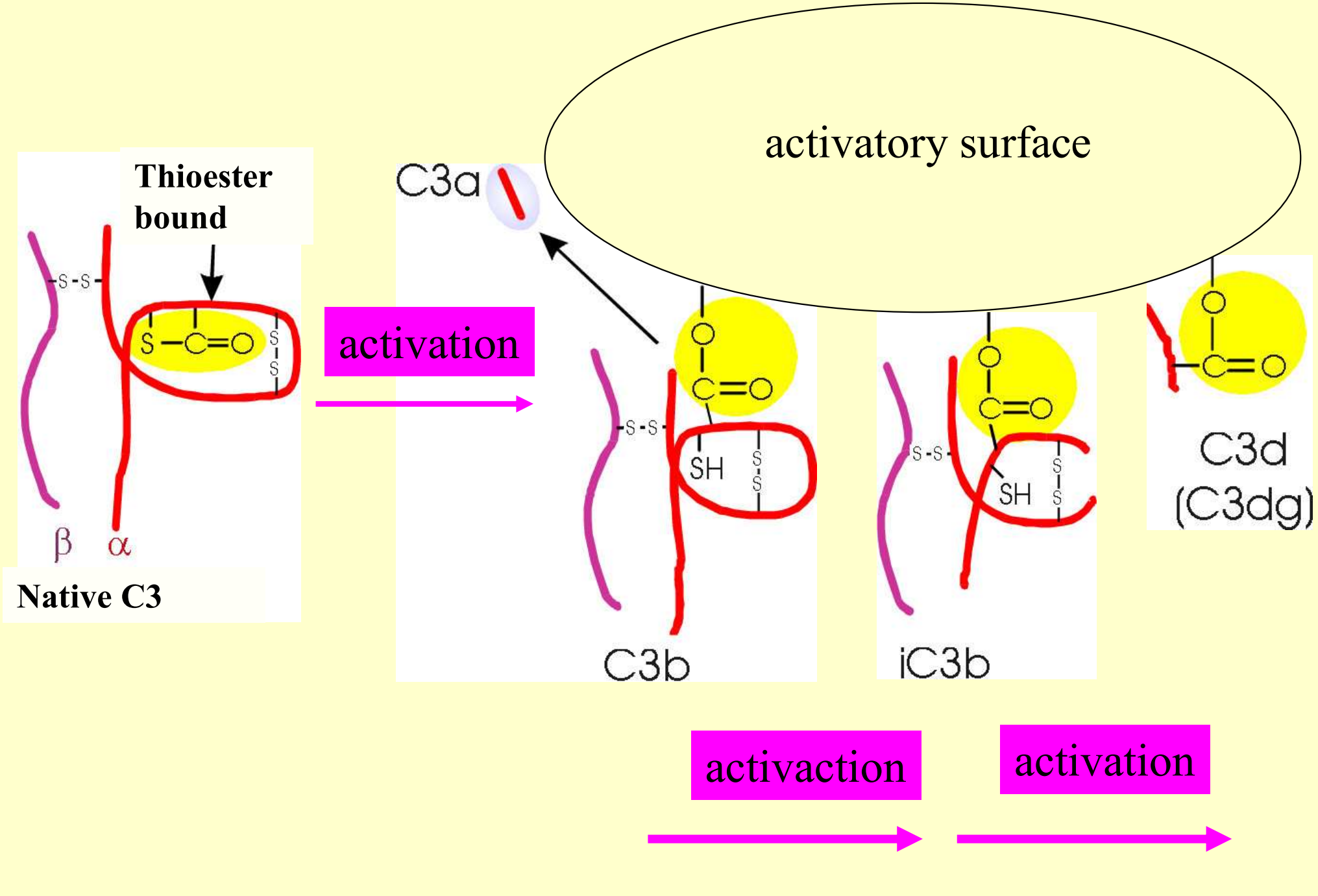








Alternative pathway: limited proteolysis of C3



The MBL forms complexes with serine proteases similarly to C1qrs

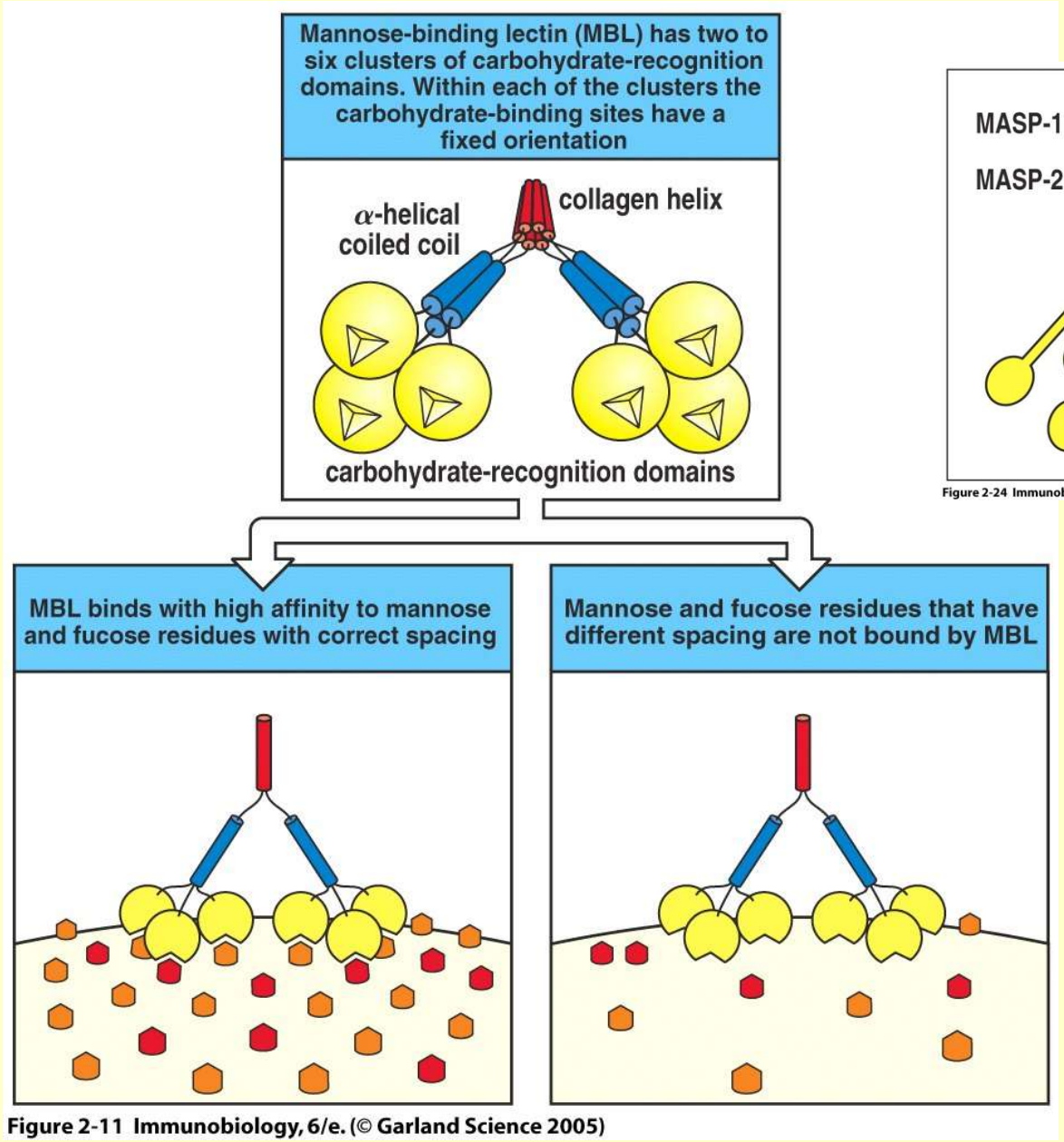
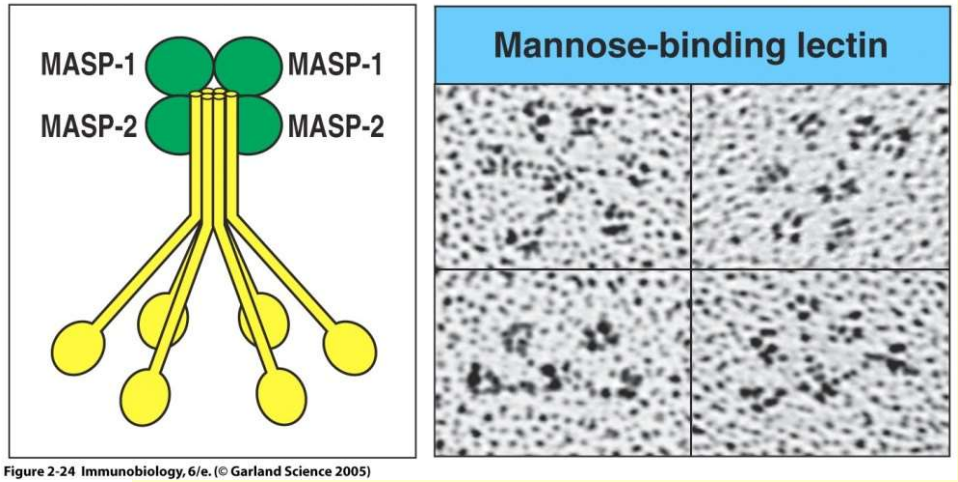


Figure 2-11 Immunobiology, 6/e. (© Garland Science 2005)



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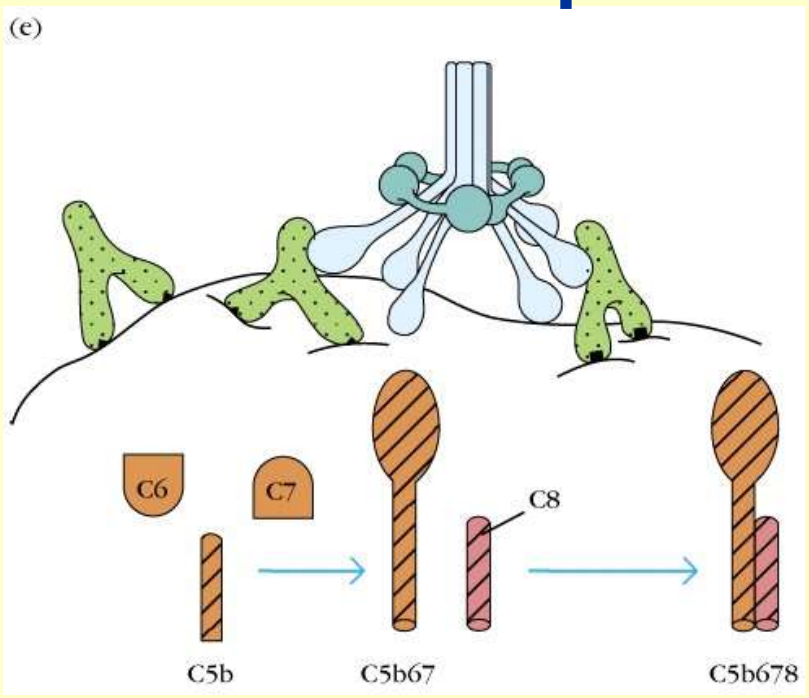
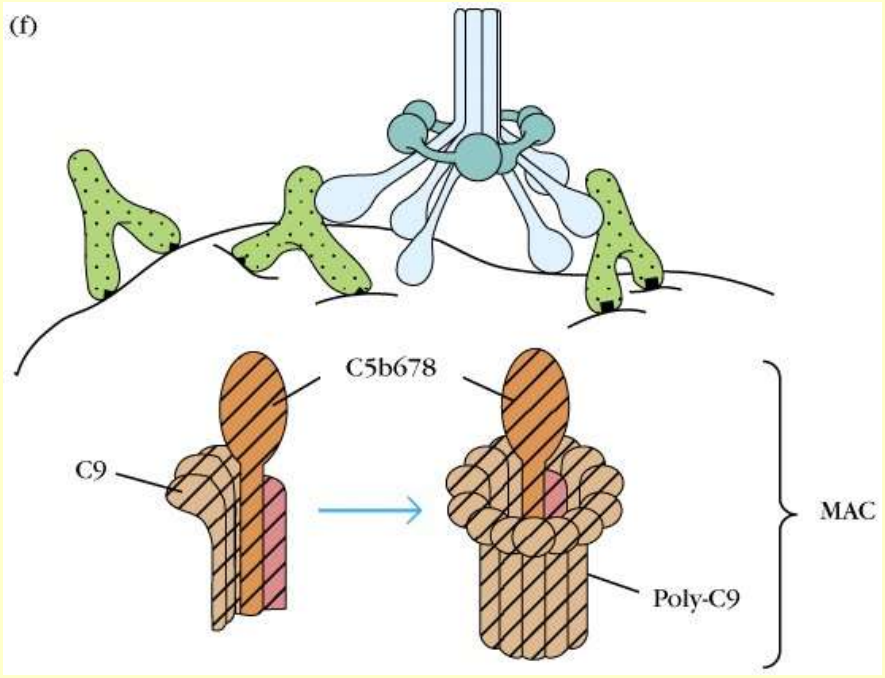
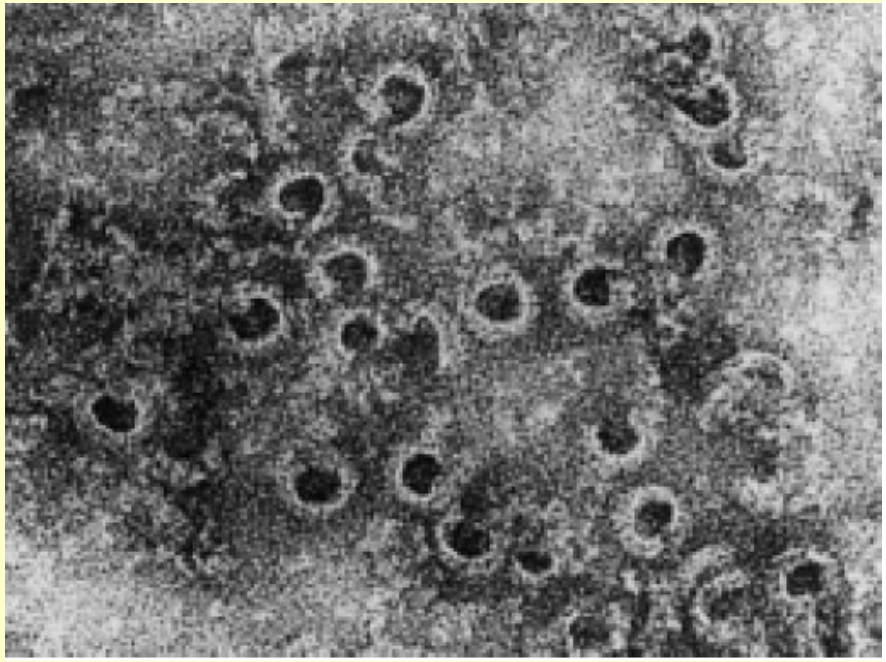
Terminal pathway: the common route



MAC formation:

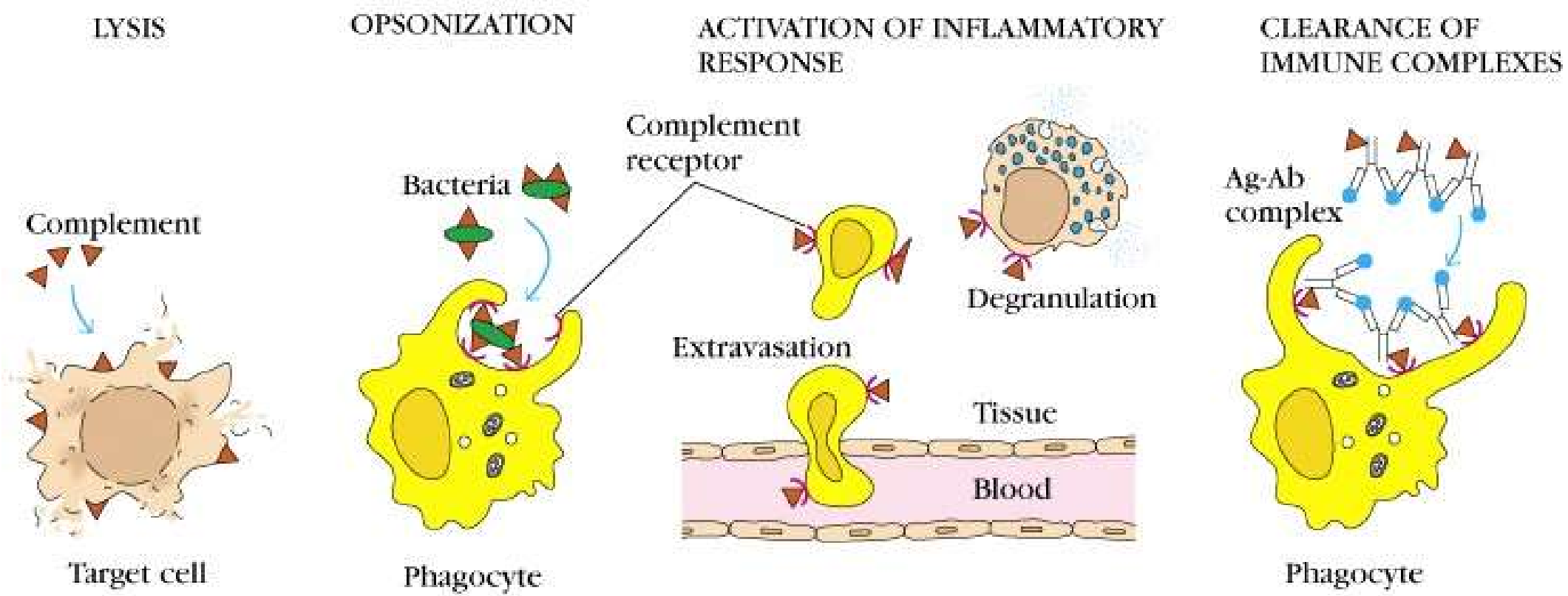
Membrane Attack Complex



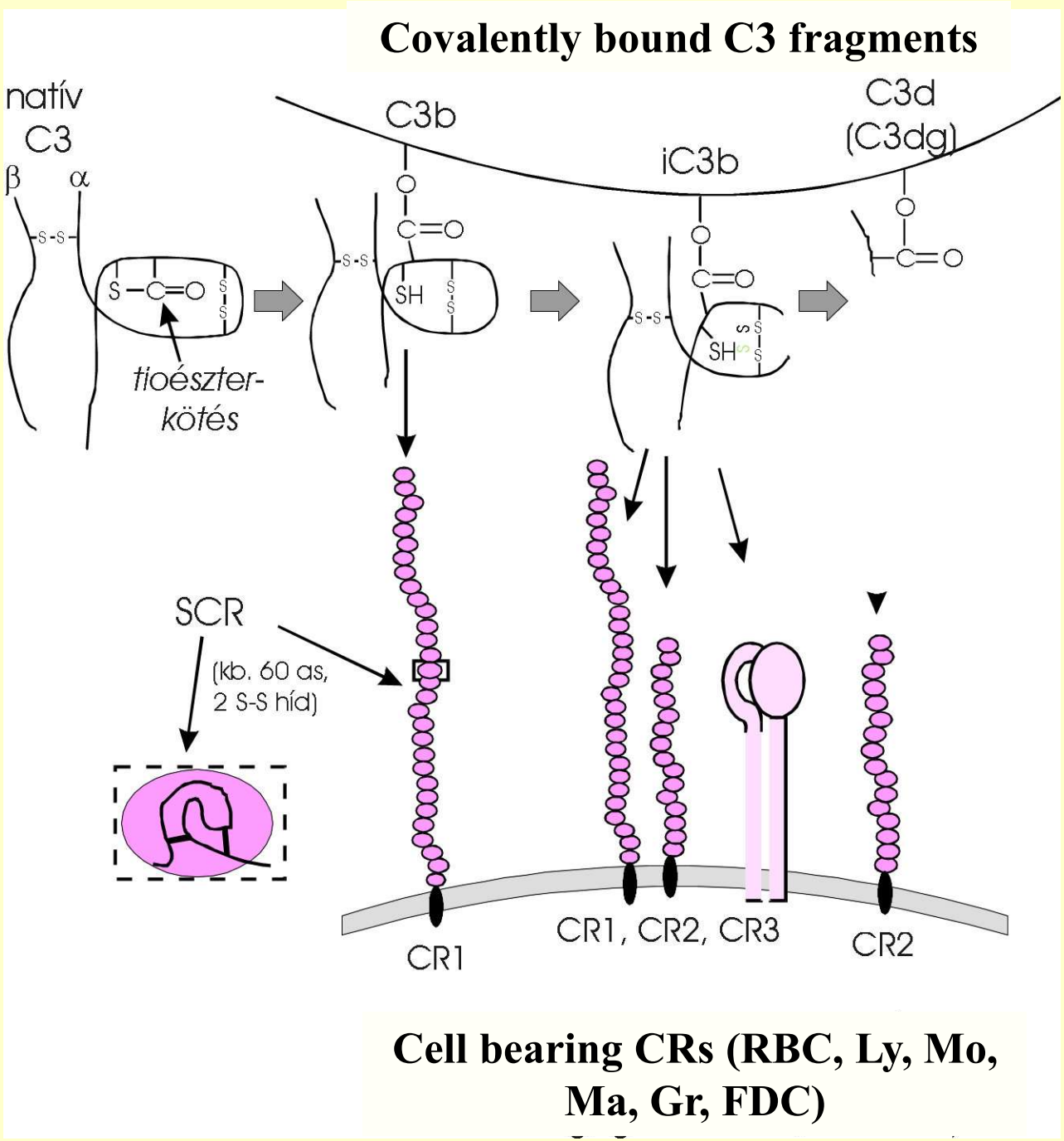


Complement functions:

- 1. Lysis: cells, bactera, fungi, viruses
- 2. Opsonization, that accelerates the phagocytosis of antigen particles
- 3. Binding to complement receptors activates the inflammatory reaction and specific immune response
- 4. Clearance of immune complexes from the circulation



C3b binding receptors

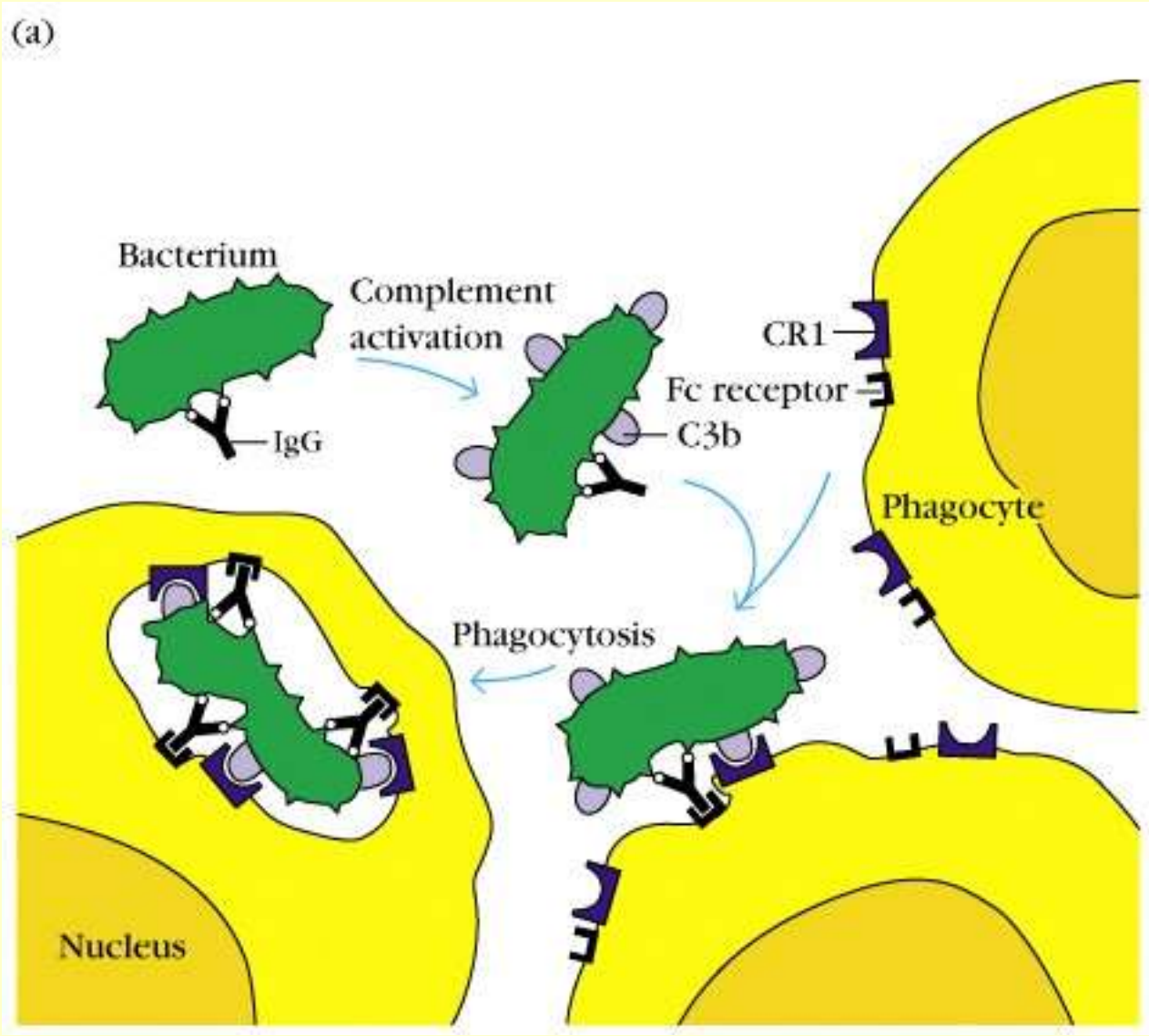


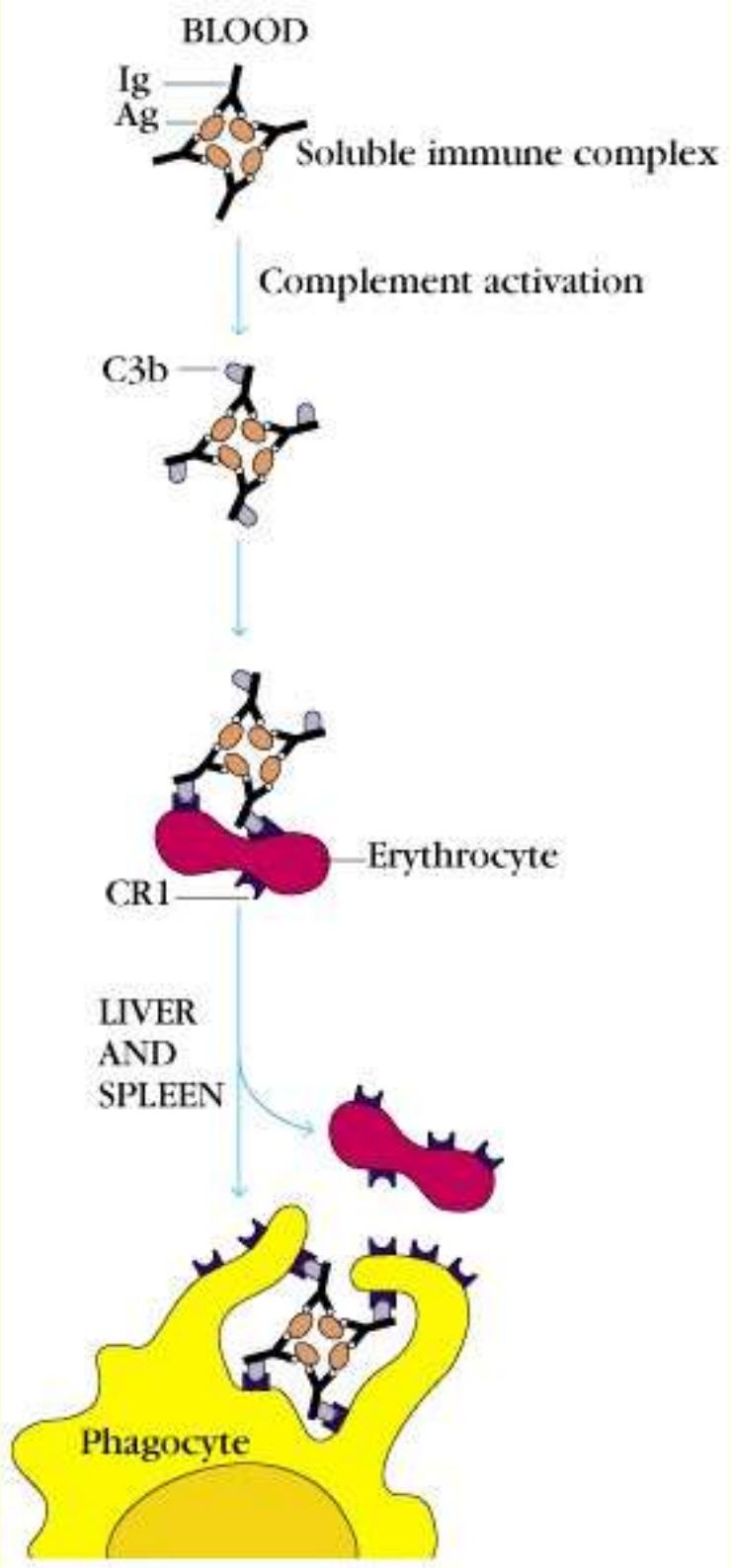
Complement receptors

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)

The role of C3b and IgG opsonization



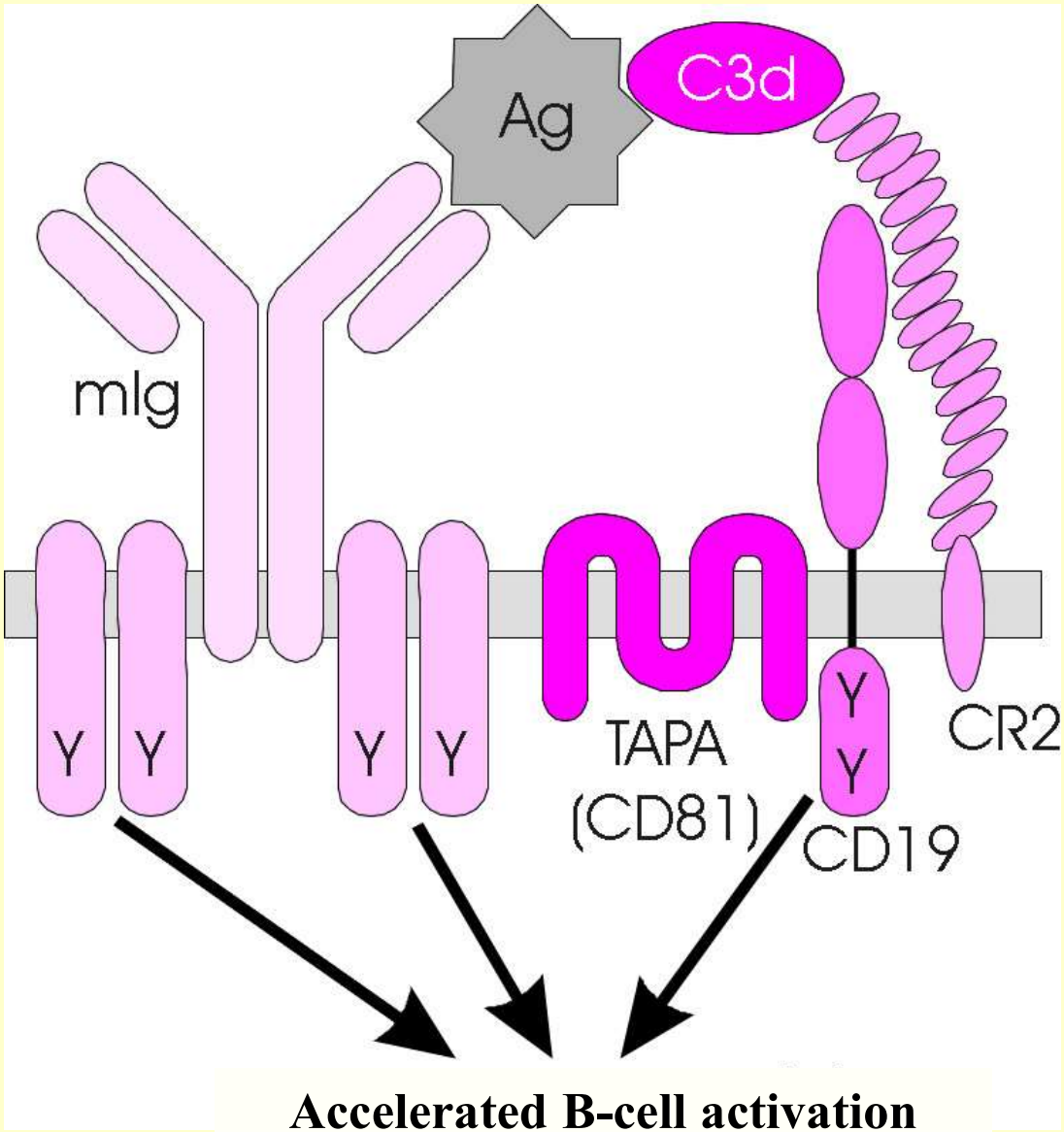


Clearence of immune complexes from blood circulation

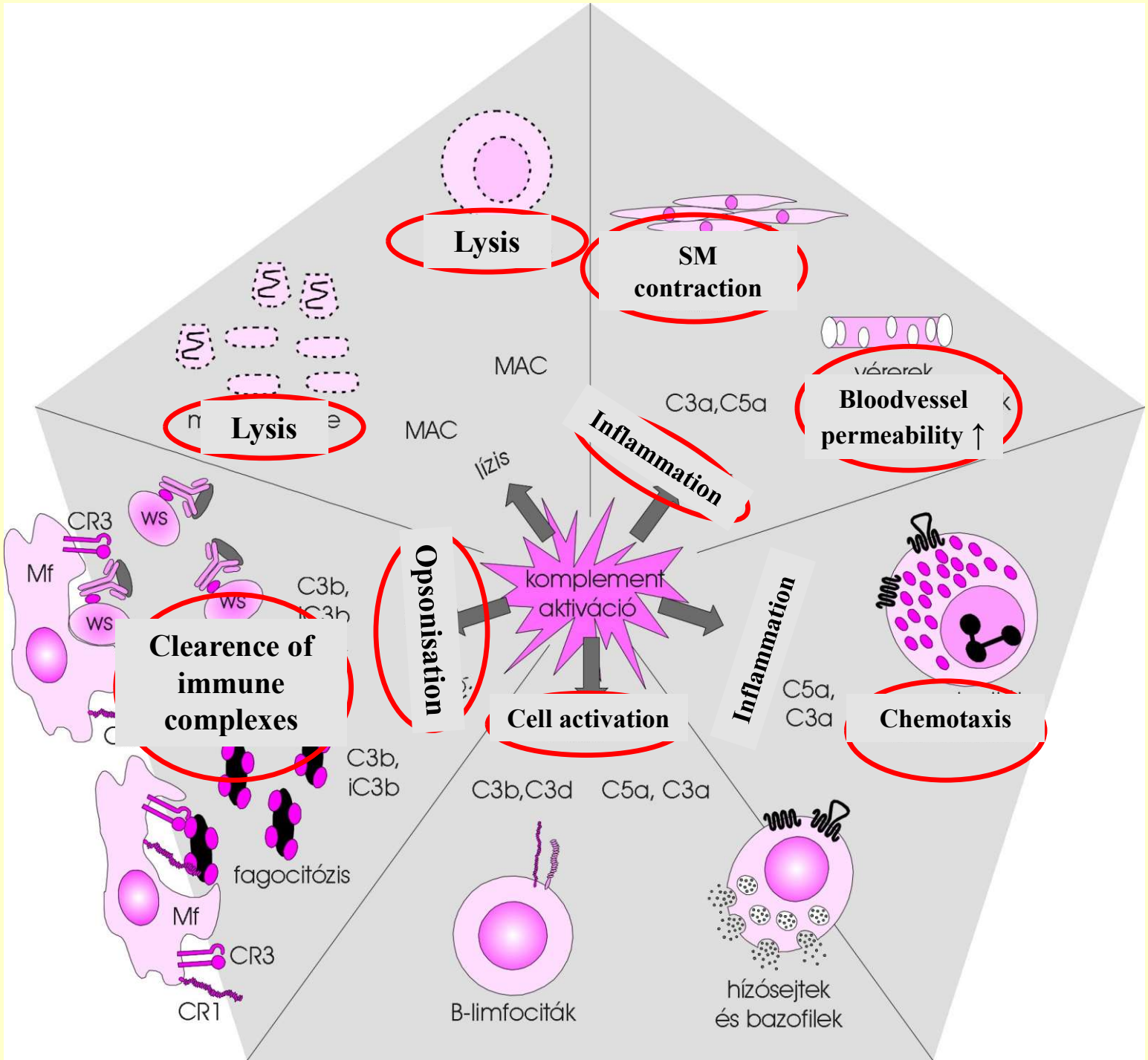
1. **Immuncomplex formation**
2. **Complement activation – C3b binding**
3. **Binding to CR1 on RBCs**
4. **Delivery to liver and spleen**
5. **Macrophages take over immuncomplexes and perform phagocytosis**

<u>Malfunction</u>: immuncomplex deposits in the kidney

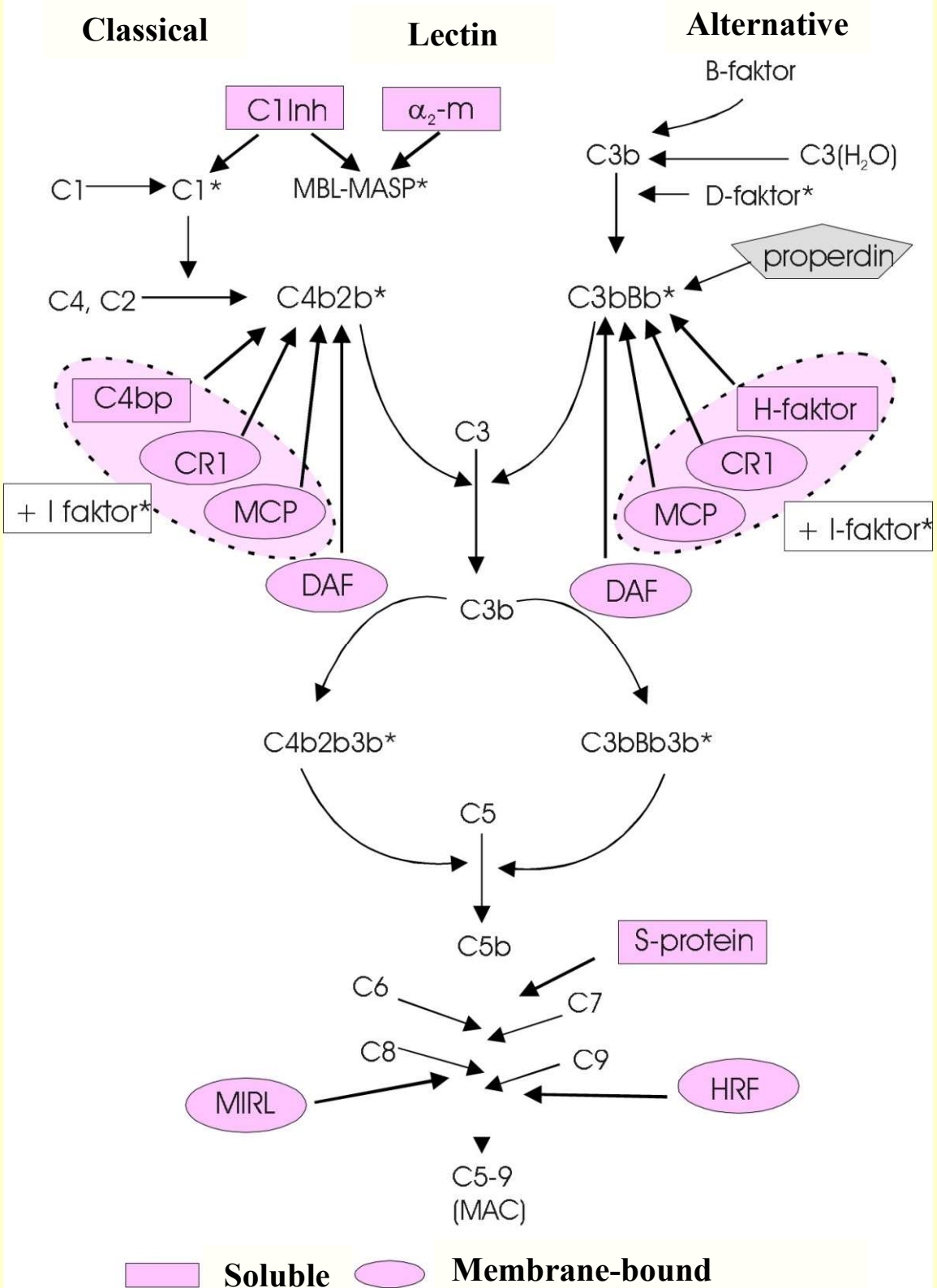
Acceleration of B cell activation



Biological effects of complement:



Regulation of complement cascade



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 allogenic cells. Widely expressed on membranes

Figure 2-36 Immunobiology, 6/e. (© Garland Science 2005)

Summary

- Three activation routes: classical, alternative, MBL-Lectin
- Several functions:
  - Lysis of pathogens
  - Regulation of inflammation: chemotaxis and activation of cells
  - Clearance of immuncomplexes and apoptotic bodies cells
  - Interactions between innate and adaptive immunity