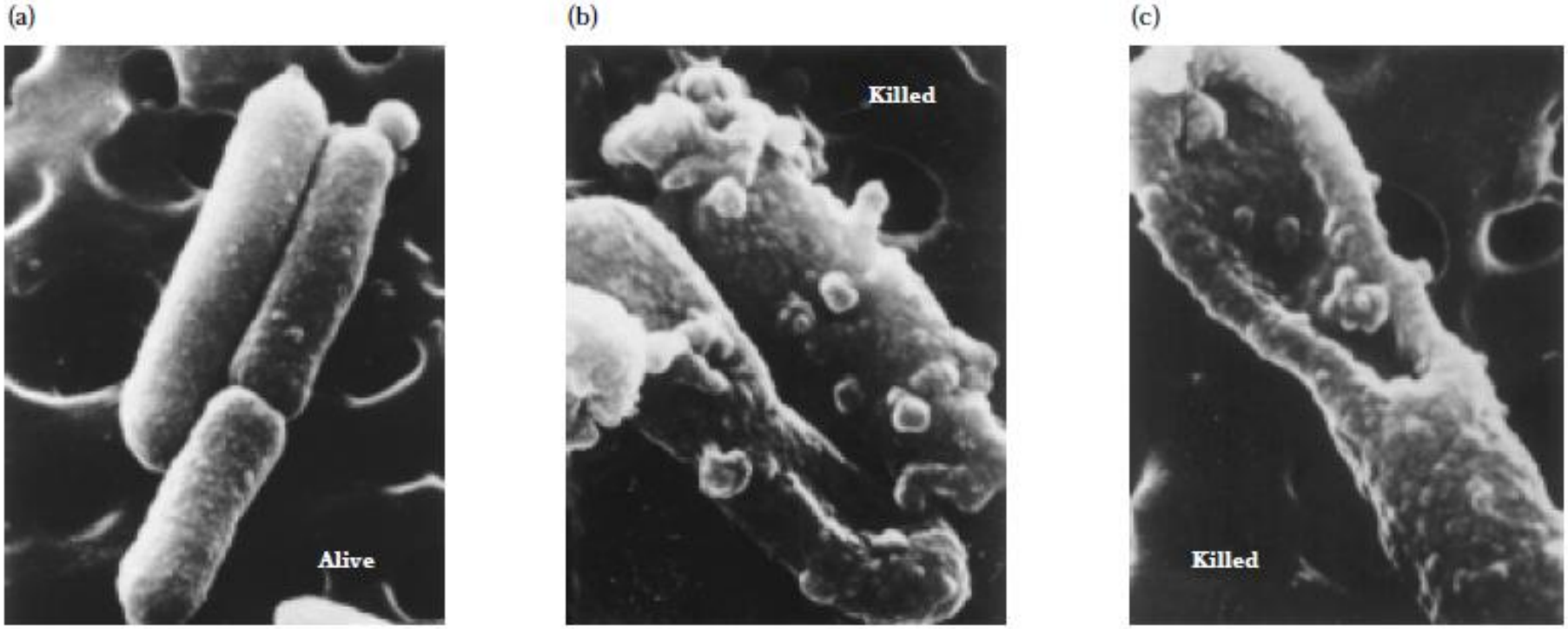
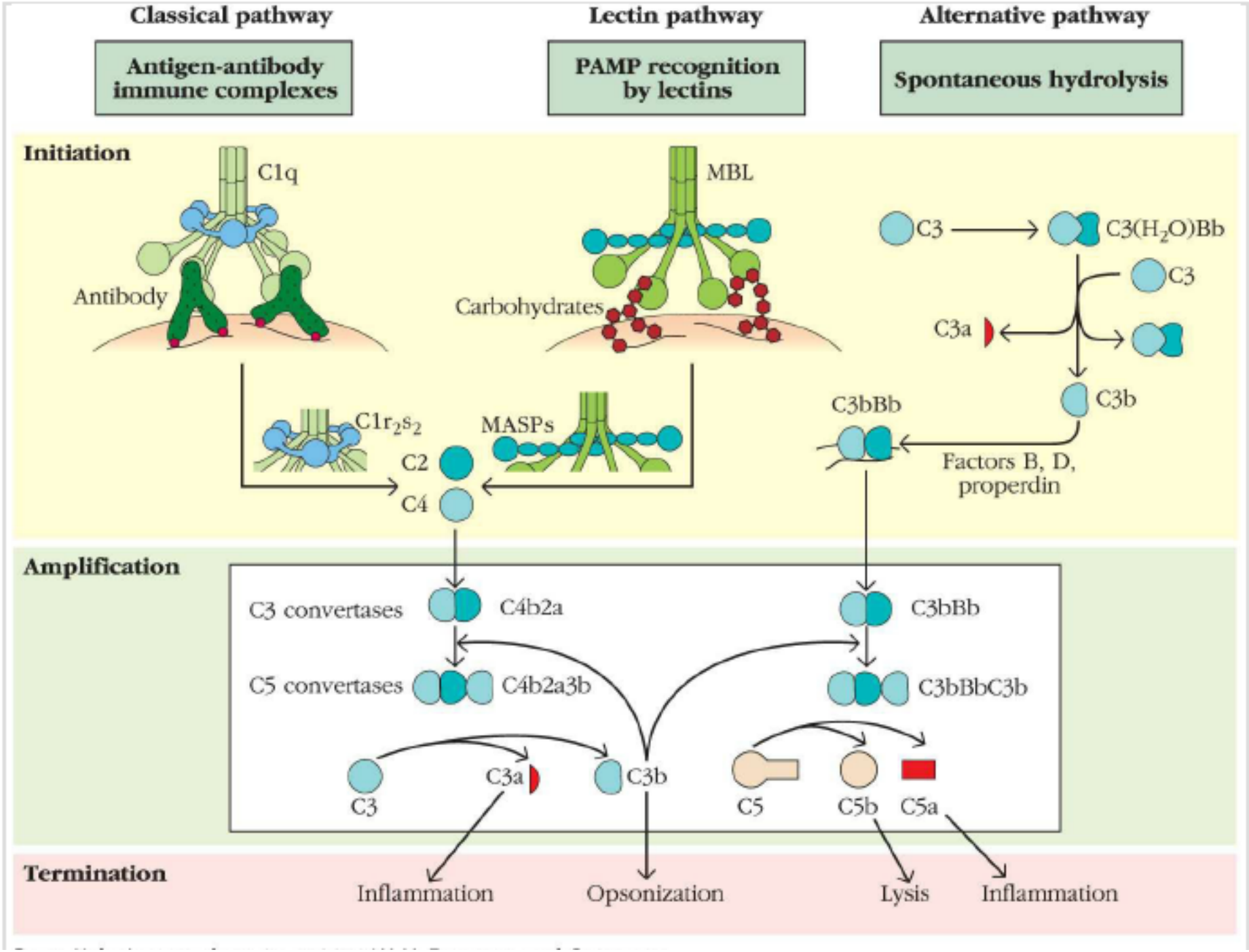
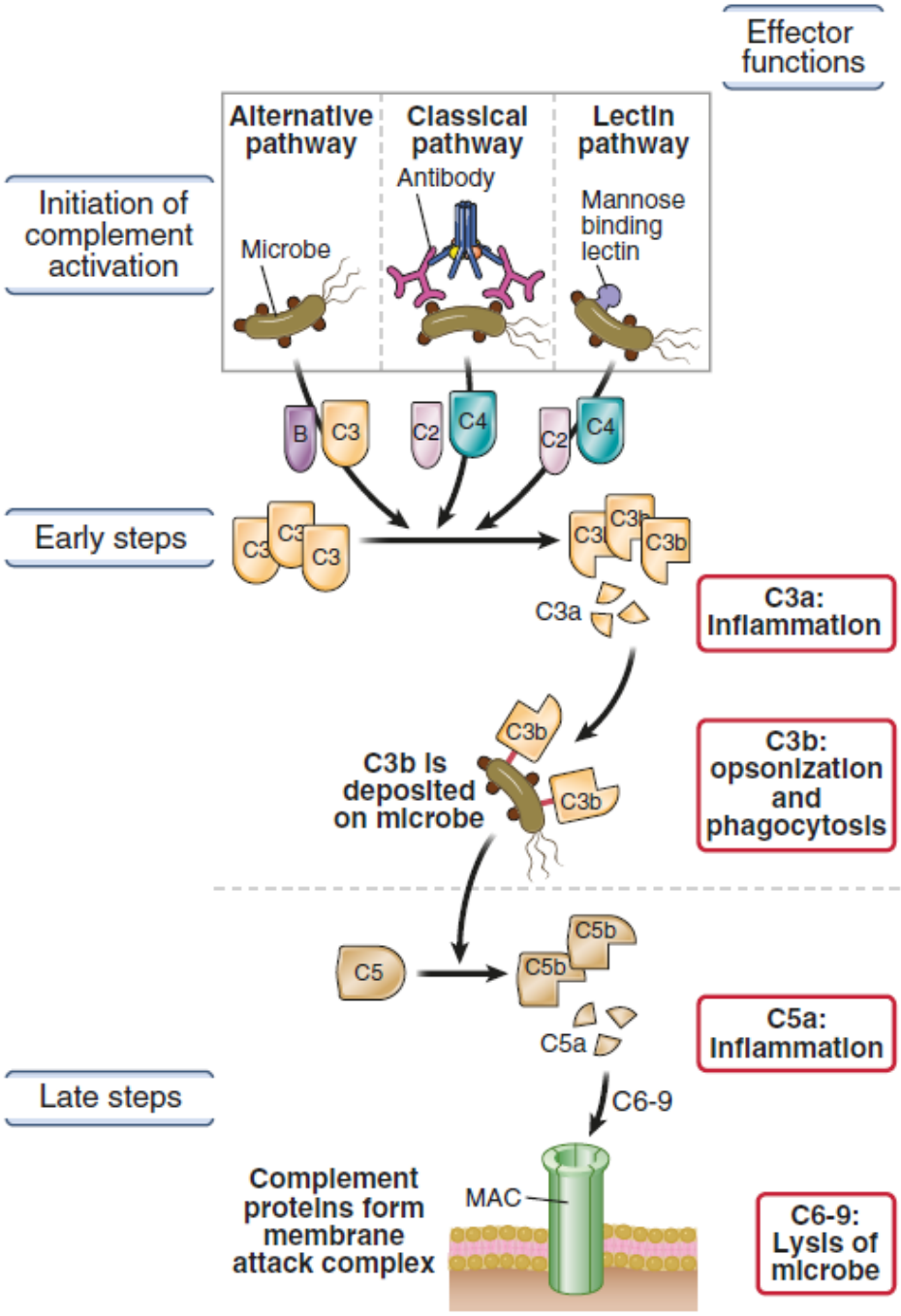


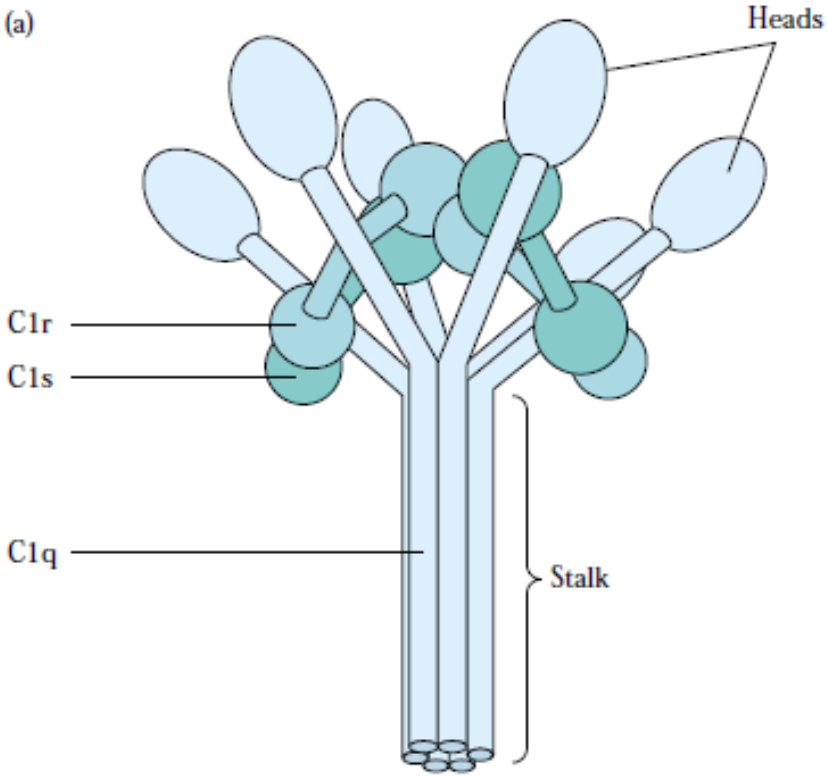
COMPLEMENT SYSTEM


Classical pathway
Antigen-antibody immune complexes
Lectin pathway
PAMP recognition by lectins
Alternative pathway
Spontaneous hydrolysis
Initiation
C1q
Antibody
MBL
Carbohydrates
C3
C3(H2O)Bb
C3
C3a
C3b
C3bBb
Factors B, D, properdin
C1r2s2
MASPs
C2
C4
Amplification
C3 convertases
C4b2a
C5 convertases
C4b2a3b
C3bBb
C3bBbC3b
C3
C3a
C3b
C5
C5b
C5a
Termination
Inflammation
Opsonization
Lysis
Inflammation


Effector functions
Alternative pathway
Classical pathway
Lectin pathway
Antibody
Mannose binding lectin
Microbe
Initiation of complement activation
B
C3
C2
C4
C2
C4
Early steps
C3
C3
C3
C3
C3b
C3b
C3a
C3a: Inflammation
C3b
C3b is deposited on microbe
C3b
C3b: opsonization and phagocytosis
C5
C5b
C5b
C5a
C5a: Inflammation
Late steps
C6-9
Complement proteins form membrane attack complex
MAC
C6-9: Lysis of microbe

INITIATION

Major Complement components



B

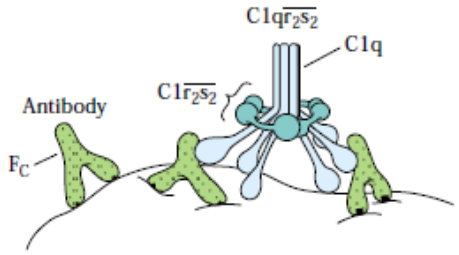
Protein	Serum conc. (ug/mL)	Function
C3	640-1660	C3b binds to the surface of microbes, where it functions as an opsonin and as a component of C3 and C5 convertases C3a stimulates inflammation
Factor B	200	Bb is a serine protease and the active enzyme of C3 and C5 convertases
Factor D	1-2	Plasma serine protease that cleaves Factor B when it is bound to C3b

C

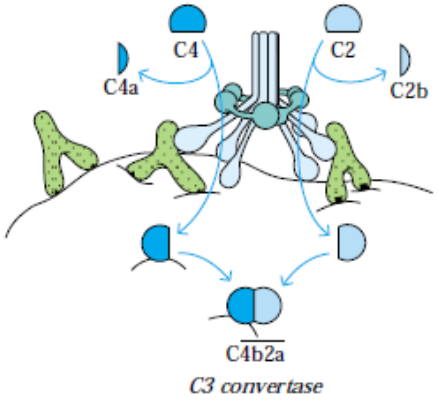
Protein	Serum conc. (ug/mL)	Function
C1 ($C1qr_2s_2$)		Initiates the classical pathway; C1q binds to Fc portion of antibody; C1r and C1s are proteases that lead to C4 and C2 activation
C4	150-450	C4b covalently binds to surfaces of microbes or cells where antibody is bound and complement is activated C4b binds to C2 for cleavage by C1s C4a stimulates inflammation
C2	20	C2a is a serine protease functioning as an active enzyme of C3 and C5 convertases
Mannose binding lectin (MBL)	0.8-1	Initiates the lectin pathway; MBL binds to terminal mannose residues of microbial carbohydrates. A MBL-associated protease activates C4 and C2, as in the classical pathway.

Classical Pathway

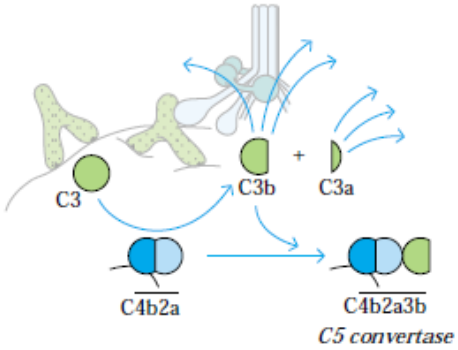
1. C1q binds antigen-bound antibody. C1r activates auto-catalytically and activates the second C1r; both activate C1s



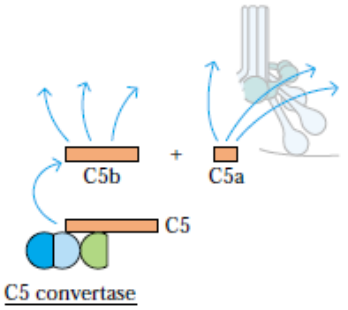
2. C1s cleaves C4 and C2. Cleaving C4 exposes the binding site for C2. C4 binds the surface near C1 and C2 binds C4, forming C3 convertase



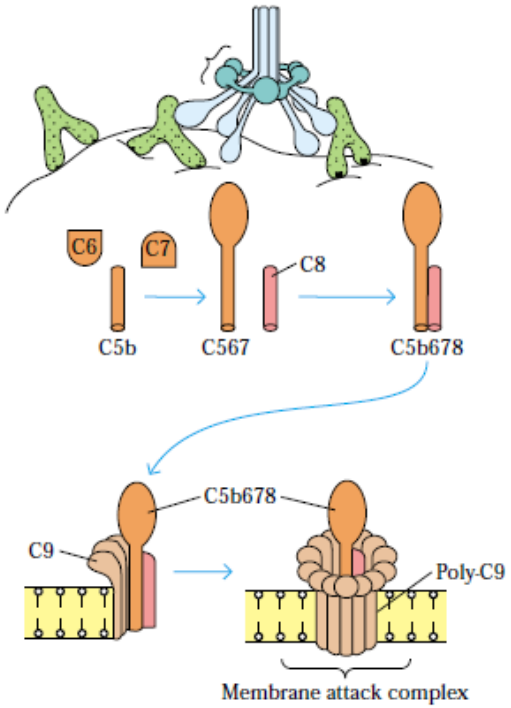
3. C3 convertase hydrolyzes many C3 molecules. Some combine with C3 convertase to form C5 convertase



4. The C3b component of C5 convertase binds C5, permitting C4b2a to cleave C5

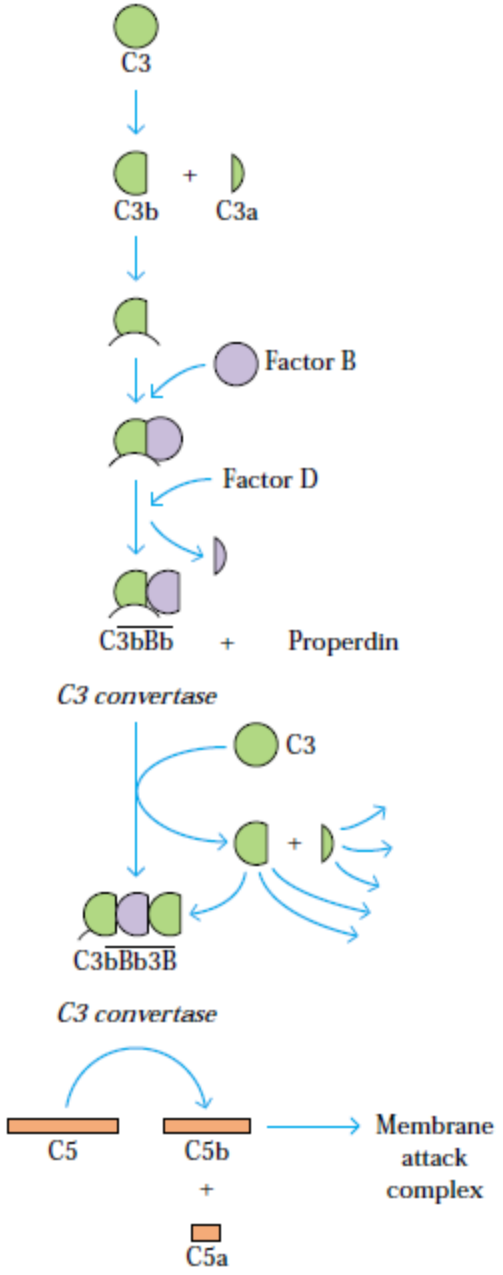


5. C5b binds C6, initiating the formation of the membrane-attac complex



Alternative Pathway

1. C3 hydrolyzes spontaneously, C3b fragment attaches to foreign surface
2. Factor B binds C3a, exposes site acted on by Factor D. Cleavage generates C3bBb, which has C3 convertase activity
3. Binding of properdin stabilizes convertase
4. Convertase generates C3b; some binds to C3 convertase activating C5' convertase. C5b binds to antigenic surface



Alternative Pathway

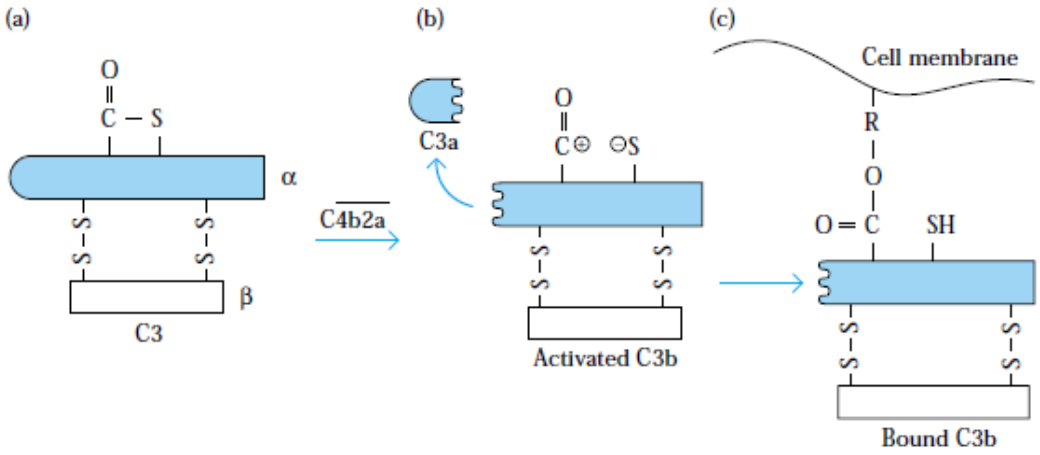
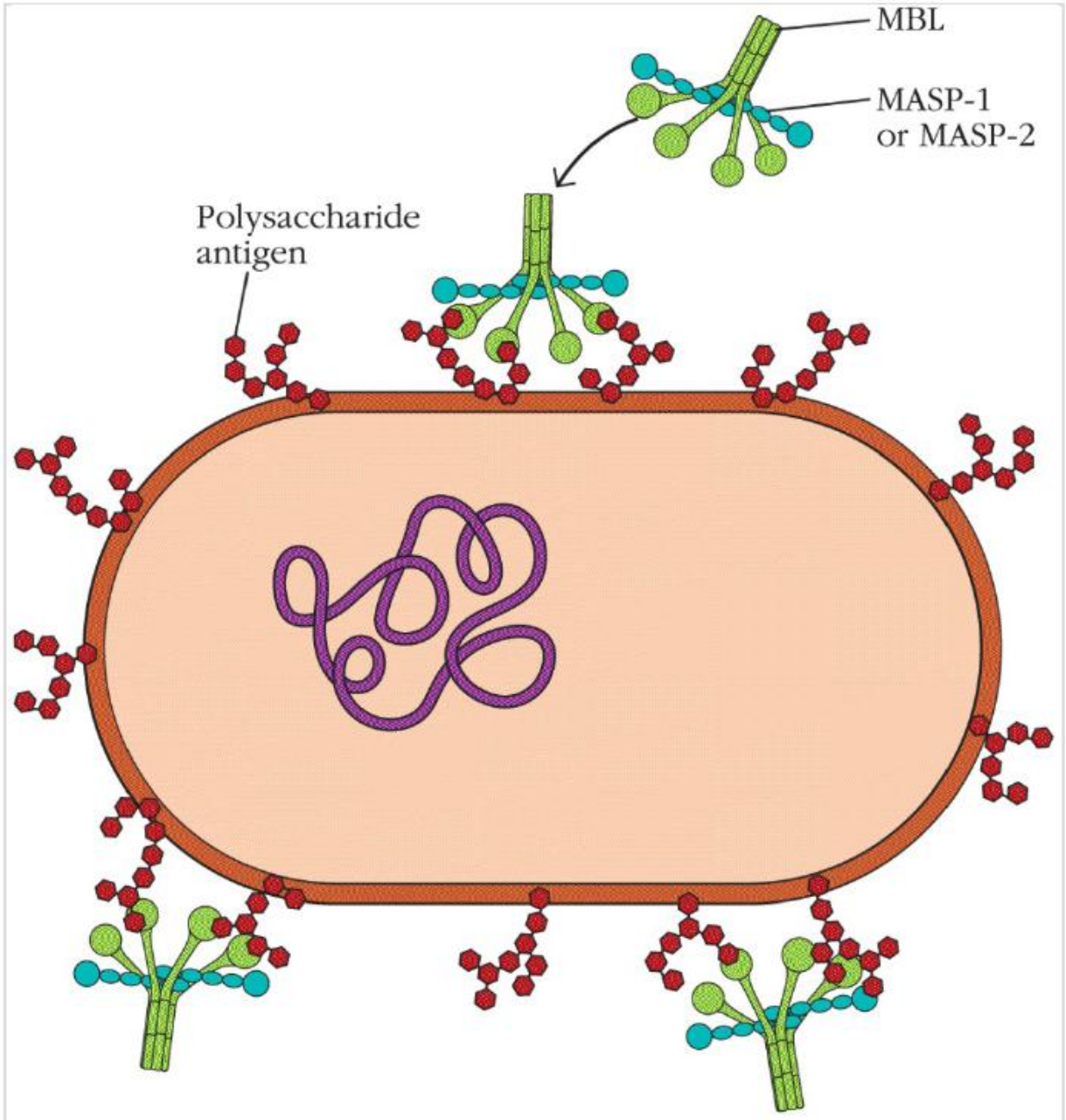


TABLE 13-1 Initiators of the alternative pathway of complement activation

PATHOGENS AND PARTICLES OF MICROBIAL ORIGIN
Many strains of gram-negative bacteria
Lipopolysaccharides from gram-negative bacteria
Many strains of gram-positive bacteria
Teichoic acid from gram-positive cell walls
Fungal and yeast cell walls (zymosan)
Some viruses and virus-infected cells
Some tumor cells (Raji)
Parasites (trypanosomes)
NONPATHOGENS
Human IgG, IgA, and IgE in complexes
Rabbit and guinea pig IgG in complexes
Cobra venom factor
Heterologous erythrocytes (rabbit, mouse, chicken)
Anionic polymers (dextran sulfate)
Pure carbohydrates (agarose, inulin)

SOURCE: Adapted from M. K. Pangburn, 1986, in *Immunobiology of the Complement System*, Academic Press.

Lectin Pathway



TERMINATION

Membrane Attack Complex (MAC)

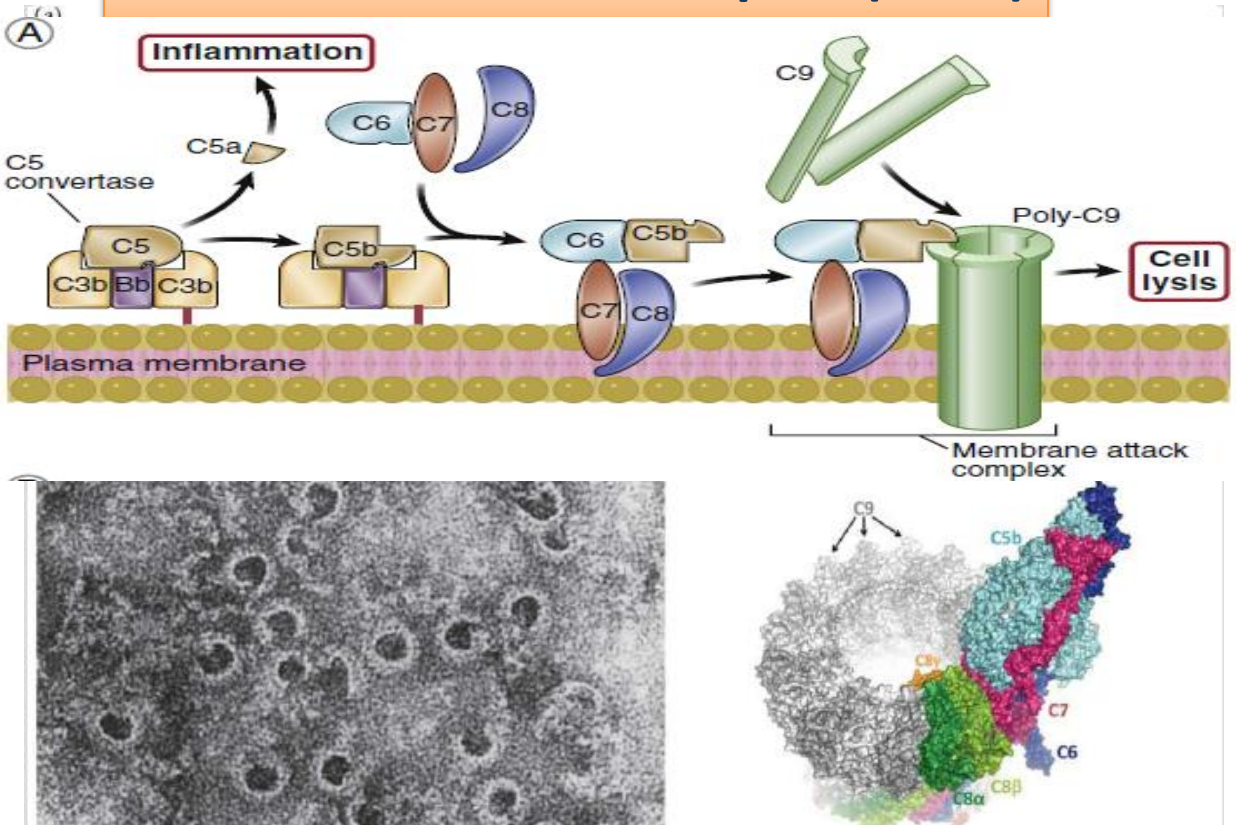


TABLE 13.7 Proteins of the Late Steps of Complement Activation

Protein	Structure	Serum Concentration (μg/mL)	Function
C5	190-kD dimer of 115- and 75-kD chains	80	C5b initiates assembly of the MAC. C5a stimulates inflammation (anaphylatoxin).
C6	110-kD monomer	45	Component of the MAC: binds to C5b and accepts C7.
C7	100-kD monomer	90	Component of the MAC: binds to C5b,6 and inserts into lipid membranes.
C8	155-kD trimer of 64-, 64-, and 22-kD chains	60	Component of the MAC: binds to C5b,6,7 and initiates the binding and polymerization of C9.
C9	79-kD monomer	60	Component of the MAC: binds to C5b,6,7,8 and polymerizes to form membrane pores.

MAC, Membrane attack complex.

Summary of Complement Pathways

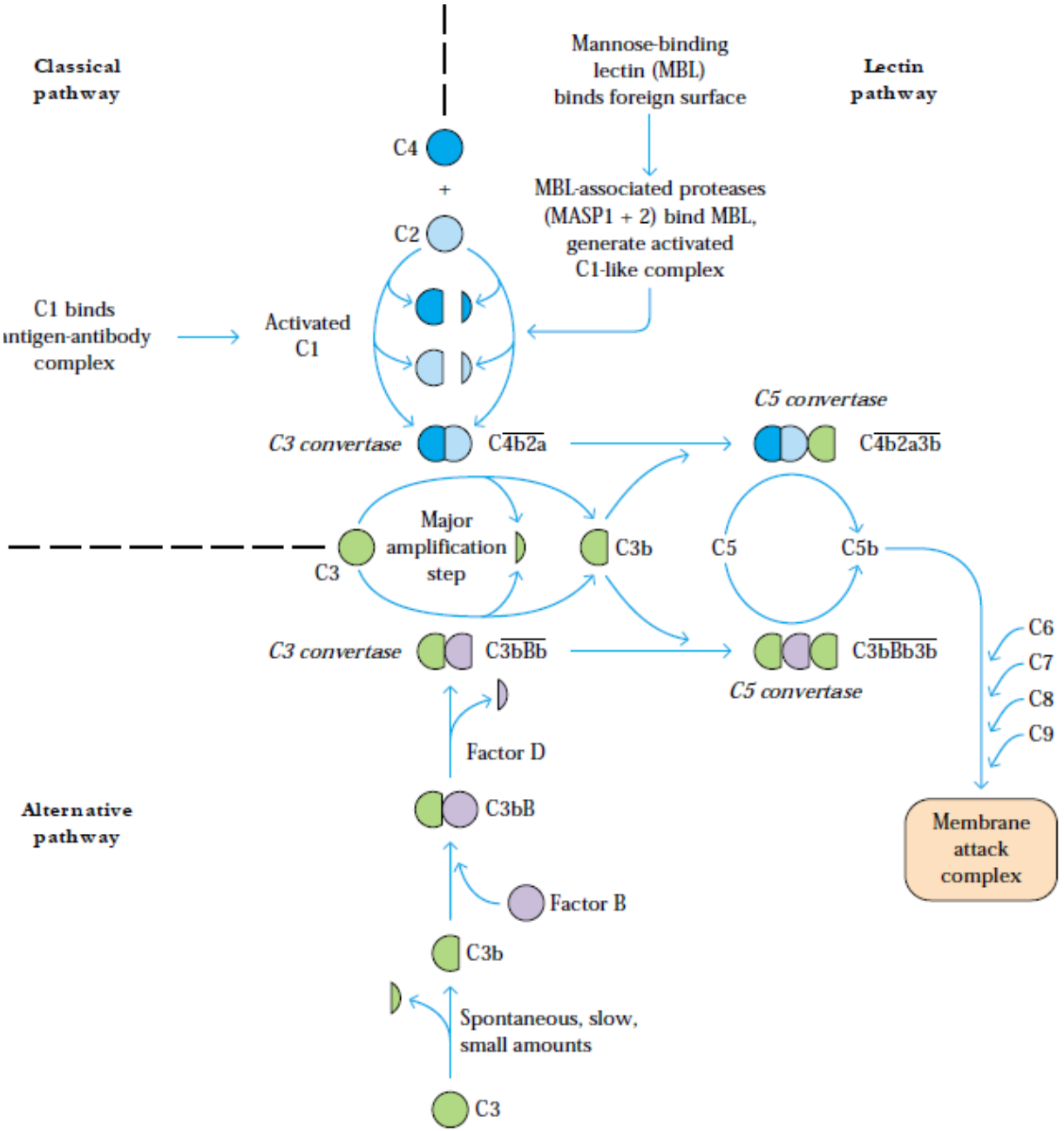


TABLE 5-4 The three main classes of complement activity in the service of host defense

Activity	Responsible complement component
Innate defense against infection	
Lysis of bacterial and cell membranes	Membrane attack complex (C5b-C9)
Opsonization	Covalently bound C3b, C4b
Induction of inflammation and chemotaxis by anaphylatoxins	C3a and C5a (anaphylatoxins) and their receptors on leukocytes
Interface between innate and adaptive immunity	
Augmentation of antibody responses	C3b and C4b and their proteolyzed fragments bound to immune complexes and antigen; C3 receptors on immune cells
Enhancement of immunologic memory	C3b and C4b and their fragments bound to antigen and immune complexes; receptors for complement components on follicular dendritic cells
Enhancement of antigen presentation	MBL, C1q, C3b, C4b, and C5a
Potential effects on T cells	C3, C3a, C3b, C5a
Complement in the contraction phase of the immune response	
Clearance of immune complexes from tissues	C1, C2, C4; covalently bound fragments of C3 and C4
Clearance of apoptotic cells	C1q; covalently bound fragments of C3 and C4. Loss of CD46 triggers immune clearance
Induction of regulatory T cells	CD46

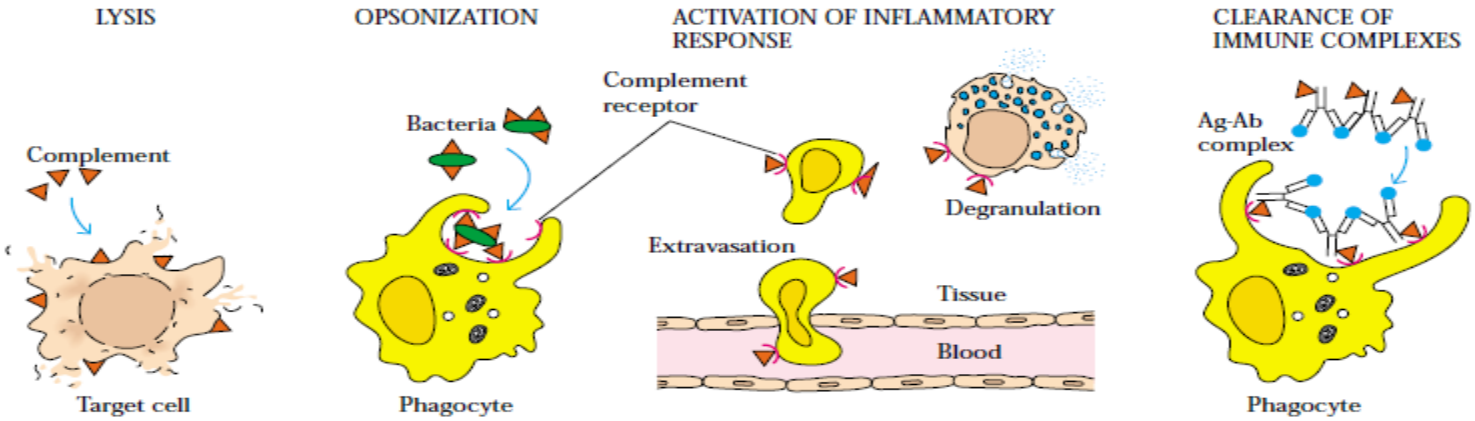
This table has been considerably modified from the superb formulation of Walport, M. 2001. Complement: first of two parts. *New England Journal of Medicine* **344:**1058 [Table 1.].

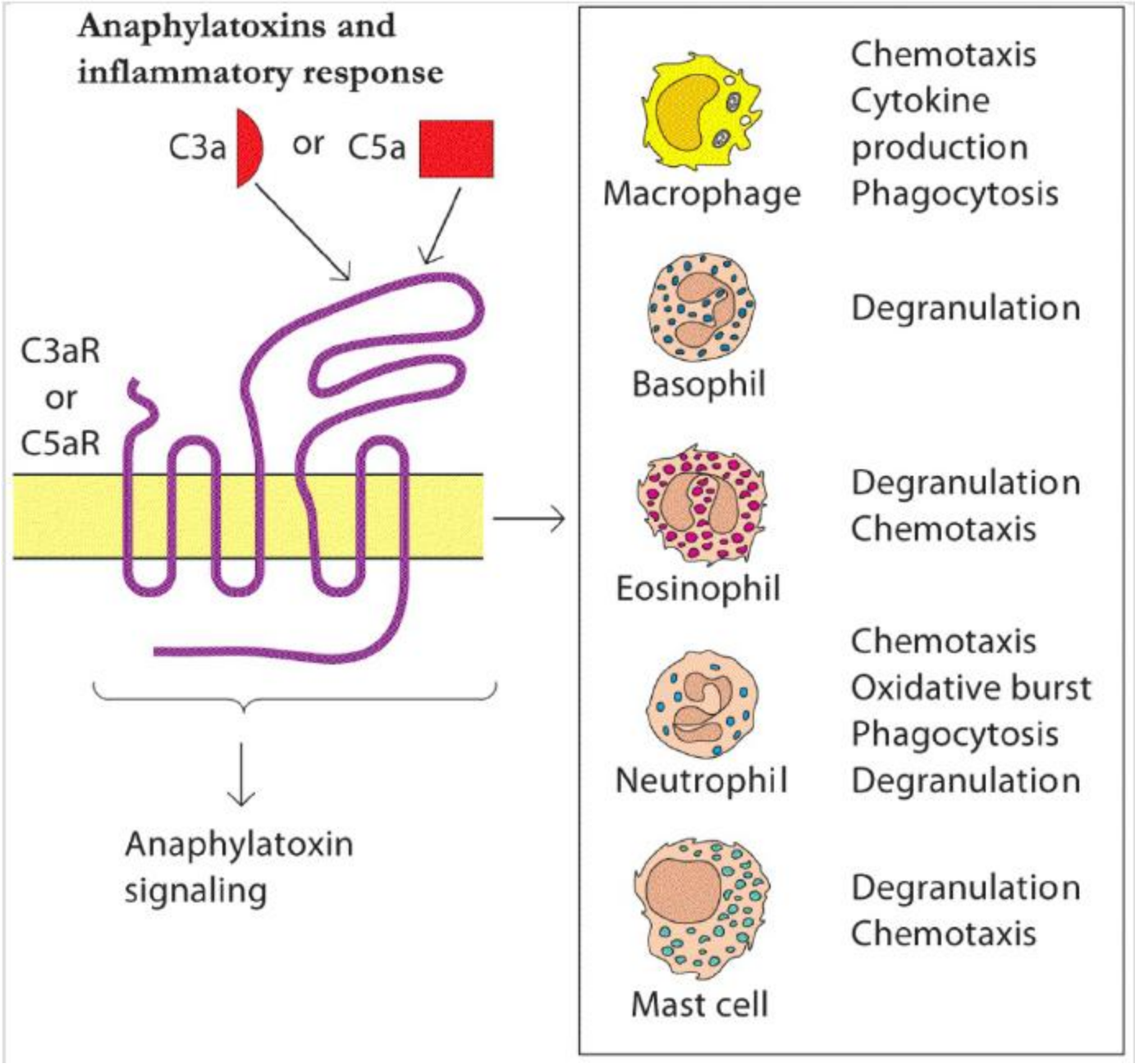
TABLE 13-3 Summary of biological effects mediated by complement products

Effect	Complement product mediating*
Cell lysis	C5b–9, the membrane-attack complex (MAC)
Inflammatory response	
Degranulation of mast cells and basophils†	C3a,C4a, and C5a (anaphylatoxins)
Degranulation of eosinophils	C3a, C5a
Extravasation and chemotaxis of leukocytes at inflammatory site	C3a, C5a, C5b67
Aggregation of platelets	C3a, C5a
Inhibition of monocyte/macrophage migration and induction of their spreading	Bb
Release of neutrophils from bone marrow	C3c
Release of hydrolytic enzymes from neutrophils	C5a
Increased expression of complement receptors type 1 and 3 (CR1 and CR3) on neutrophils	C5a
Opsonization of particulate antigens, increasing their phagocytosis	C3b, C4b, iC3b
Viral neutralization	C3b, C5b–9 (MAC)
Solubilization and clearance of immune complexes	C3b

*Boldfaced component is most important in mediating indicated effect.

†Degranulation leads to release of histamine and other mediators that induce contraction of smooth muscle and increased permeability of vessels.




Anaphylatoxins and inflammatory response
C3a
or
C5a
C3aR
or
C5aR
Anaphylatoxin signaling
Macrophage
Chemotaxis
Cytokine production
Phagocytosis
Basophil
Degranulation
Eosinophil
Degranulation
Chemotaxis
Neutrophil
Chemotaxis
Oxidative burst
Phagocytosis
Degranulation
Mast cell
Degranulation
Chemotaxis

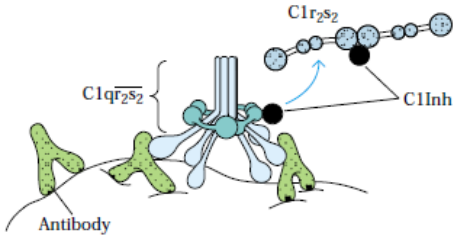
Regulation of Complement System

VISUALIZING CONCEPTS

Regulation of the Complement System

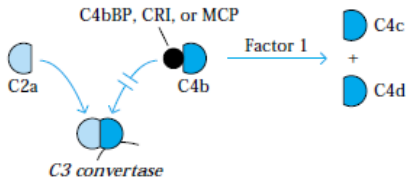
(a) Before assembly of convertase activity

1. C1 inhibitor (C1Iab) binds $C1r_2s_2$, causing dissociation from C1q



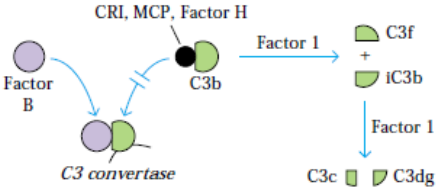
2. Association of C4b and C2a is blocked by binding C4b-binding protein (C4bBP), complement receptor type I, or membrane cofactor protein (MCP)

3. Inhibitor-bound C4b is cleaved by Factor 1



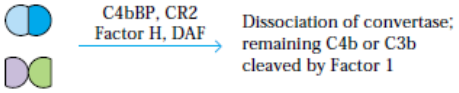
4. In alternative pathway, CR1, MCP, or Factor H prevent binding of C3b and Factor B

5. Inhibitor-bound C3b is cleaved by Factor 1



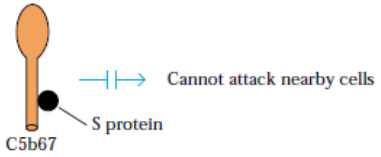
(b) After assembly of convertase

C3 convertases are dissociated by C4bBP, CR1, Factor H, and decay-accelerating Factor (DAF)

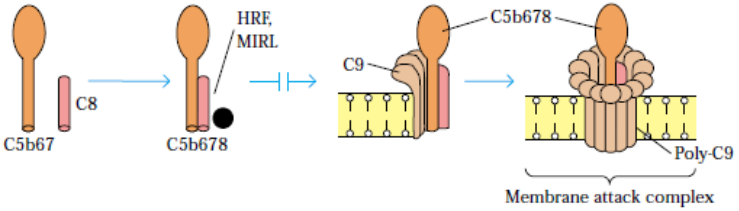


(c) Regulation at assembly of membrane-attack complex (MAC)

1. S protein prevents insertion of C5b67 MAC component into the membrane



2. Homologous restriction factor (HRF) and membrane inhibitor of reactive lysis (MIRL or CD59) bind $C8_1$, preventing assembly of poly-C9 and blocking formation of MAC




Thank You!