

Basic immunology

Lecture 16.

The complement system

Timea Berki

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

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

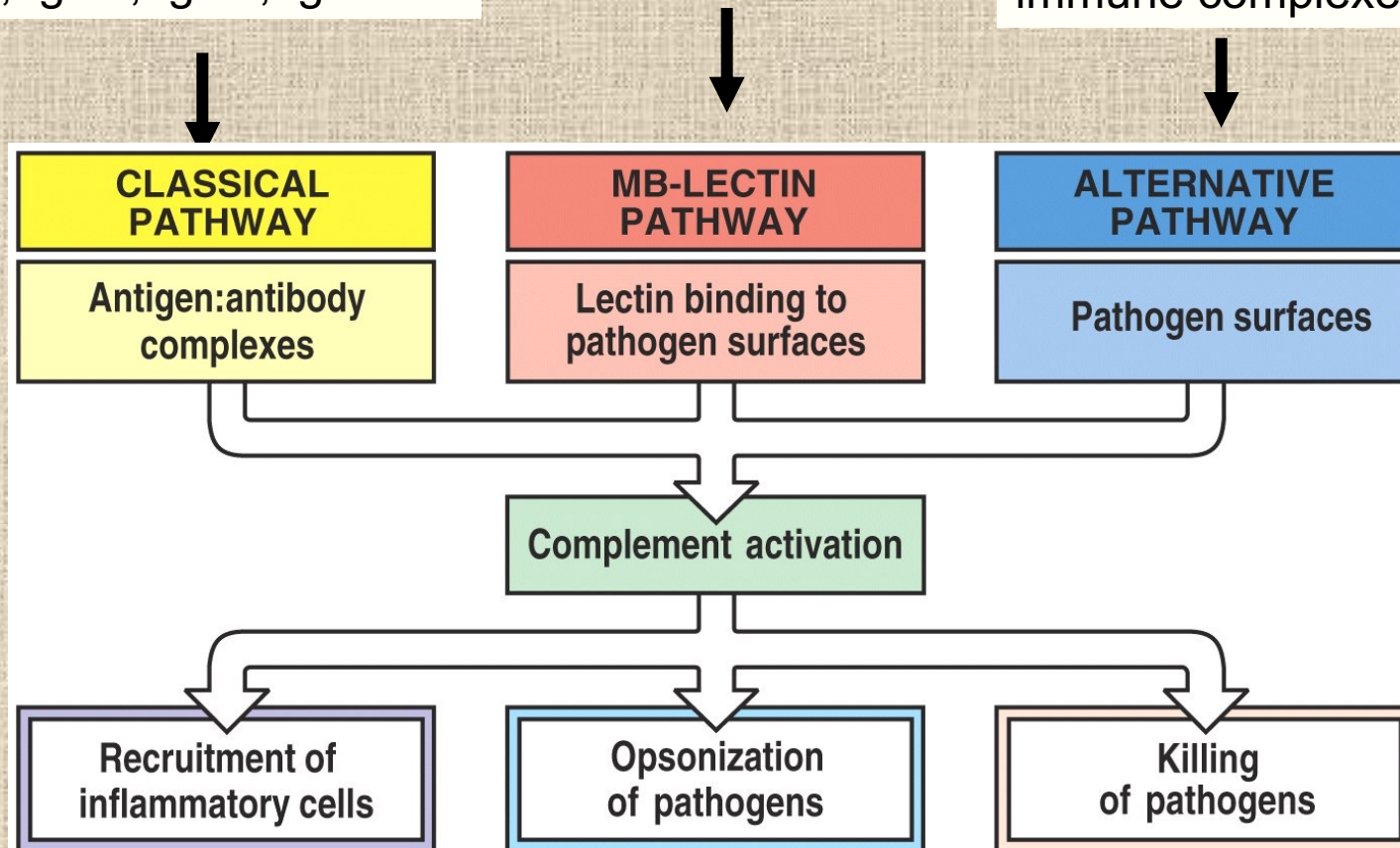


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

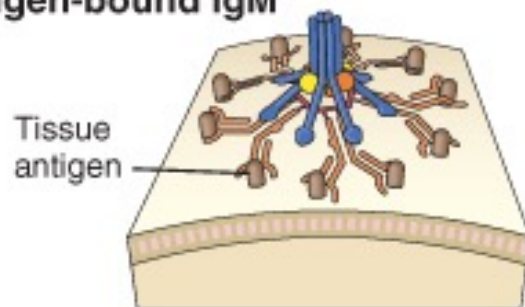
Complement activation

(A) Soluble IgM (inaccessible Fc)



No

(B) Antigen-bound IgM



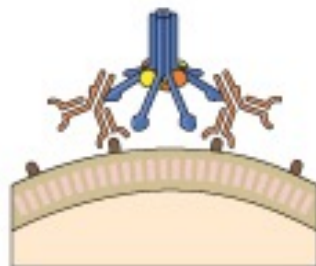
Yes

(C) Soluble IgG (Fc portions not adjacent)



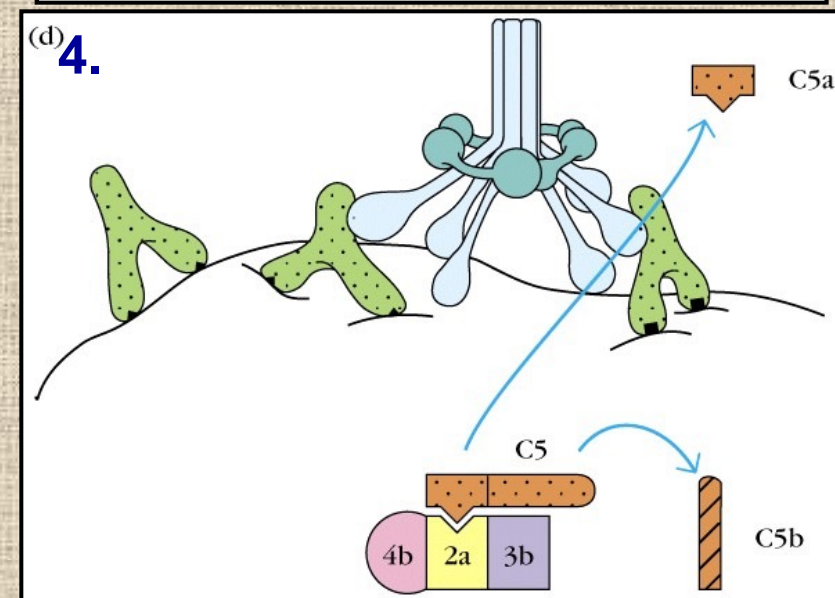
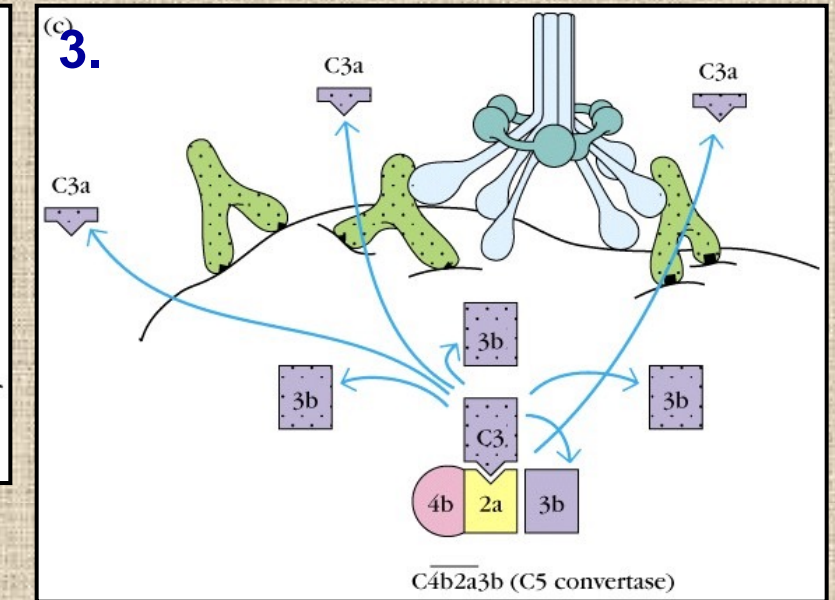
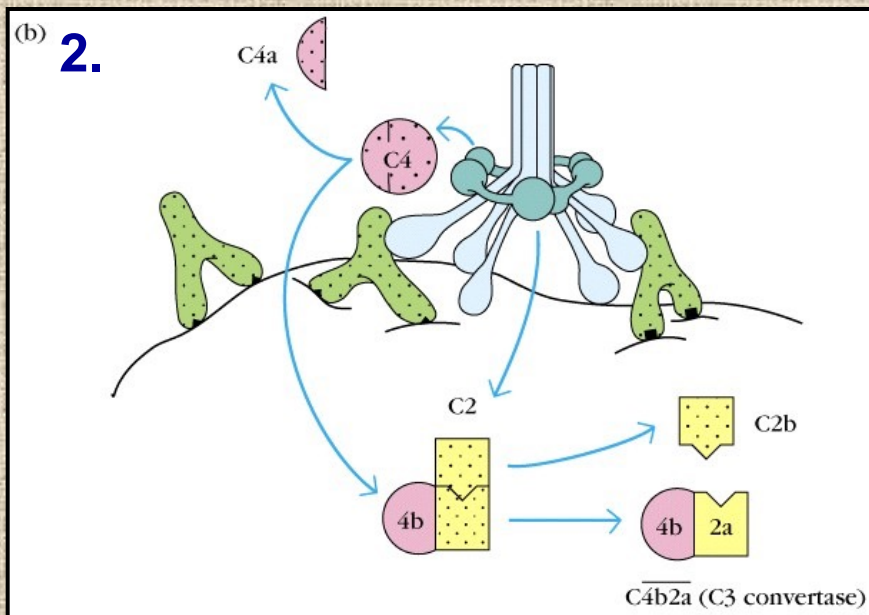
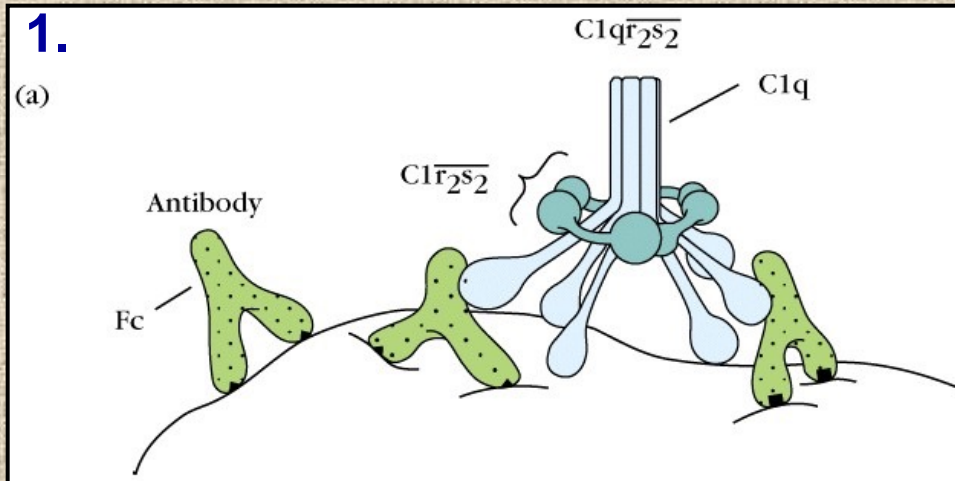
No

(D) Antigen-bound IgG

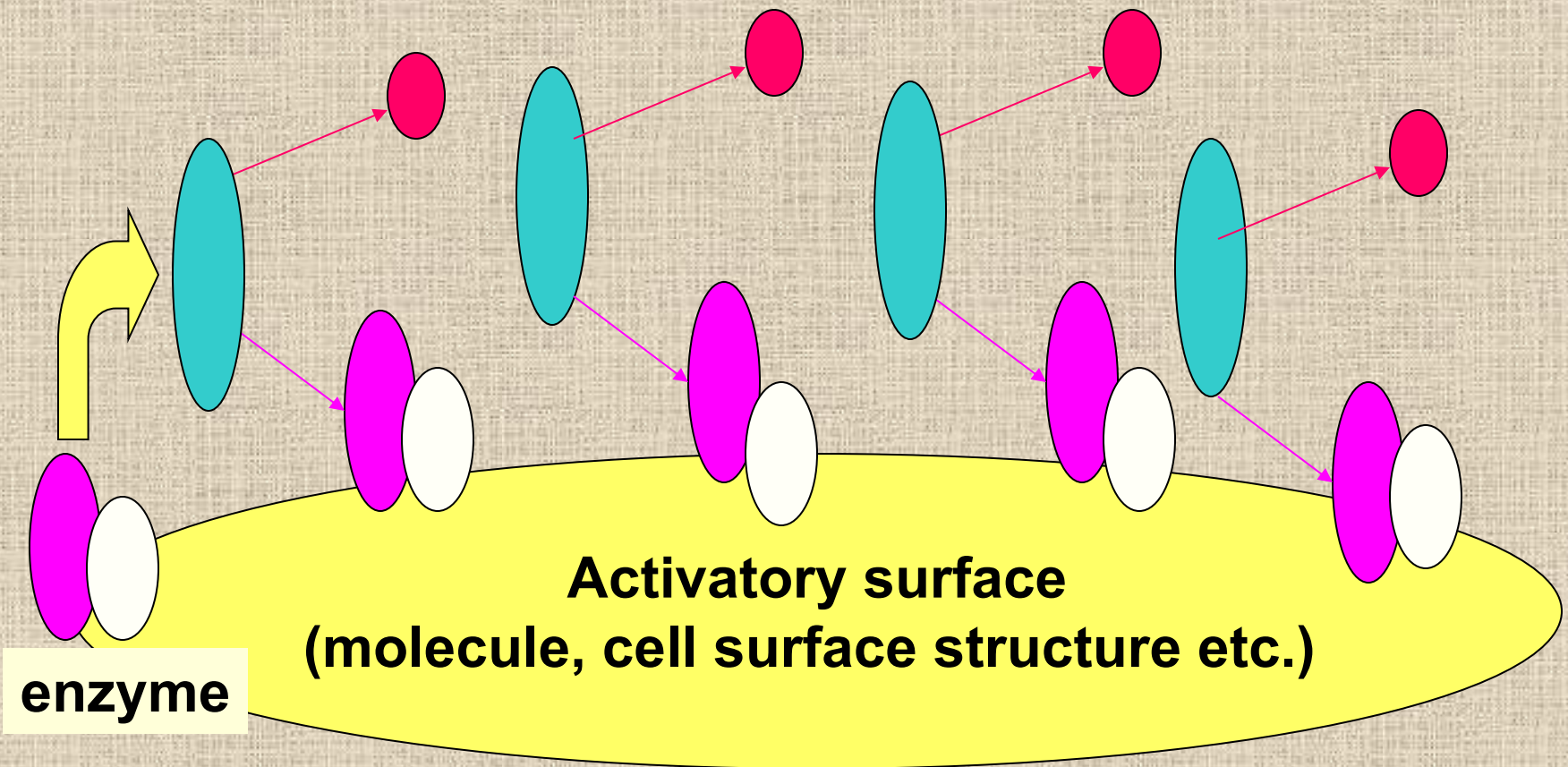


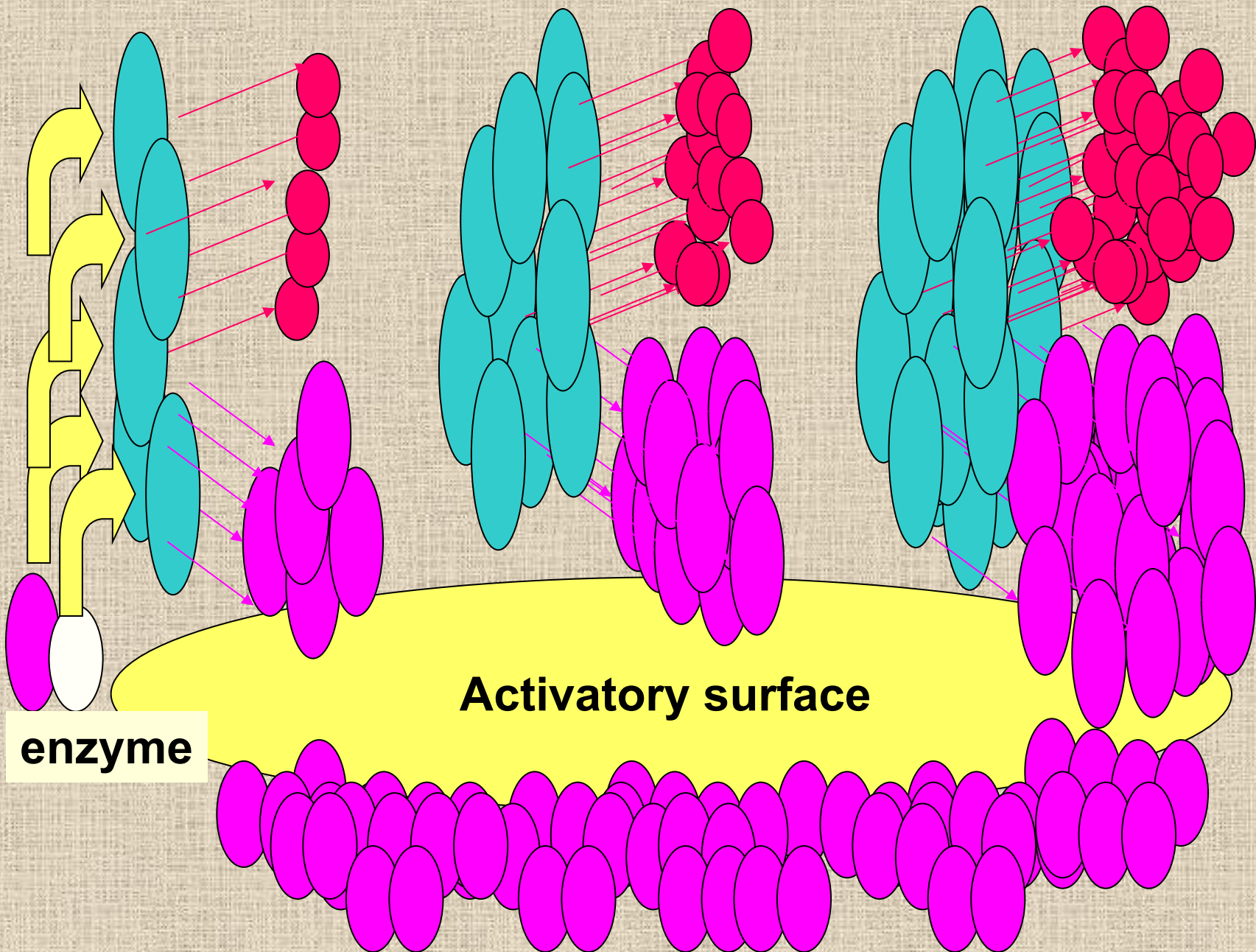
Yes

Components of the classical pathway



- Cascade-like activation
- Limited proteolysis: $C3 \rightarrow C3a + C3b$
- Amplification





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

MBL

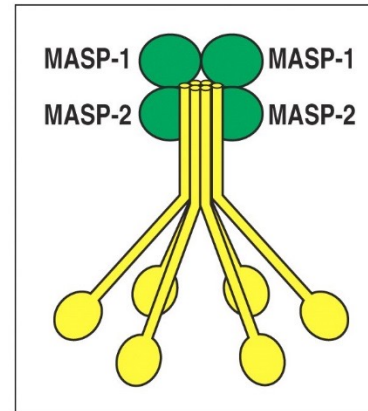
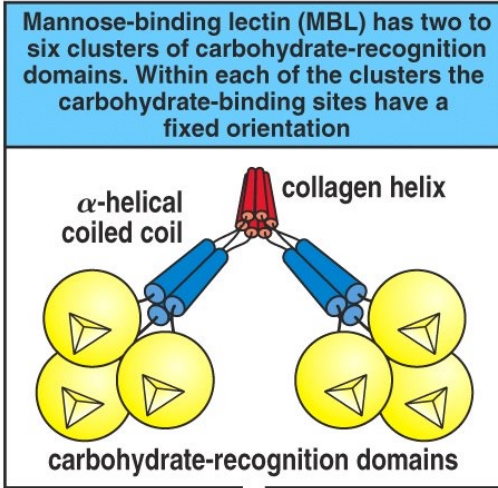
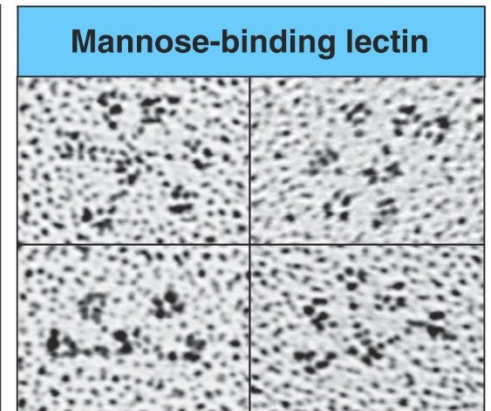
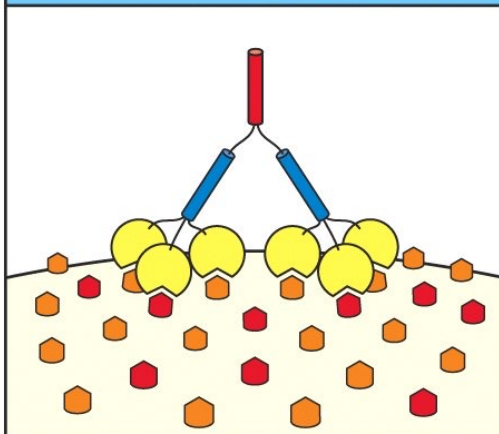


Figure 2-24 Immunobiology, 6/e. (© Garland Science 2005)



MBL binds with high affinity to mannose and fucose residues with correct spacing



Mannose and fucose residues that have different spacing are not bound by MBL

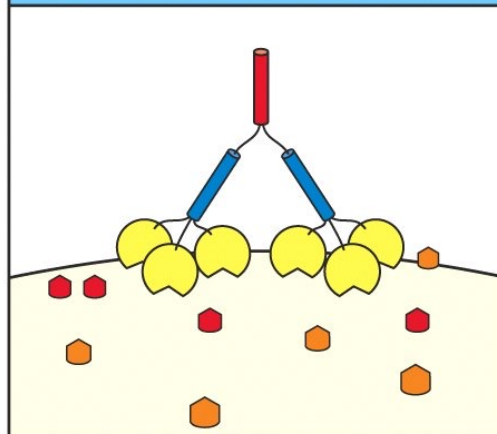


Figure 2-11 Immunobiology, 6/e. (© Garland Science 2005)

MASP

MBL: mannose binding lectin

MASP: mannose associated serine protease

Main components and effector actions of complement

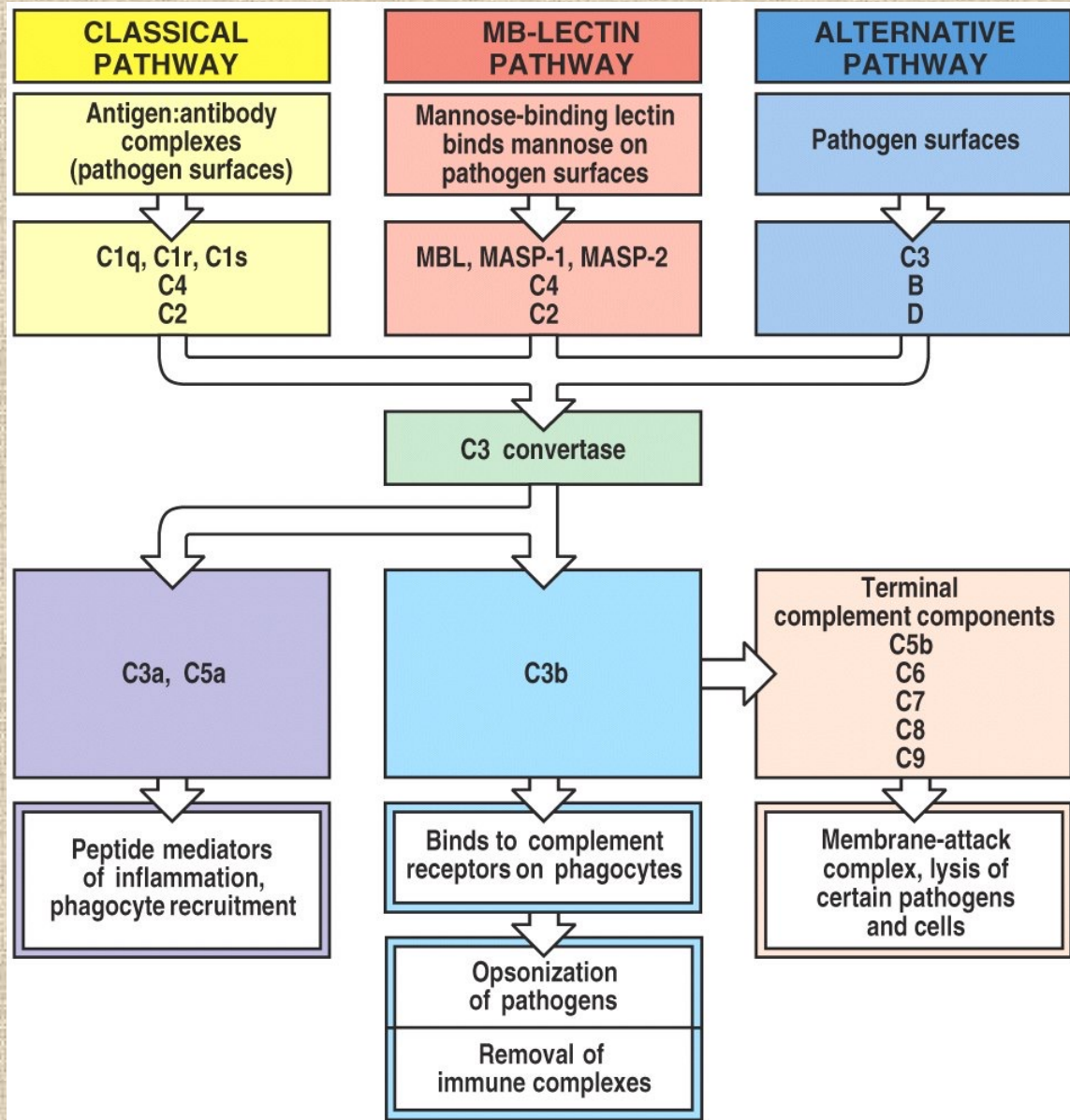
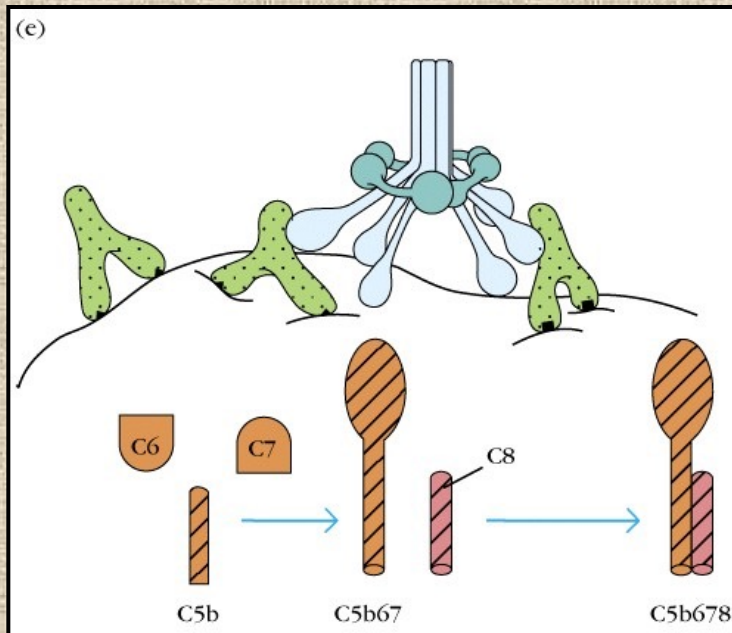
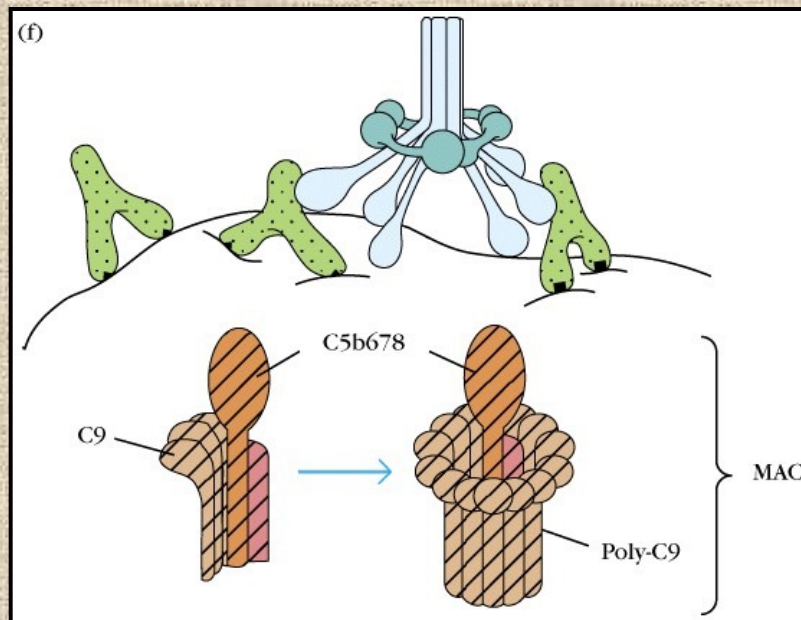


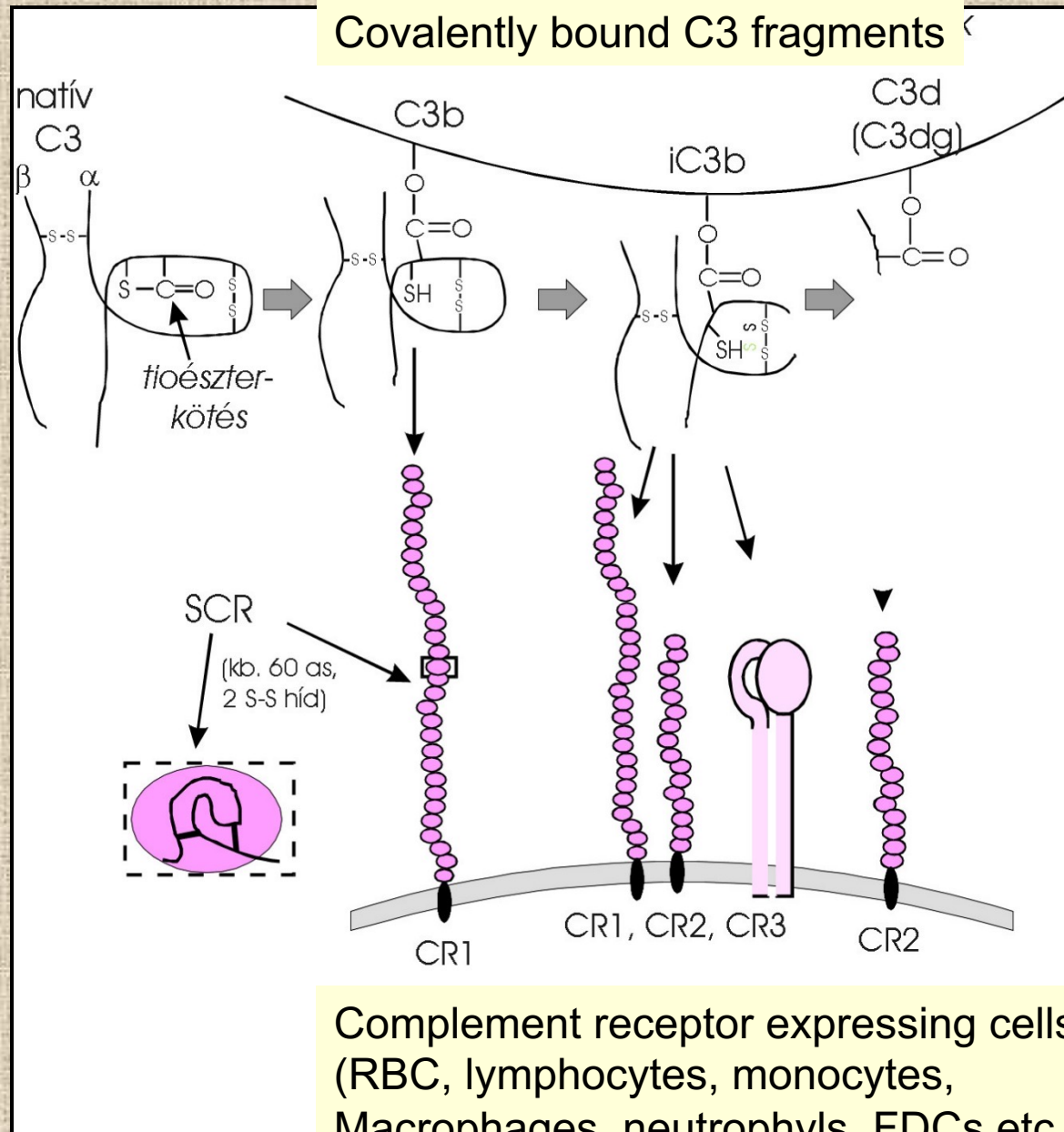
Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)



Membrane Attack Complex (MAC)



C3b-binding receptors



Complement receptors

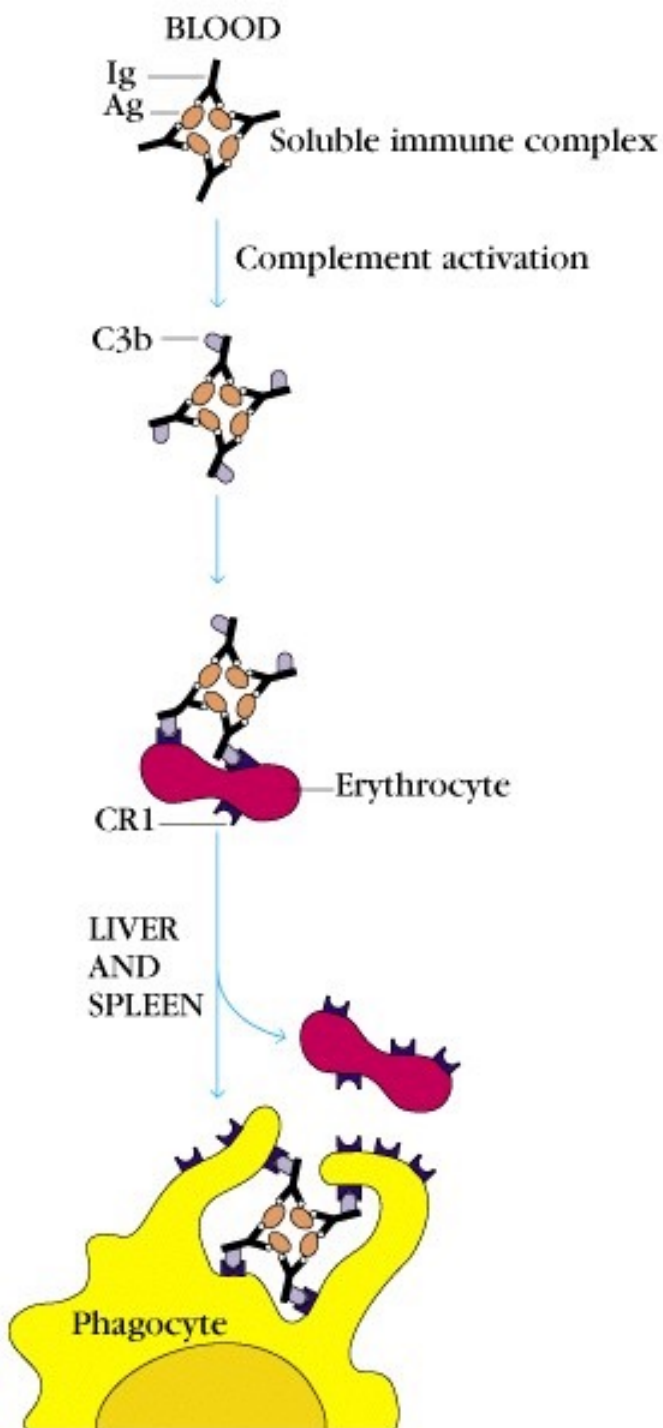
Receptor	Specificity	Functions	Cell types
CR1 (CD35)	C3b, C4b iC3b	Promotes C3b and C4b decay Stimulates phagocytosis Erythrocyte transport of immune complexes	Erythrocytes, macrophages, monocytes, polymorphonuclear leukocytes, B cells, FDC
CR2 (CD21)	C3d, iC3b, C3dg Epstein– Barr virus	Part of B-cell 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)

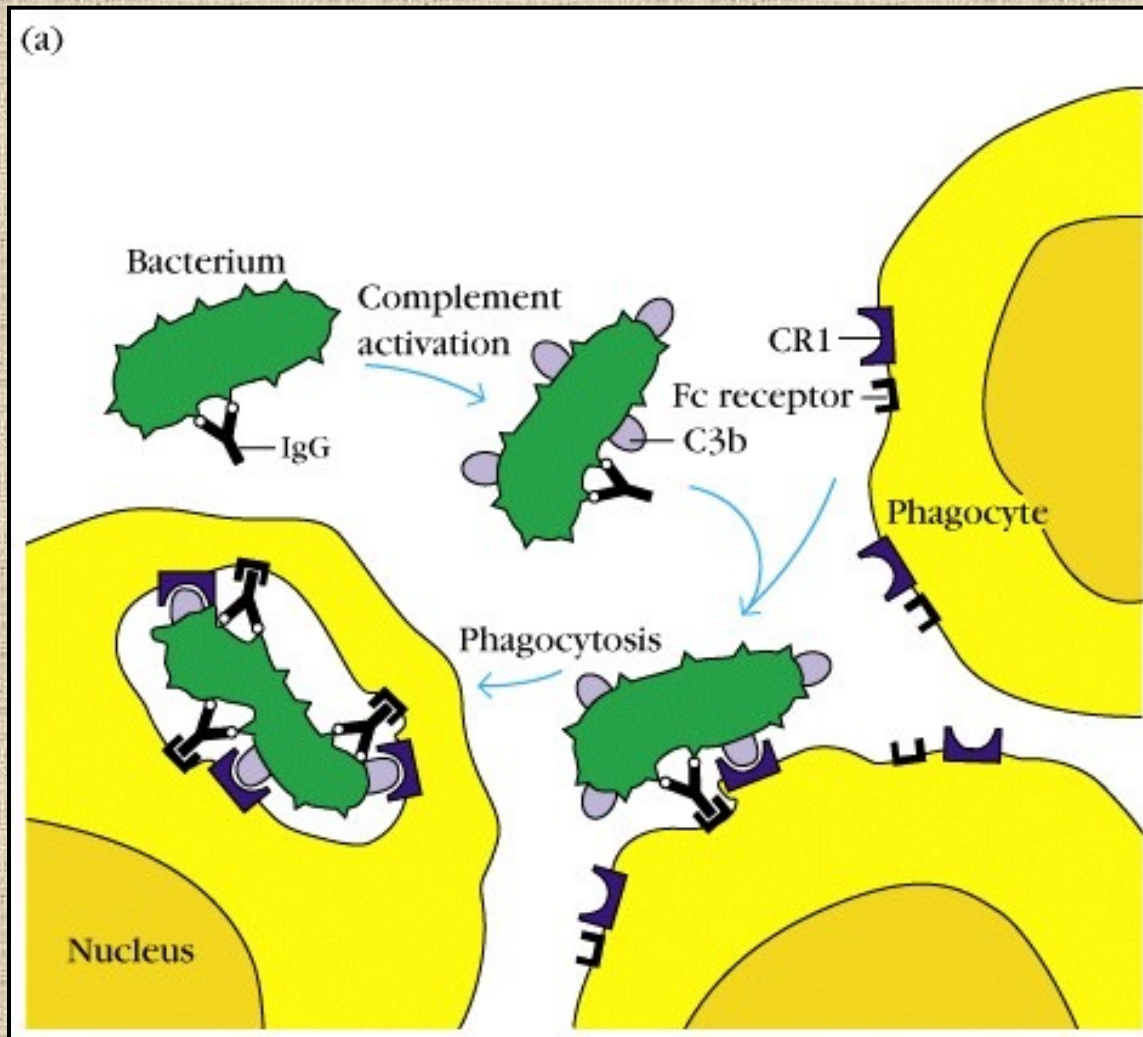
Clearance of immunocomplexes from blood

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

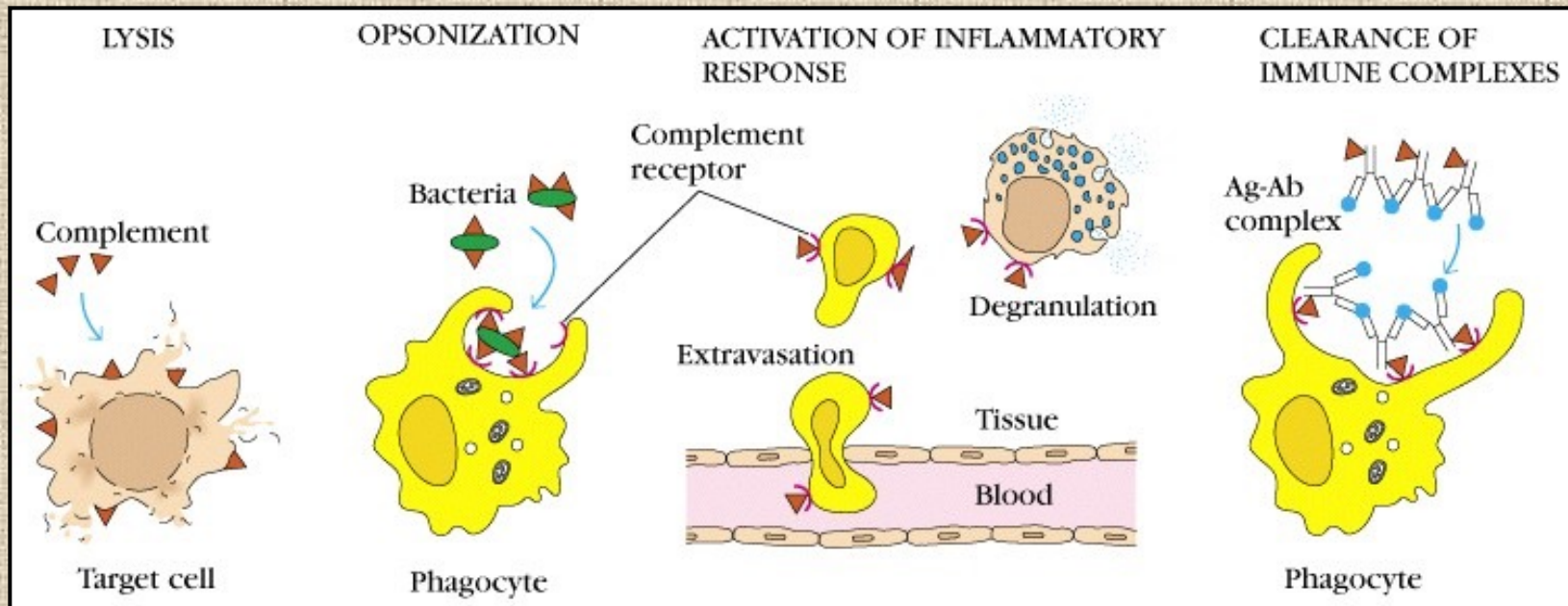


OPSONIZATION: C3b and IgG serve as opsonins

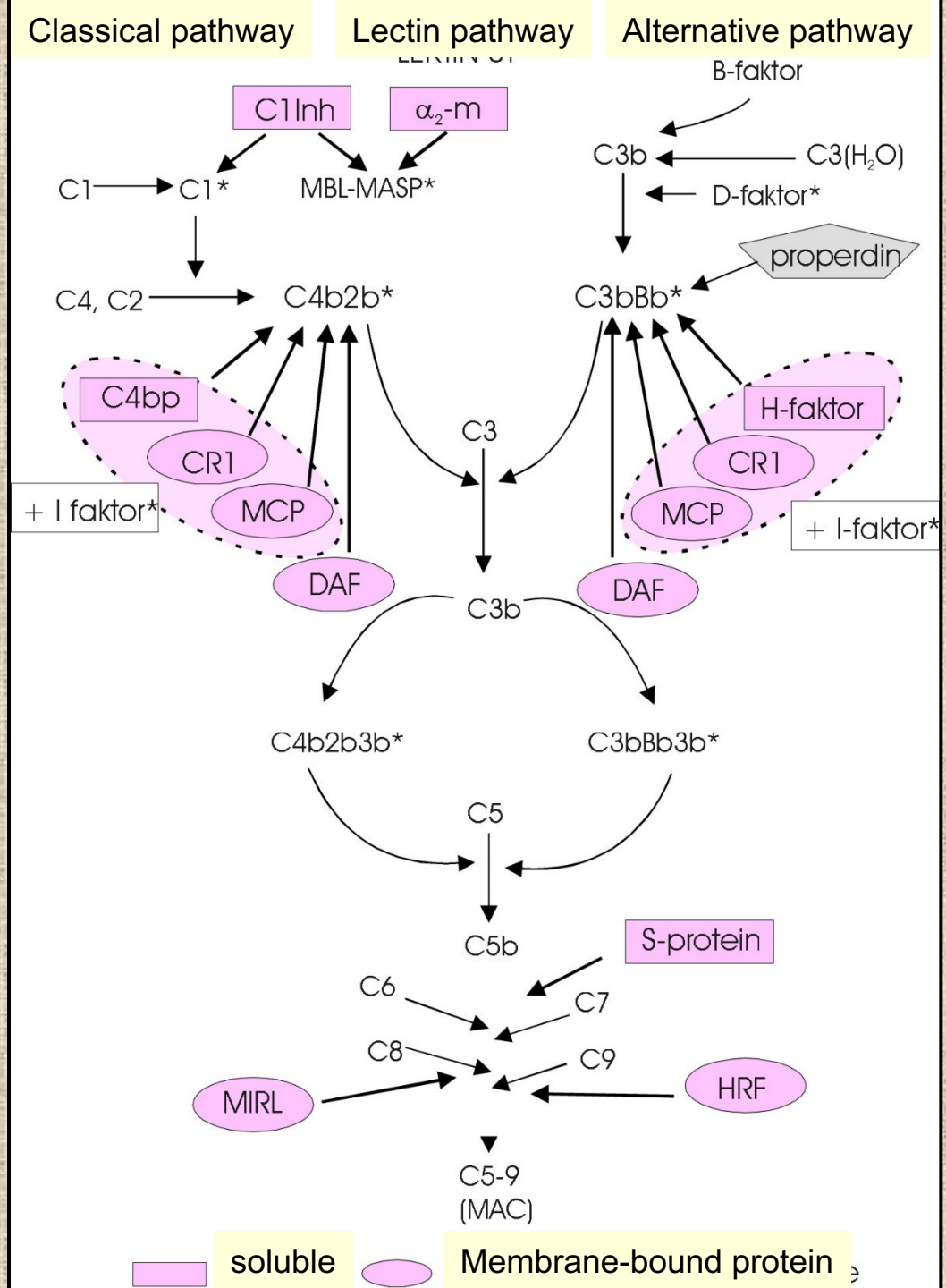


Functions of the complement:

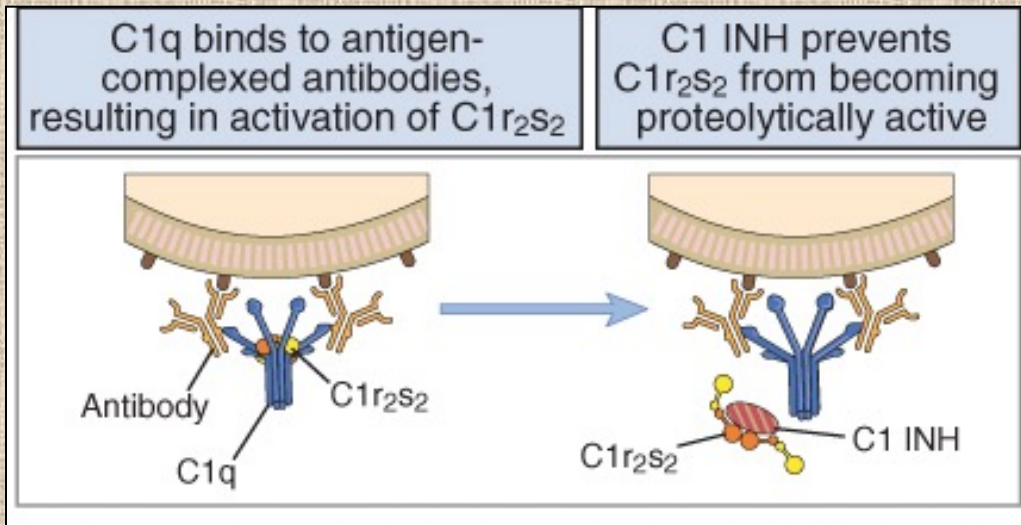
1. Lysis of cells, bacteria, viruses
2. Opsonization, which promotes phagocytosis of particulate antigens
3. Binding to complement receptors results activation of the inflammatory response and specific IR
4. Immune clearance of immune complexes from circulation



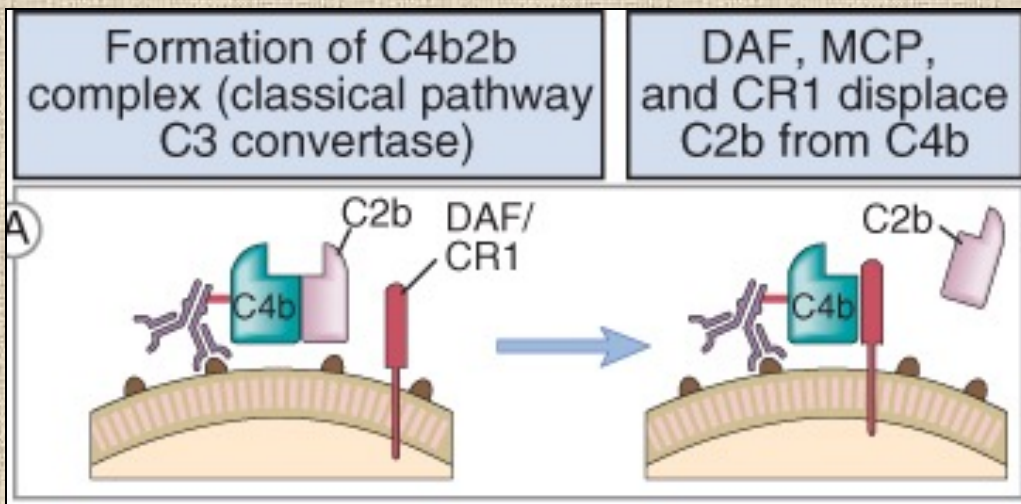
Regulatory proteins



Regulatory proteins of classical pathway



C1 INHIBITOR



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

Regulation of alternative pathway

