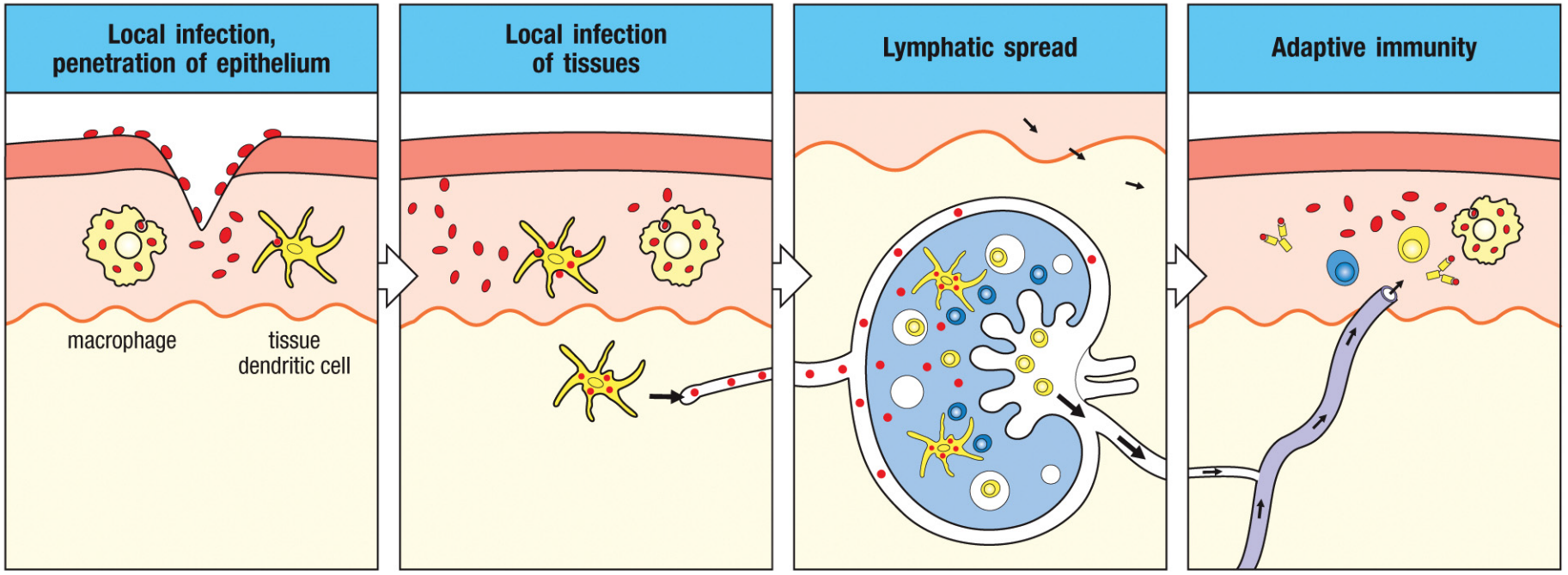
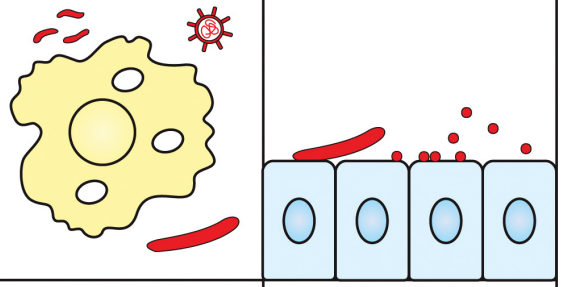
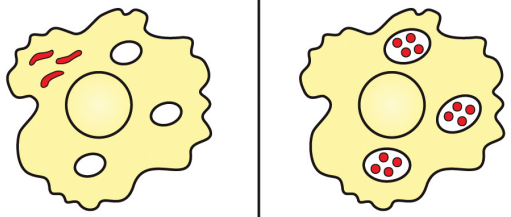
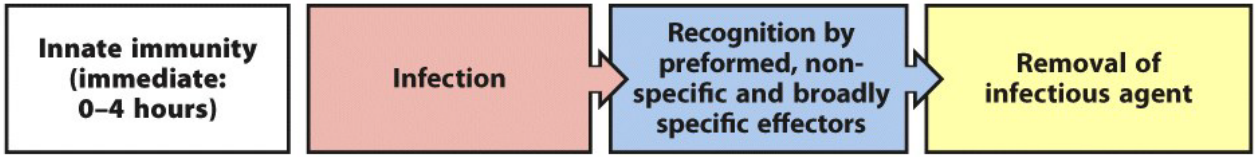
Activation of the Immune Response



Specific Defenses Against Specific Pathogens

	Extracellular		Intracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces	Cytoplasmic	Vesicular
Site of infection				
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Streptococcus pneumoniae* *Vibrio cholerae* *Helicobacter pylori* *Candida albicans* Worms	Viruses *Chlamydia* spp. *Rickettsia* spp. Protozoa	*Mycobacterium* spp. *Yersinia pestis* *Legionella pneumophila* *Cryptococcus neoformans* *Leishmania* spp.
Protective immunity	Complement Phagocytosis Antibodies	Antimicrobial peptides Antibodies, especially IgA	NK cells Cytotoxic T cells	T cell–dependent and NK cell–dependent macrophage activation

Course of Immune Activation

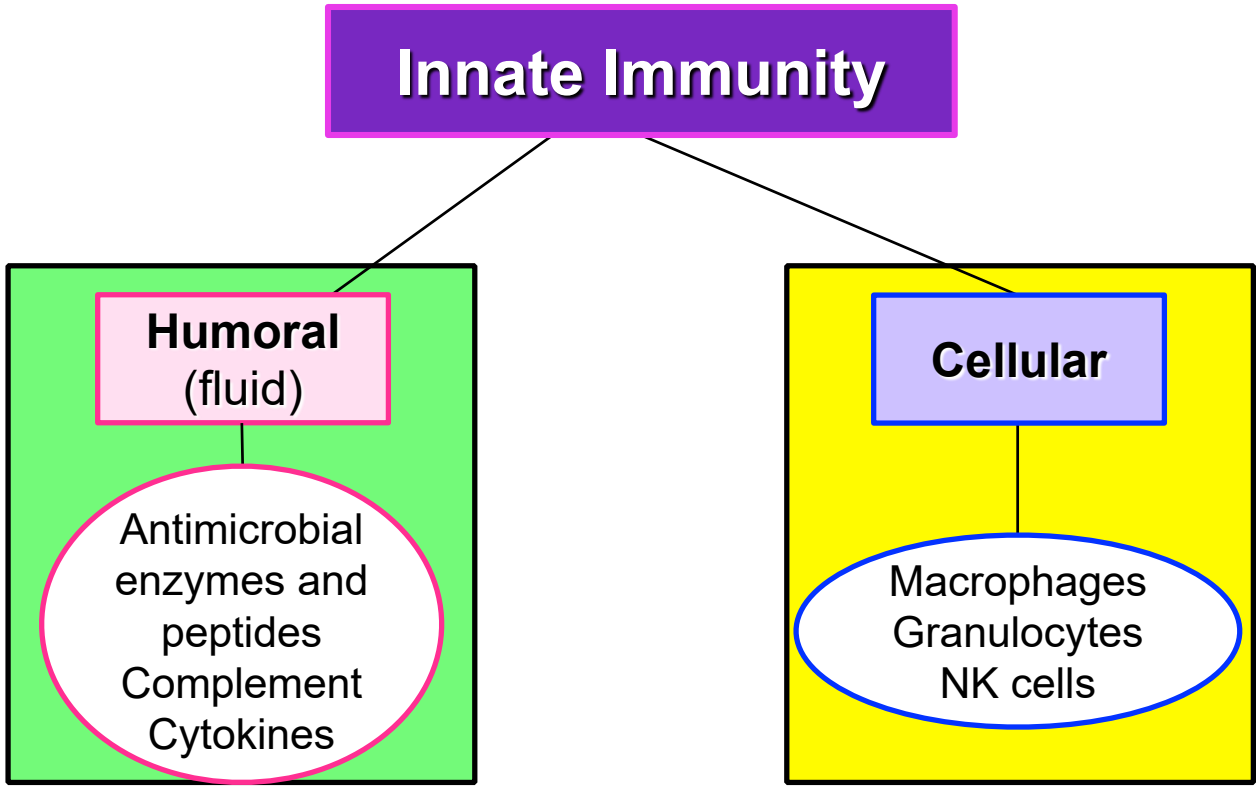


Complement

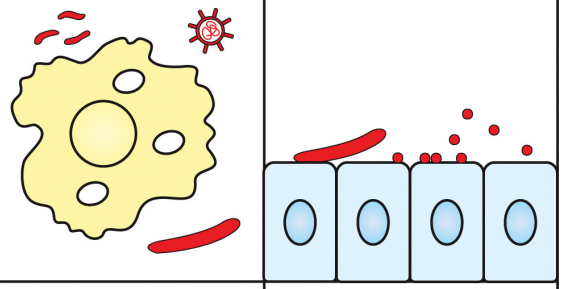
- 1890 by Jules Bordet - “A heat labile component of normal plasma that augmented the opsonization and killing of bacterial by antibodies”

- An activity that “complement” the action of antibodies

Innate Immune System



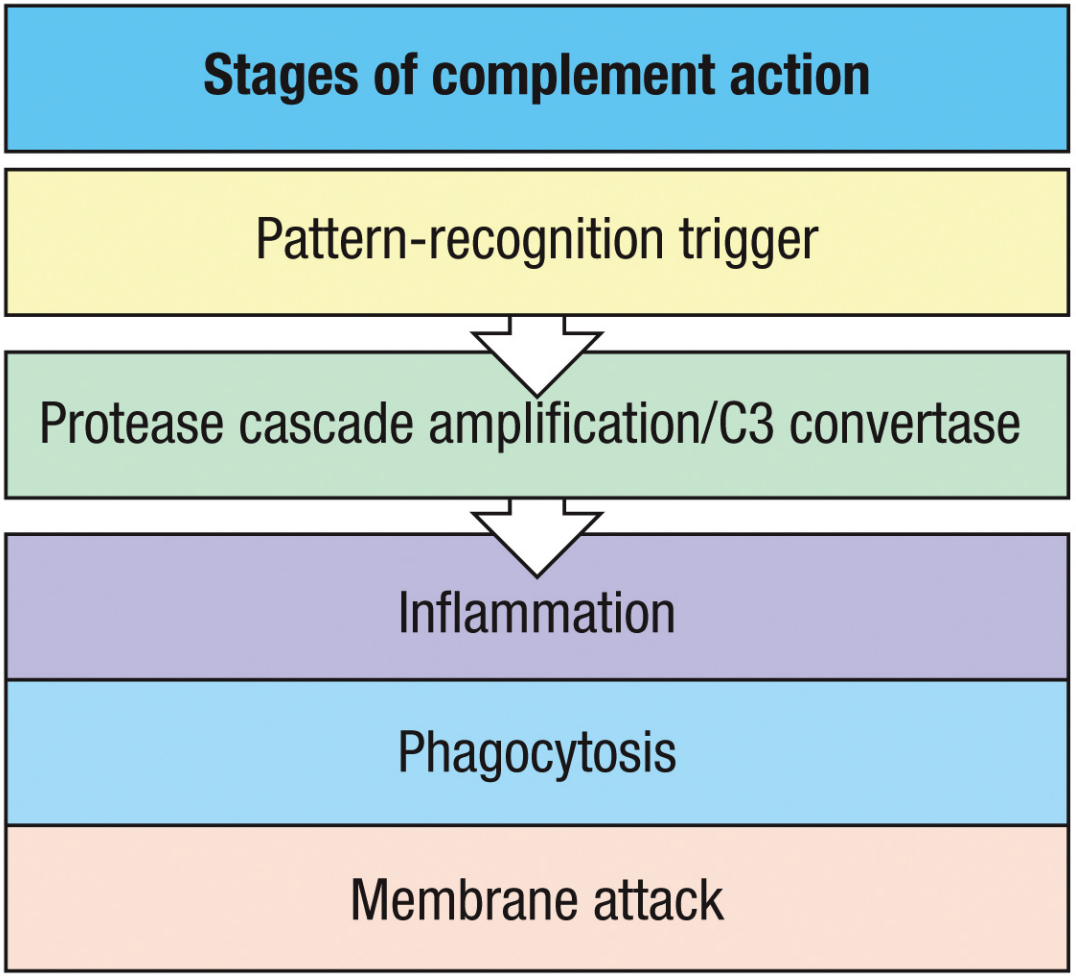
Extracellular Pathogens Activate Complement

	Extracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces
Site of infection		
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Streptococcus pneumoniae* *Vibrio cholerae* *Helicobacter pylori* *Candida albicans* Worms
Protective immunity	Complement Phagocytosis Antibodies	Antimicrobial peptides Antibodies, especially IgA

Outline

- Complement pathways
  - Classical pathway
  - Lectin pathway
  - Alternative pathway
- Effector functions
  - Complement mediated phagocytosis
  - Complement mediated inflammatory response
  - Complement mediated pathogen clearance
- Regulation of complement

Stages of Complement Activation



Overview of Complement Cascade

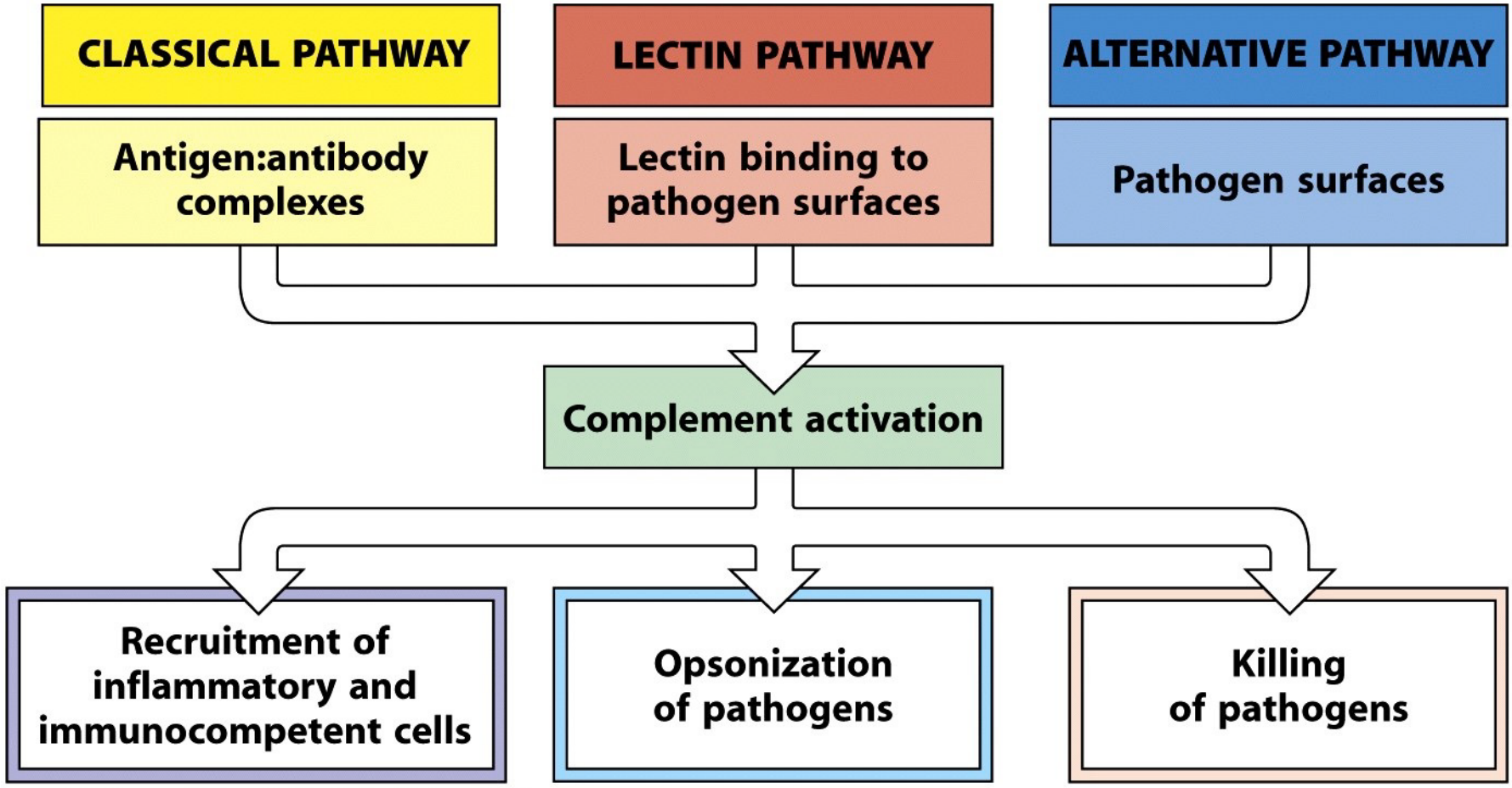
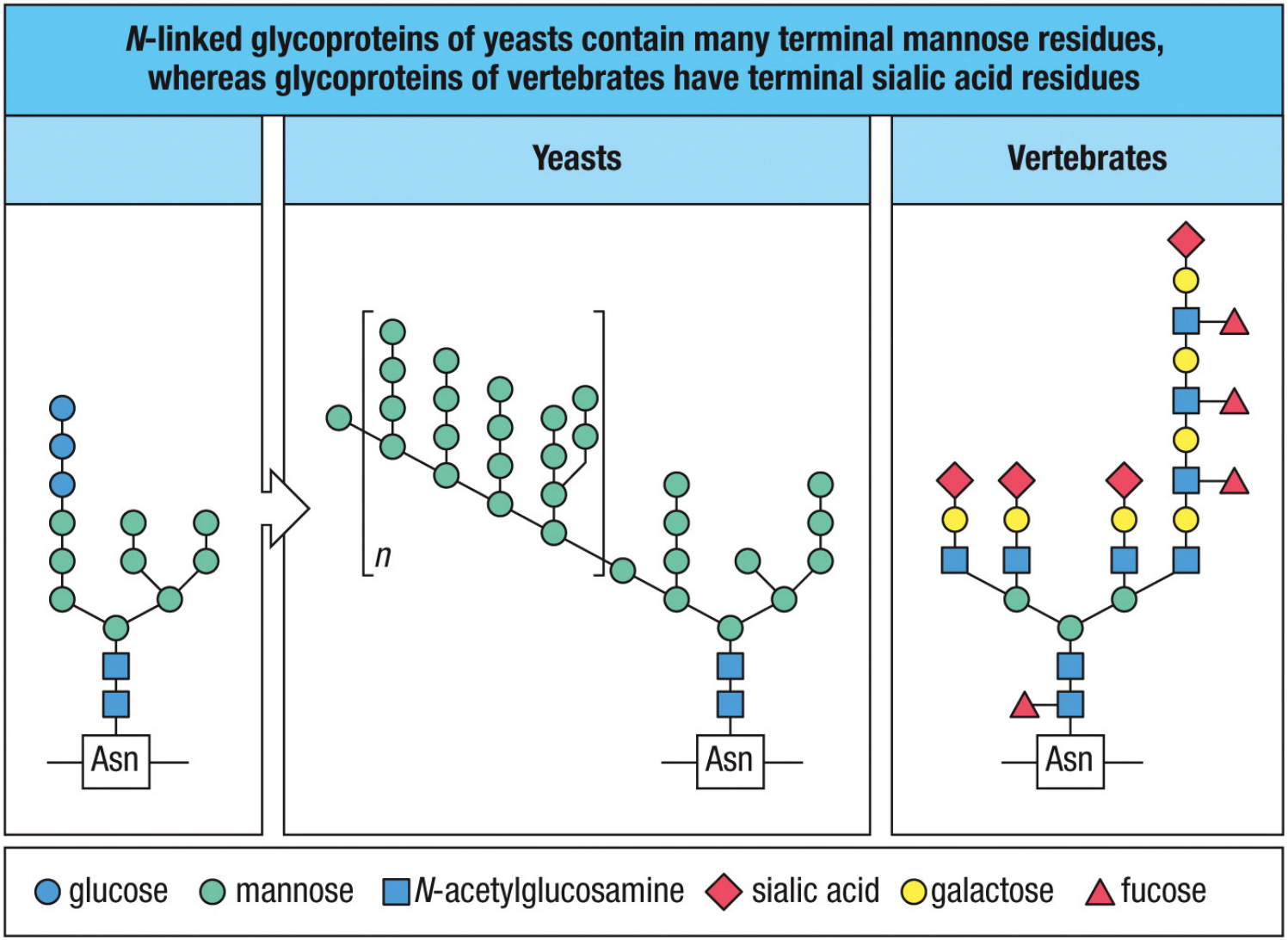


Figure 2-24 Immunobiology, 7ed. (© Garland Science 2008)

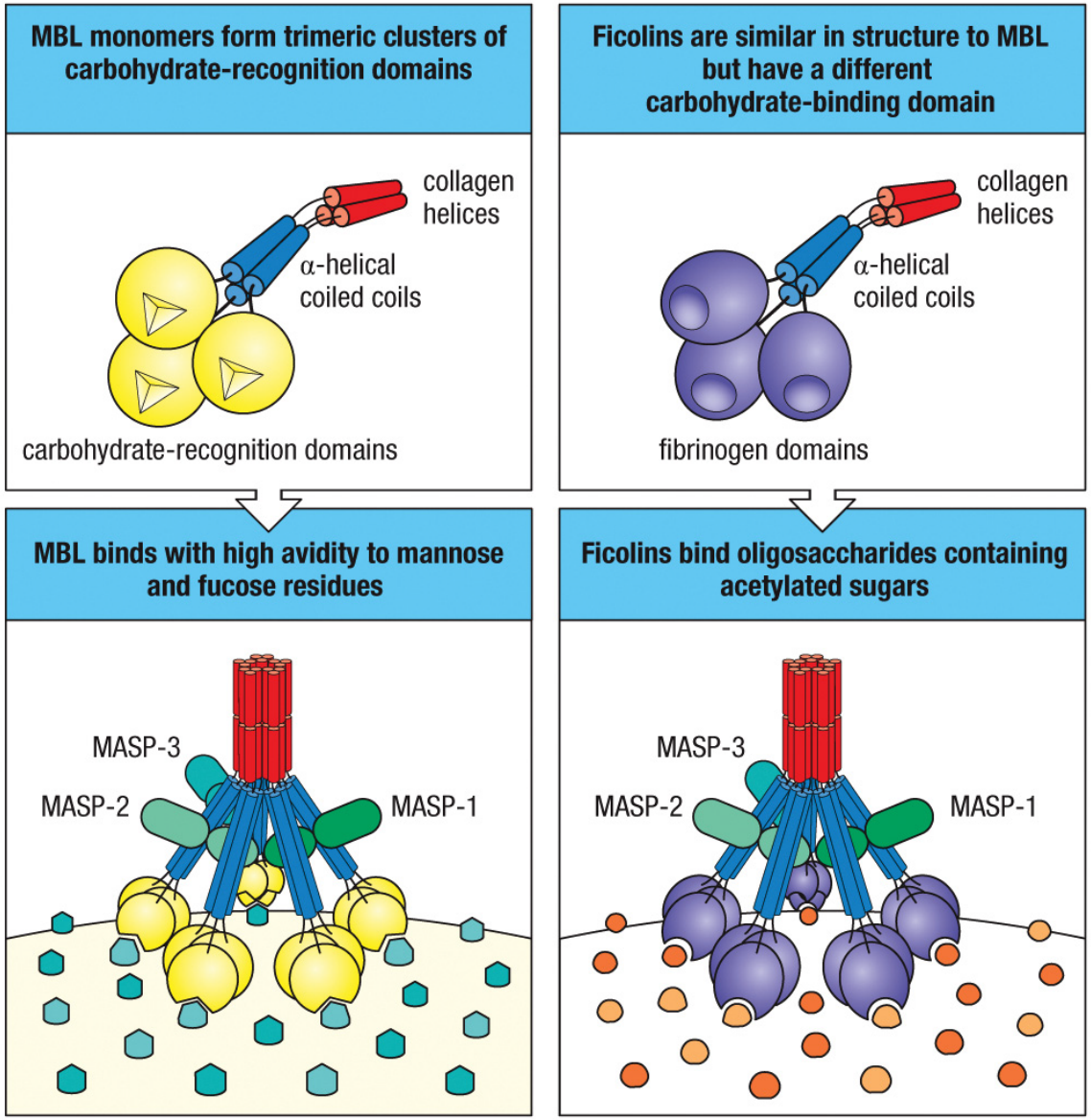
Outline

- Complement pathways
  - Lectin pathway
  - Classical pathway
  - Alternative pathway
- Effector functions
  - Complement mediated phagocytosis
  - Complement mediated inflammatory response
  - Complement mediated pathogen clearance
- Regulation of complement

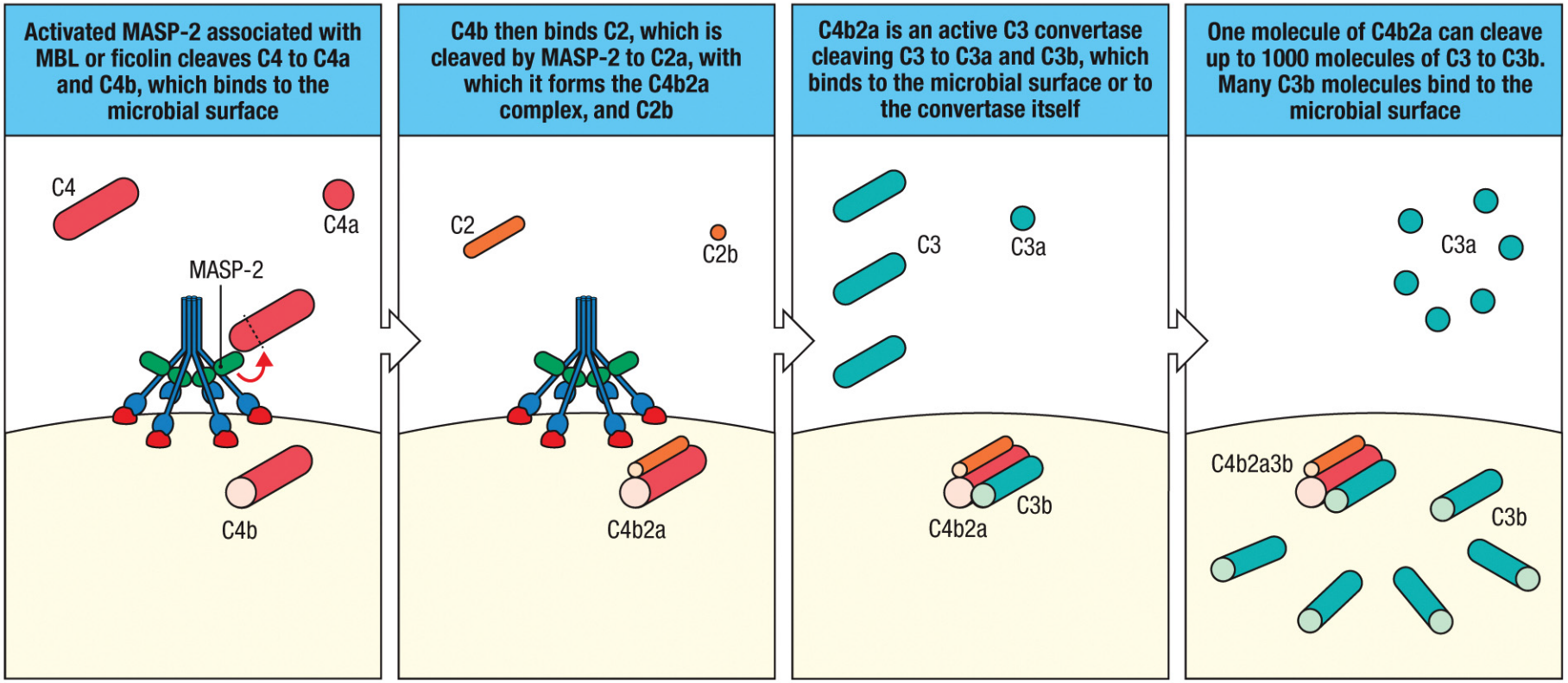
Mannonse-binding Lectin Receptor



Mannose-Binding Lectin Recognizes Carbohydrate Patterns on Bacterial Surfaces



Activation of the Lectin Pathway

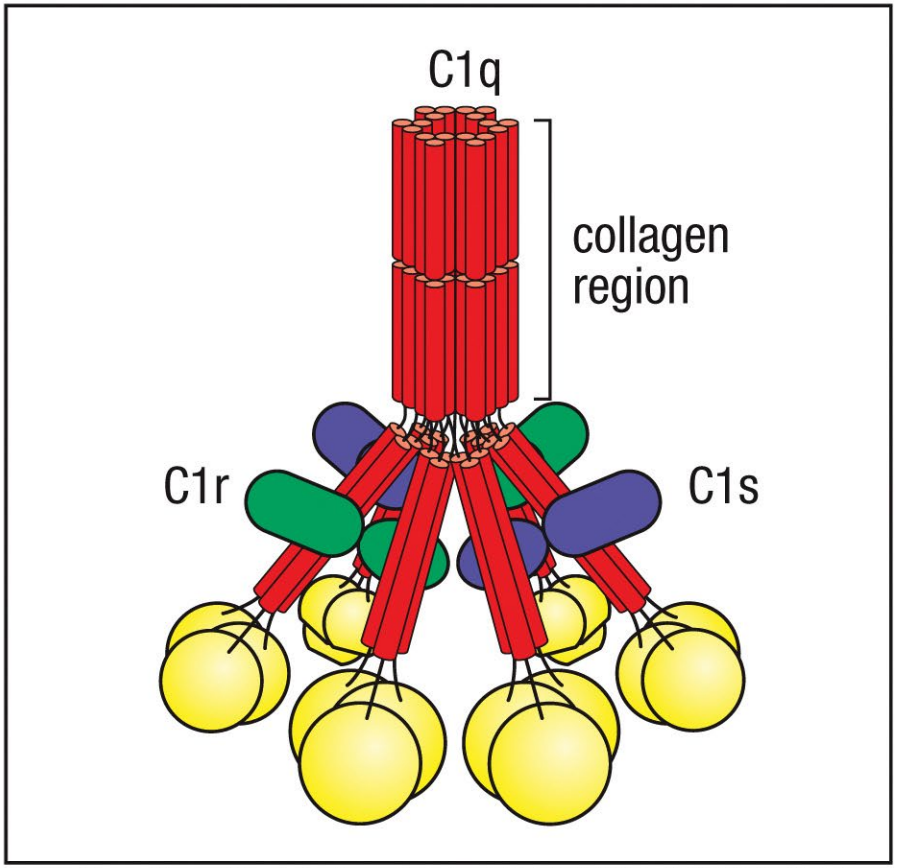


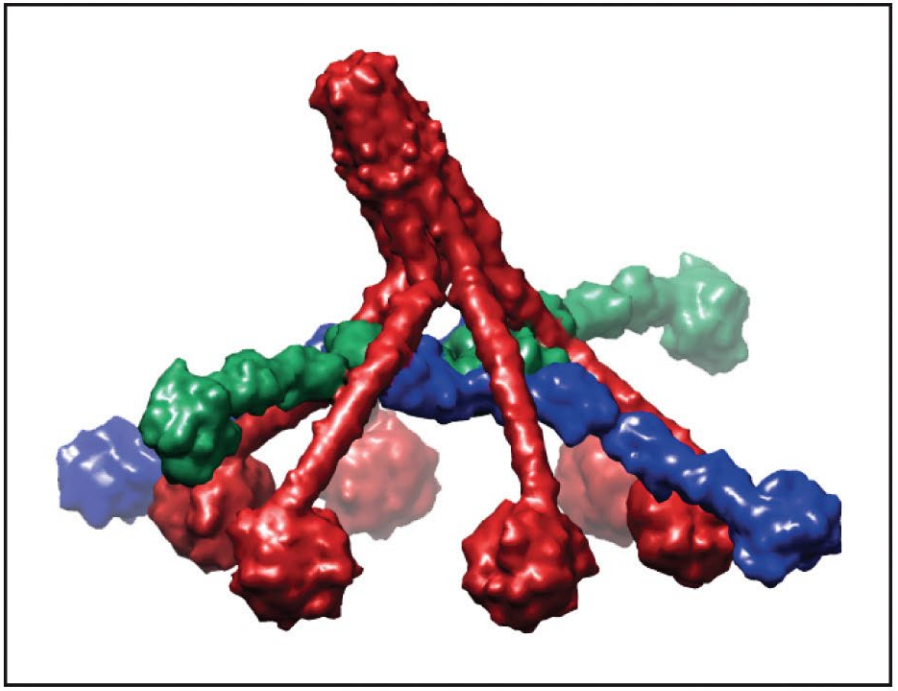
MASP-2 of MBL cleaves C4 and C2
C3 convertase is composed of C4b and C2a
C2a is the active protease cleaving C3 into C3a and C3b

Outline

- Complement pathways
  - Lectin pathway
  - Classical pathway
  - Alternative pathway
- Effector functions
  - Complement mediated phagocytosis
  - Complement mediated inflammatory response
  - Complement mediated pathogen clearance
- Regulation of complement

C1 Is the First Protein Activated in the Classical Pathway





Modified from Sharp, T.H., et al.: *Proc. Natl. Acad. Sci. USA* 2019, 116:11900–11905.

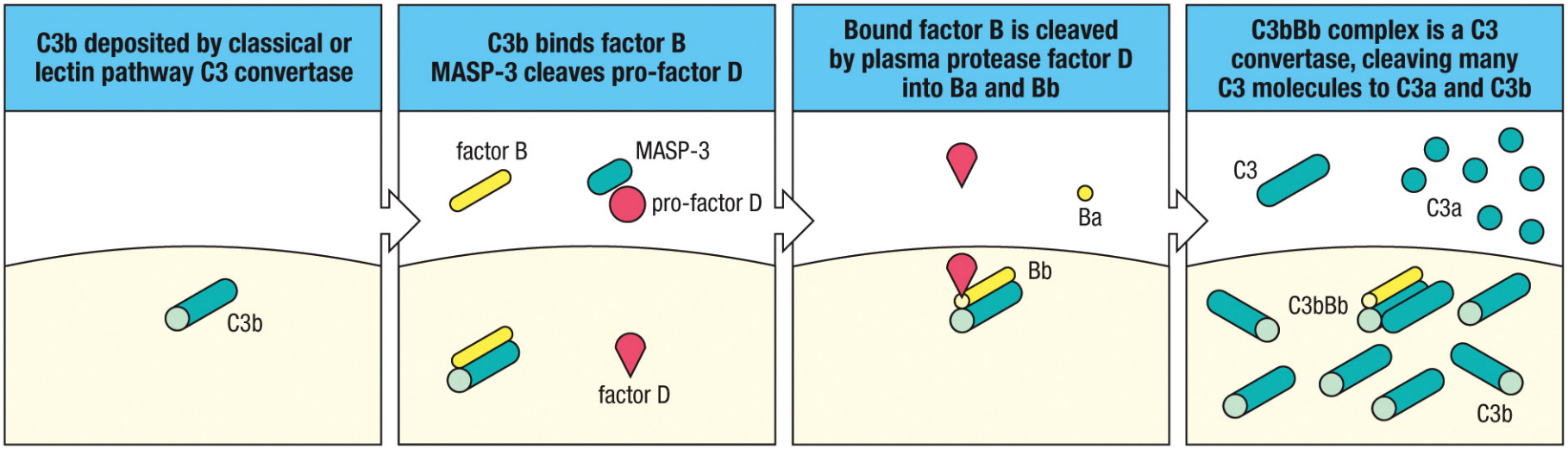
Proteins of the classical pathway of complement activation

Native component	Active form	Function of the active form
C1 (C1q: $C1r_2$:$C1s_2$)	C1q	Binds directly to pathogen surfaces or indirectly to antibody bound to pathogens, thus allowing autoactivation of C1r
	C1r	Cleaves C1s to active protease
	C1s	Cleaves C4 and C2
C4	C4b	Covalently binds to pathogen and opsonizes it. Binds C2 for cleavage by C1s
	C4a	Peptide mediator of inflammation (weak activity)
C2	C2a	Active enzyme of classical pathway C3/C5 convertase: cleaves C3 and C5
	C2b	Inactive small fragment
C3	C3b	Binds to pathogen surface and acts as opsonin. Initiates amplification via the alternative pathway. Binds C5 for cleavage by C2a
	C3a	Peptide mediator of inflammation (intermediate activity)

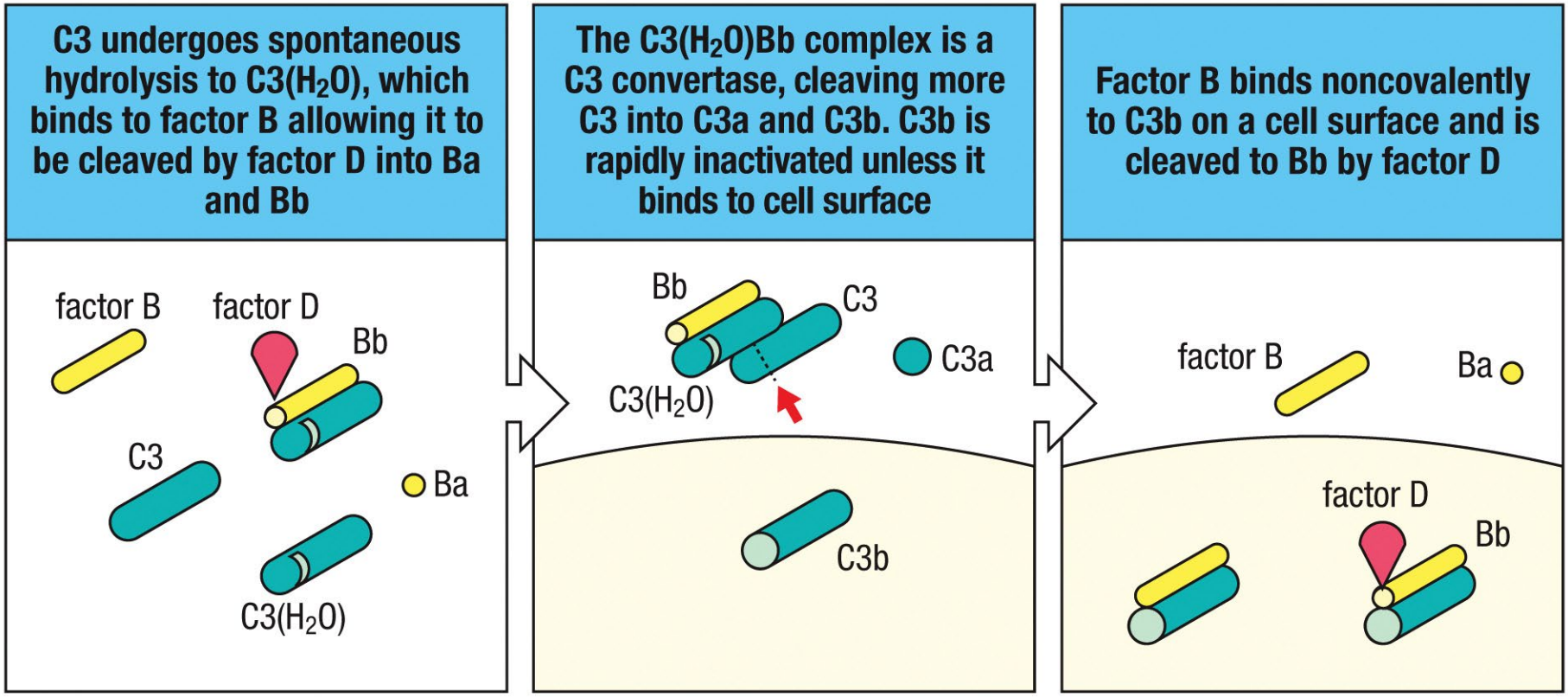
Outline

- Complement pathways
  - Lectin pathway
  - Classical pathway
  - Alternative pathway
- Effector functions
  - Complement mediated phagocytosis
  - Complement mediated inflammatory response
  - Complement mediated pathogen clearance
- Regulation of complement

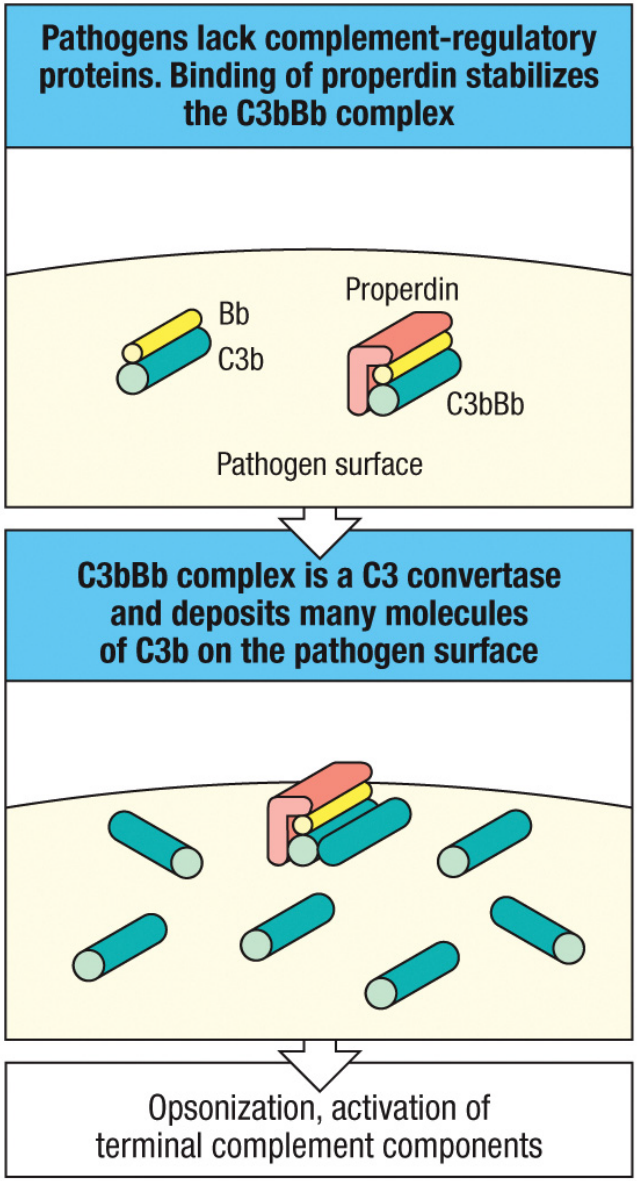
Alternative Pathway Can Amplify Classical and Lectin Pathways



Alternative Pathway



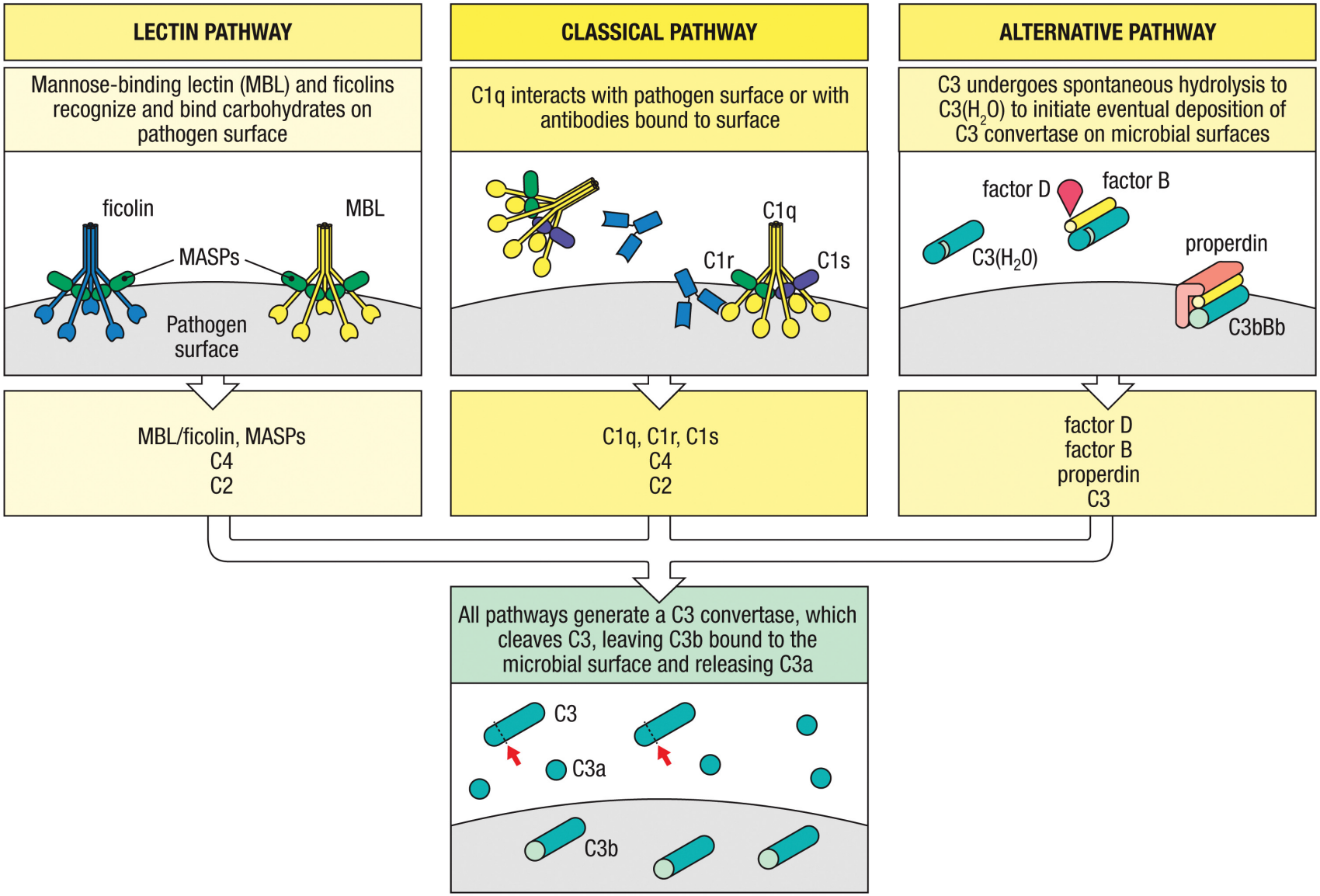
Alternative Pathway



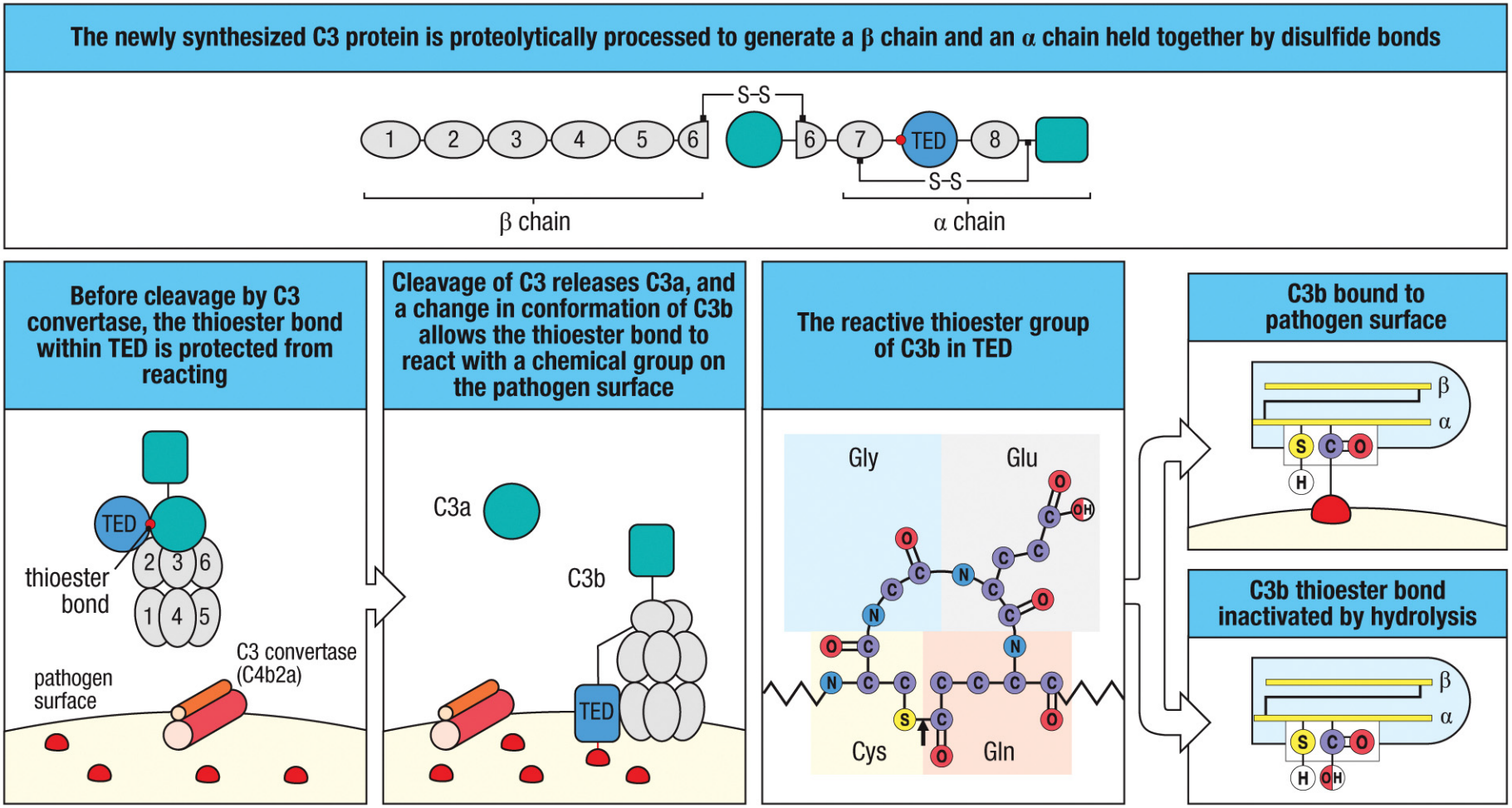
Proteins of the alternative pathway of complement activation

Native component	Active fragments	Function
C3	C3b	Binds to pathogen surface; binds B for cleavage by D; C3bBb is a C3 convertase and $C3b_2Bb$ is a C5 convertase
Factor B (B)	Ba	Small fragment of B, unknown function
	Bb	Bb is the active enzyme of the C3 convertase C3bBb and the C5 convertase $C3b_2Bb$
Factor D (D)	D	Plasma serine protease, cleaves B when it is bound to C3b to Ba and Bb
Properdin (P)	P	Plasma protein that binds to bacterial surfaces and stabilizes the C3bBb convertase

Overview of Complement Cascade



C3, Center of the Complement Pathway



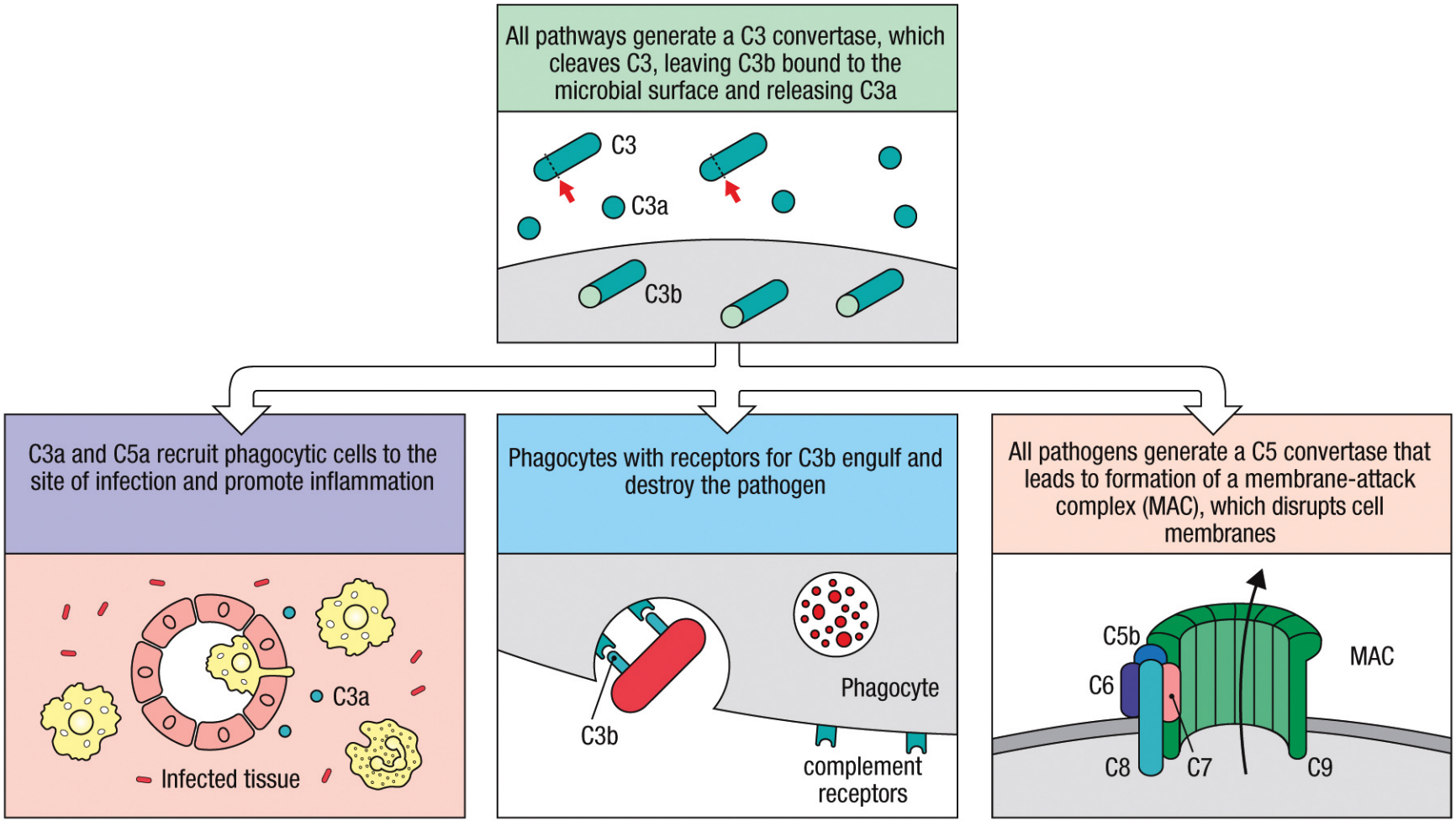
Question

- What are the three pathways of complement activation?
- What is common between all three pathways?

Outline

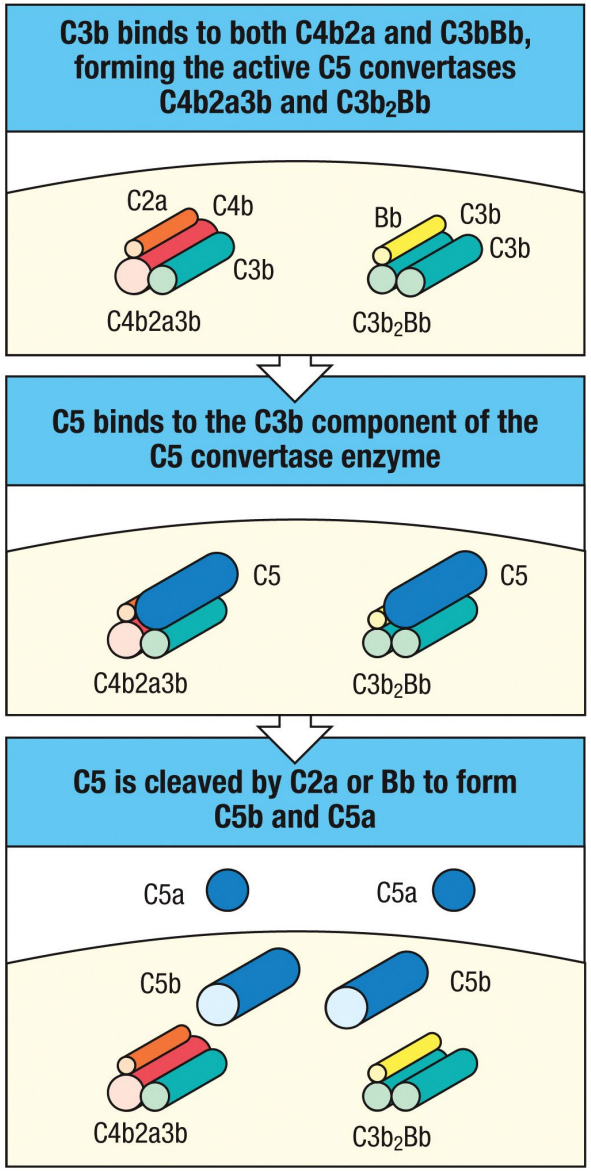
- Complement pathways
  - Lectin pathway
  - Classical pathway
  - Alternative pathway
- Effector functions
  - Complement mediated phagocytosis
  - Complement mediated inflammatory response
  - Complement mediated pathogen clearance
- Regulation of complement

Overview of Complement Cascade Components



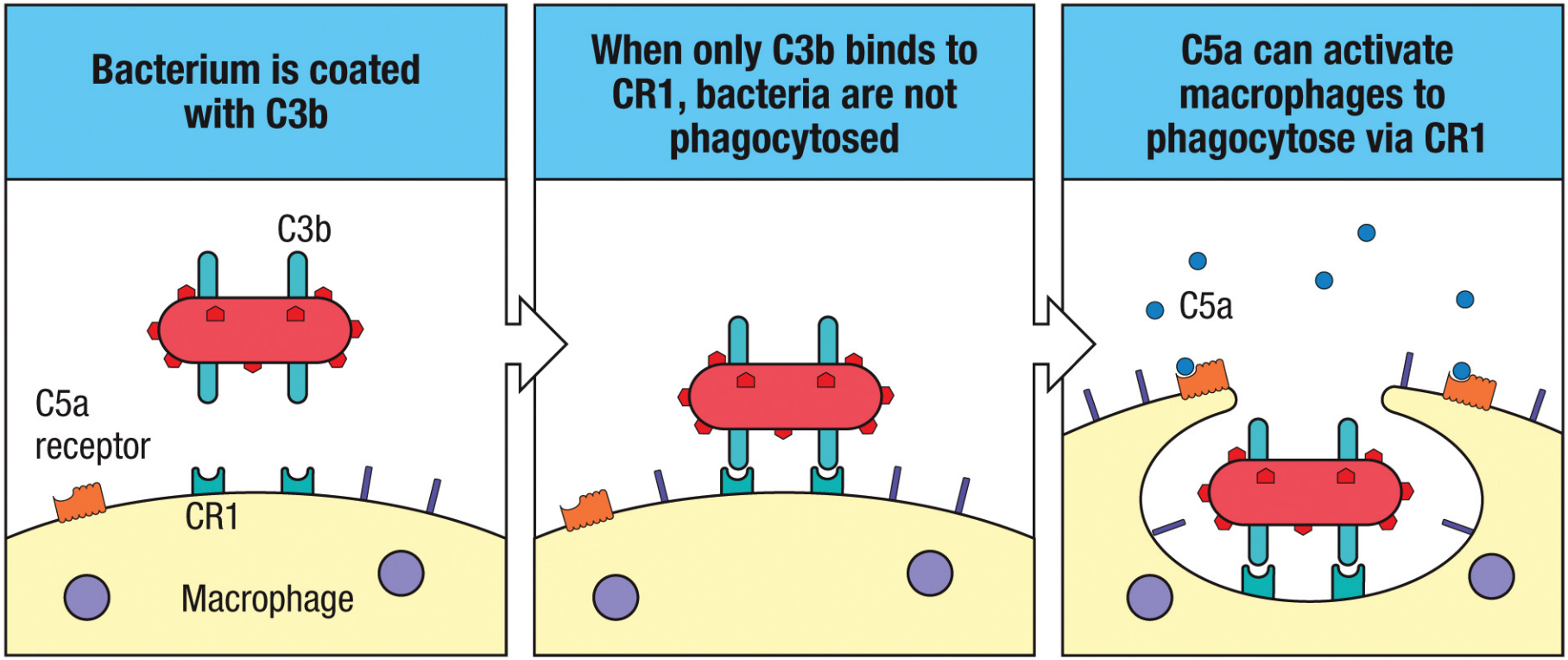
Formation of the C5 Convertase

Classical C5 convertase
C4b, C2a, C3b



Alternative C5 convertase
C3b, factor Bb, C3b

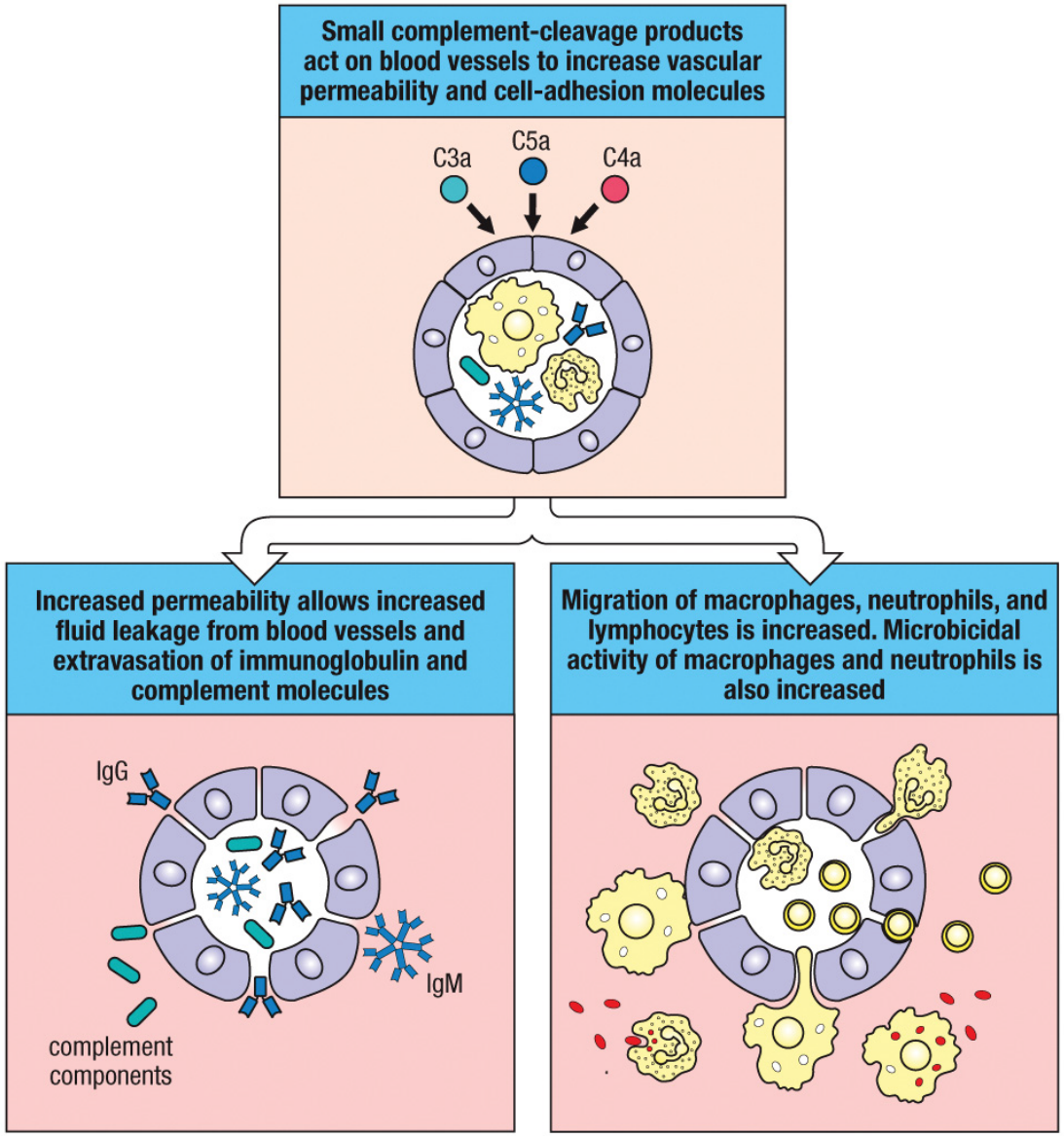
Immune Mediators Activate Phagocytosis After C3b Binding to CR1



Outline

- Complement pathways
  - Lectin pathway
  - Classical pathway
  - Alternative pathway
- Effector functions
  - Complement mediated phagocytosis
  - Complement mediated inflammatory response
  - Complement mediated pathogen clearance
- Regulation of complement

C3a, C5a, C4a Induce Local Inflammatory Responses

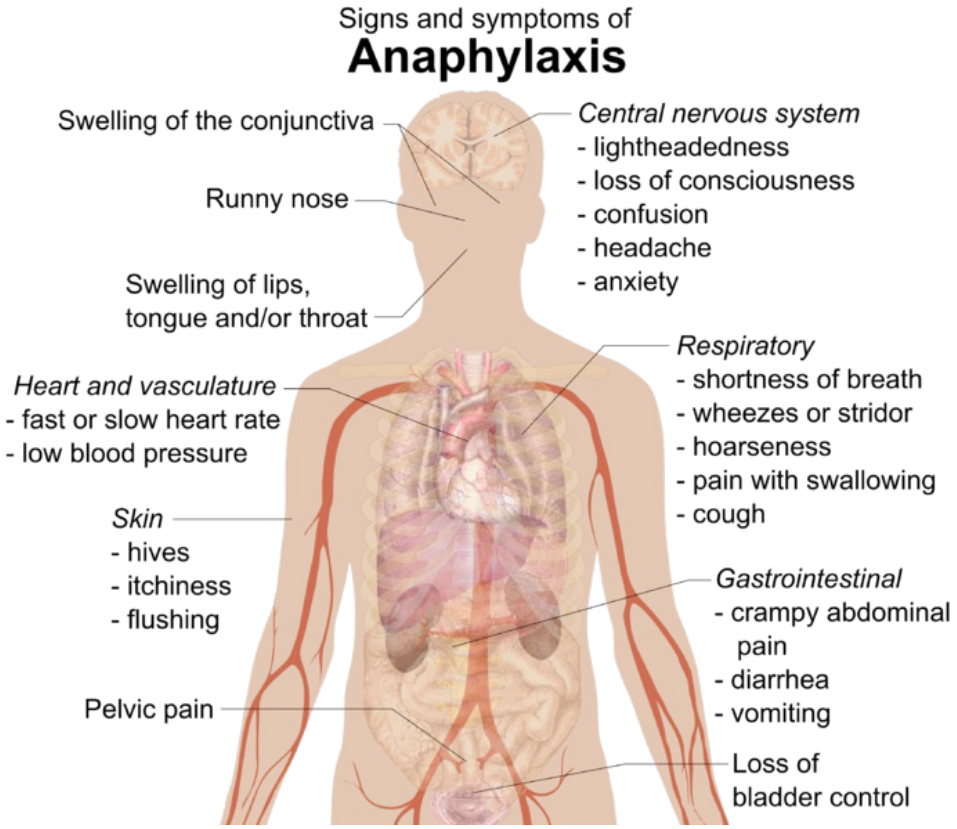


Systemic release of small complement fragments can lead to anaphylactic shock

- Low blood pressure
- Abnormal heart rhythm (arrhythmia)
- Rapid pulse
- Skin that is blue from lack of oxygen
- Mental confusion
- Swelling (angioedema) in the throat that may

be severe enough to block the airway

- Fluid in the lungs (pulmonary edema)
- Wheezing
- Swelling of the eyes or face
- Hives
- Weakness

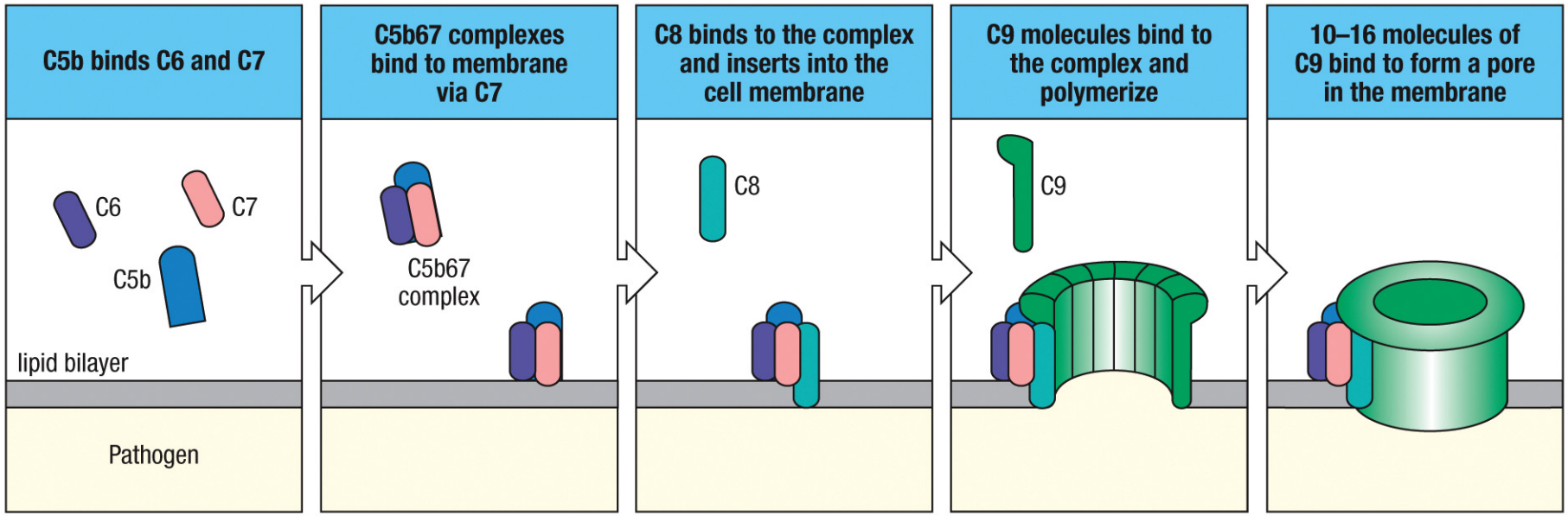


Mikael Häggström

Outline

- Complement pathways
  - Lectin pathway
  - Classical pathway
  - Alternative pathway
- Effector functions
  - Complement mediated phagocytosis
  - Complement mediated inflammatory response
  - Complement mediated pathogen clearance
- Regulation of complement

Assembly of the Membrane Attack Complex



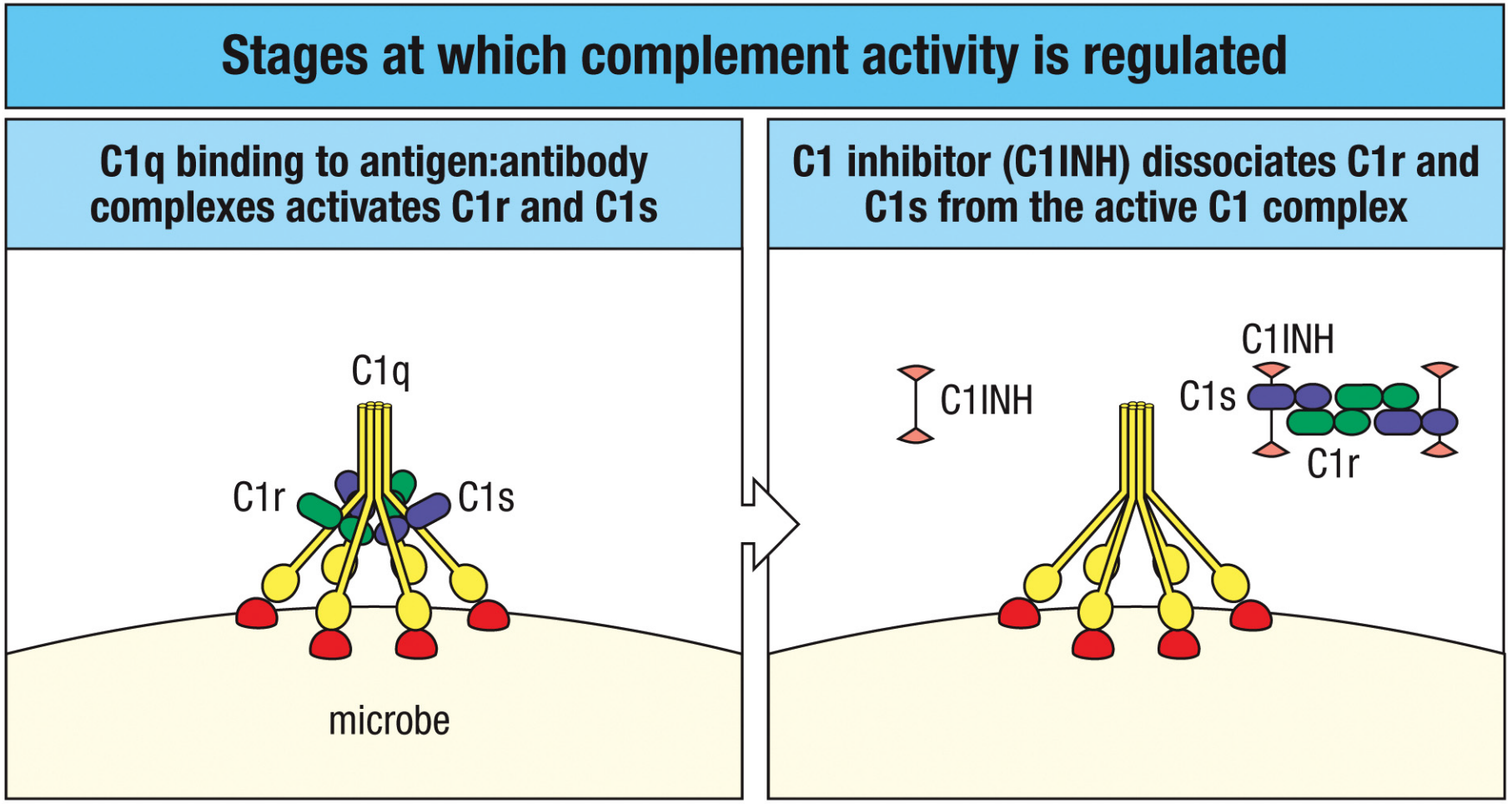
Question

- What are the effector functions of the complement pathway?

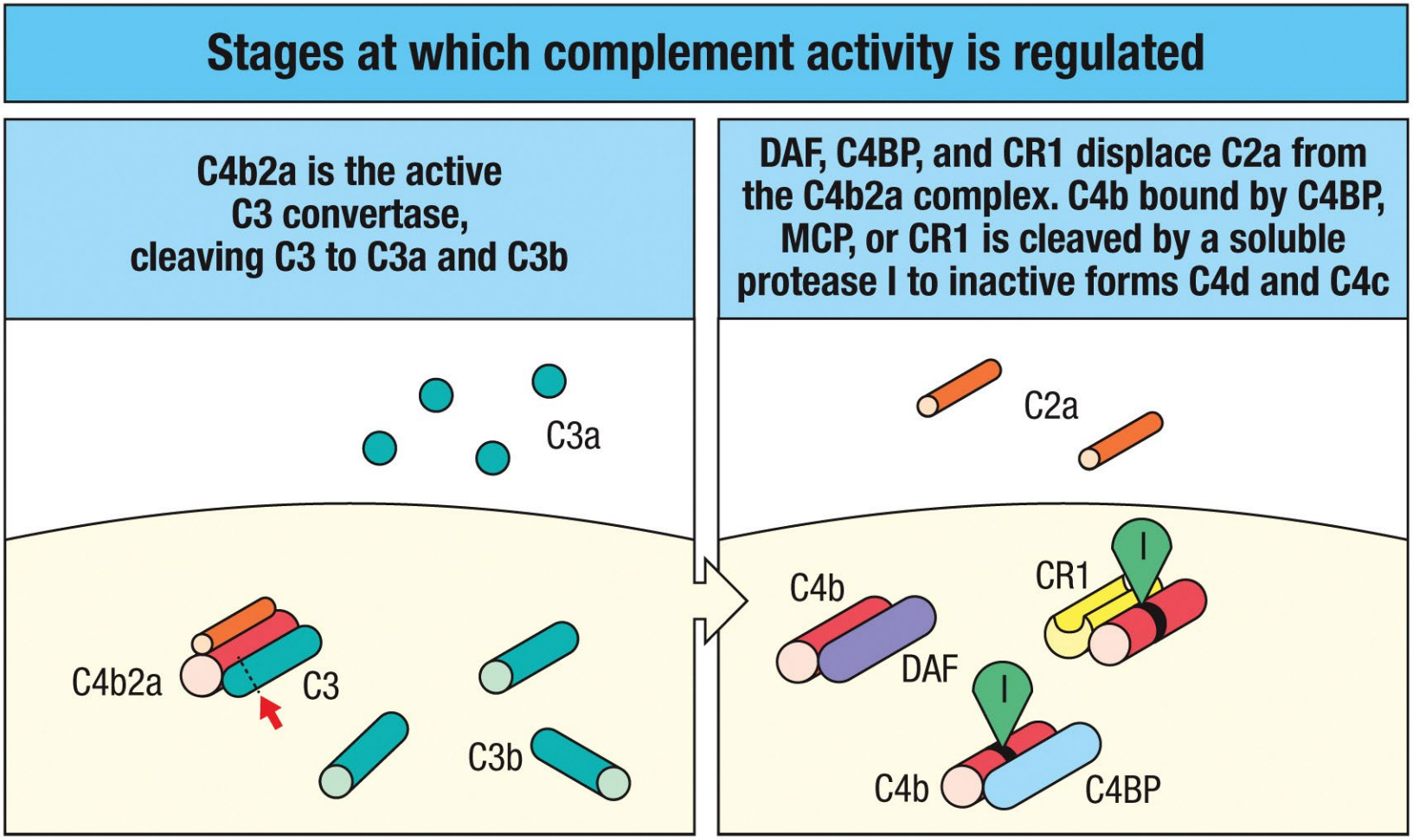
Outline

- Mannose-binding lectin
- Complement pathways
  - Classical pathway
  - Lectin pathway
  - Alternative pathway
- Complement mediated phagocytosis
- Complement mediated inflammatory response
- Complement mediated pathogen clearance
- Regulation of complement

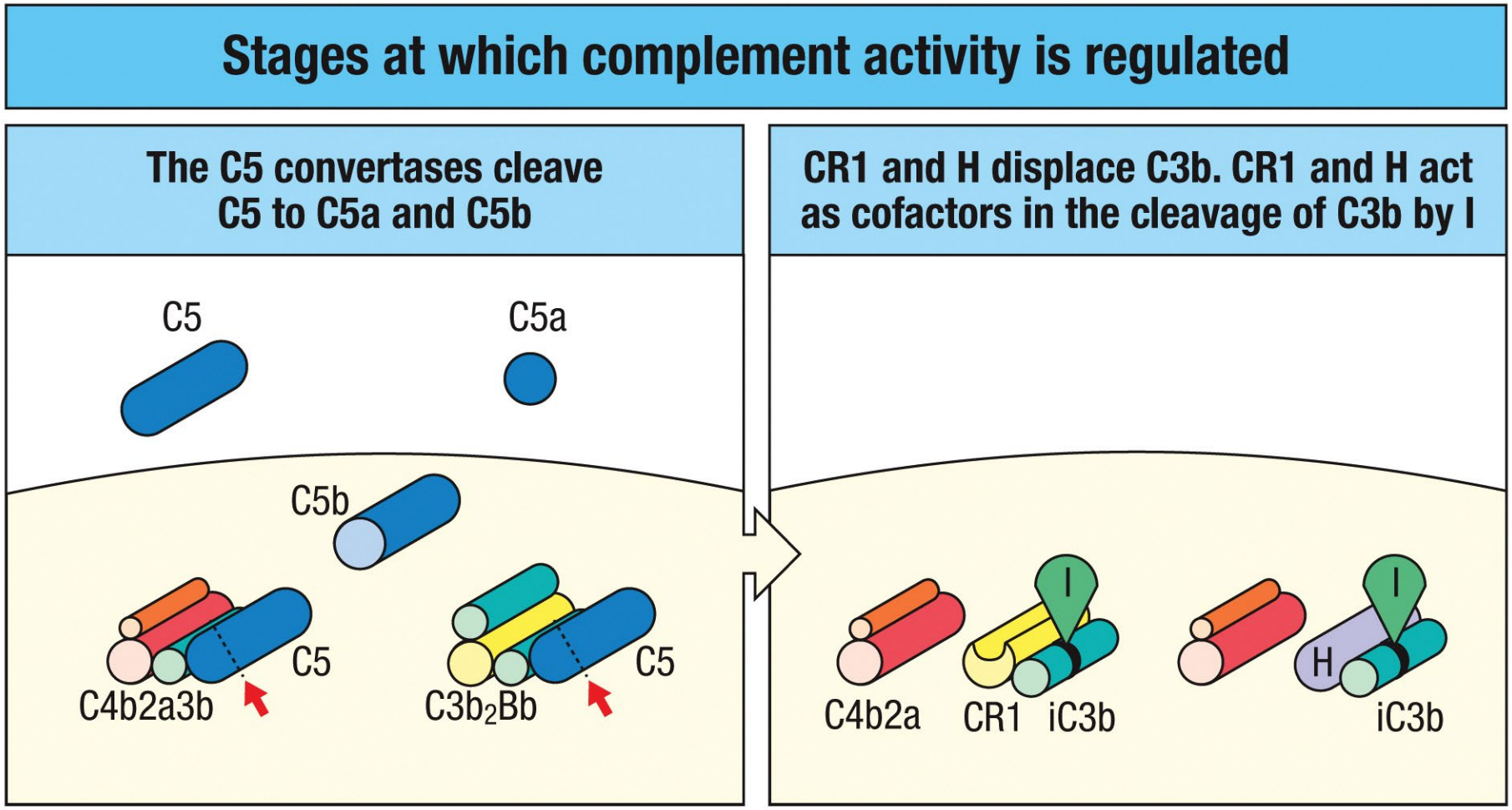
Inhibition of Initiation



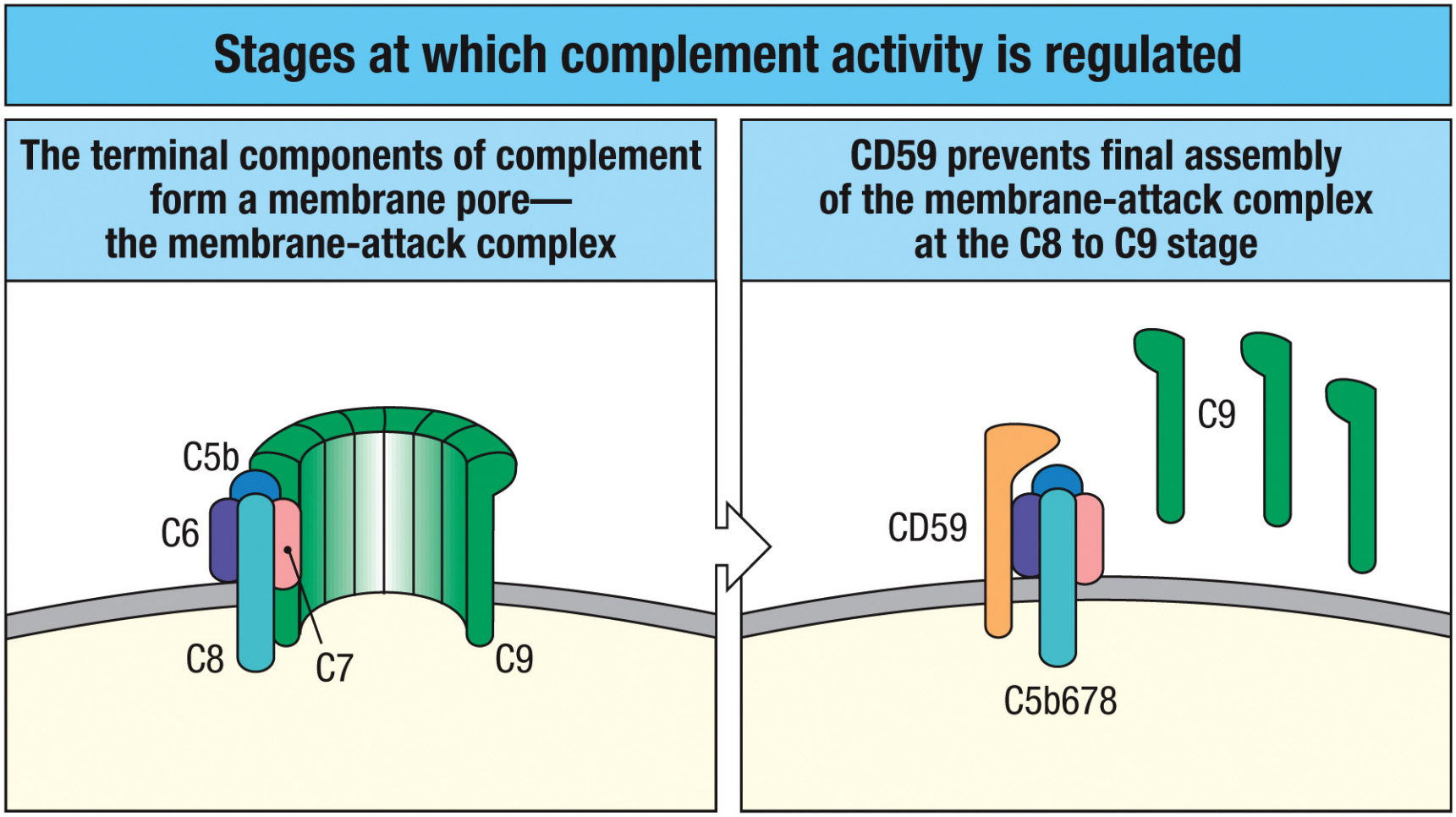
Inhibition at C3 Convertase



Inhibition at C5 Convertase



Inhibition at Membrane Attack Complex



Regulatory proteins of the classical and alternative pathways

Soluble factors regulating complement			
Name	**Ligand/ Binding factor**	**Action**	**Pathology if defective**
C1 inhibitor (C1INH)	C1r, C1s (C1); MASP-2 (MBL)	Binds and deactivates C1r, C1s, and MASP-2	Hereditary angiodema
C4-binding protein (C4BP)	C4b	Displaces C2a from C4b cofactor for C4b cleavage by factor I	
CPN1 (Carboxypeptidase N)	C3a, C5a	Inactivates C3a and C5a	Recurrent angioedema
Factor H	C3b	Displaces Bb from C3b, cofactor for C3b cleavage by factor I	Age-related macular degeneration, atypical hemolytic uremic syndrome
Factor I	C3b, C4b	Serine protease, cleaves C3b and C4b	Low C3 levels, atypical hemolytic uremic syndrome

Regulatory proteins of the classical and alternative pathways

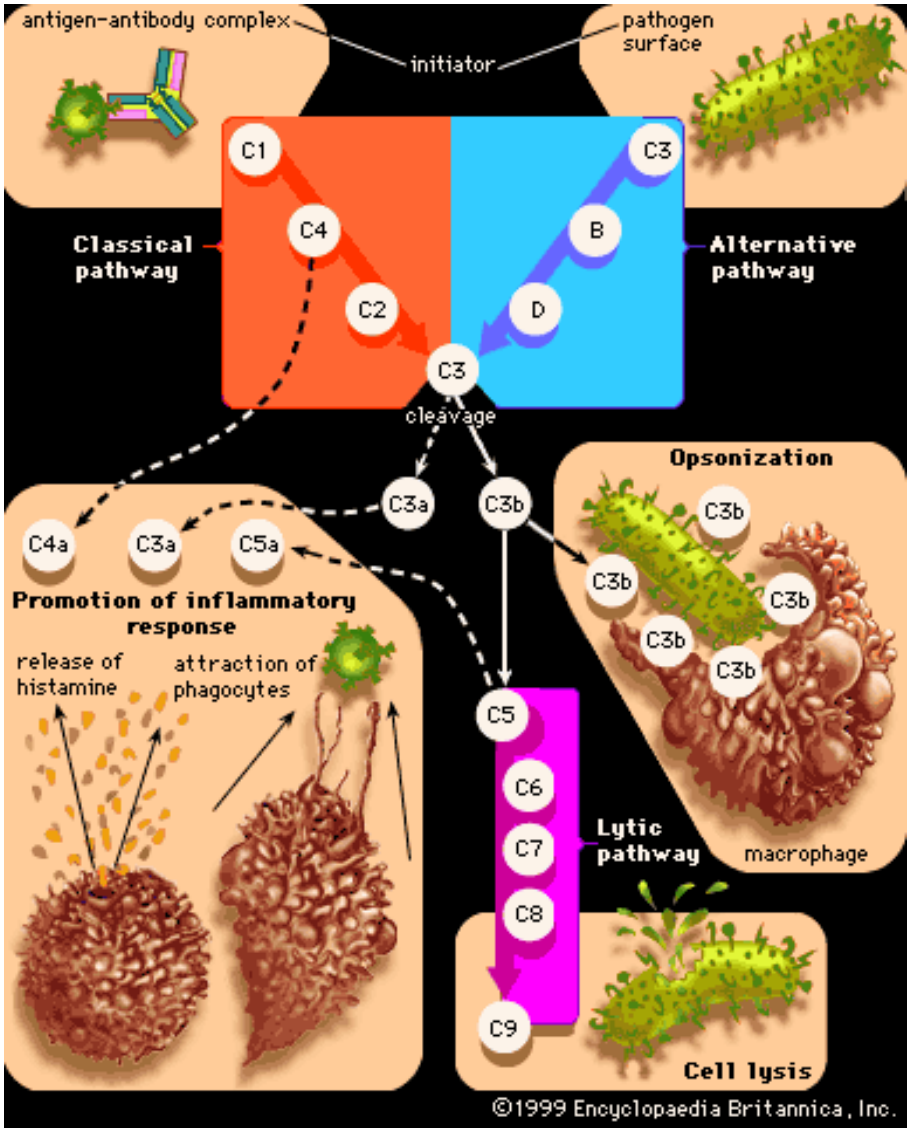
Membrane-bound factors regulating complement

Name	Ligand/ Binding factor	Action	Pathology if defective
CRIg	C3b, iC3b	Inhibits activation of alternative pathway	Increased susceptibiity to blood-borne infections
Complement receptor 1 (CR1, CD35)	C3b, C4b	Cofactor for factor I; displaces Bb from C3b, and C2a from C4b	
Decay-accelerating factor (DAF, CD55)	C3 convertase	Displaces Bb and C2a from C3b and C4b respectively	Paroxysmal nocturnal hemoglobinuria
Membrane cofactor of proteolysis (MCP, CD46)	C3b, C4b	Cofactor for factor I	Atypical hemolytic uremic syndrome
Protectin (CD59)	C8	Inhibits MAC formation	Paroxysmal nocturnal hemoglobinuria

What is not true regarding to complement regulation?

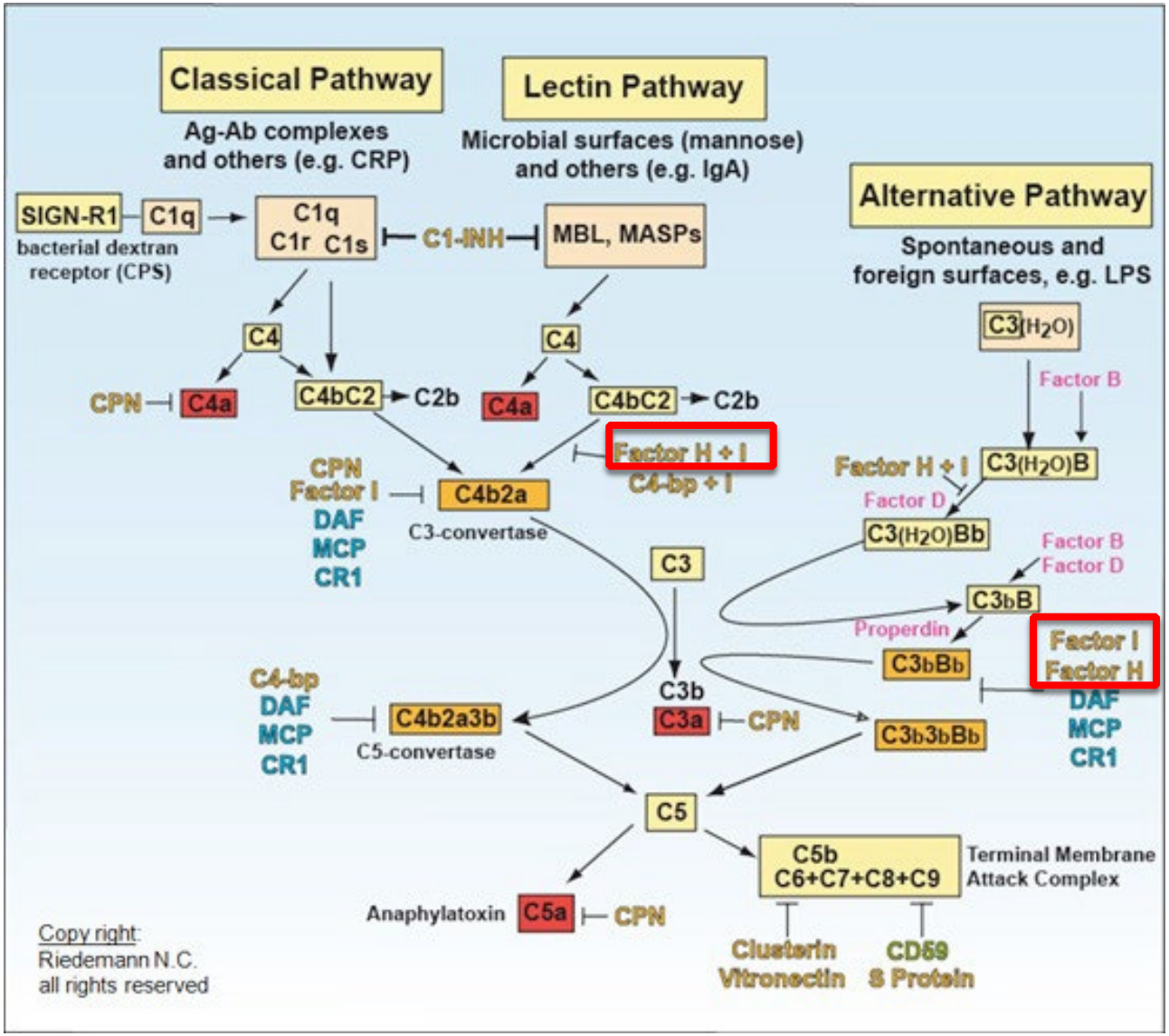
- A) Sequential activation of zymogens
- B) Complement components are quickly inactivated unless they bind to pathogen surface.
- C) Positive regulatory proteins
- D) Negative regulatory proteins
- E) None of the above

Complement Assists in Clearance of Pathogens



http://media-2.web.britannica.com/eb-media/03/20903-004-379E4AF3.gif

Overview of the Complement System



http://www.inflarx.com/images/complement-1.jpg

Case studies

Deficiency of C8 complement component

Deficiency of the C8 Complement Component

Patient:

- Female student
- Cough and diarrhea
- Stiff neck, confusion
- Decreased blood pressure, increased pulse and respiratory rate, fever
- Reddish-purple rash, red throat, enlarged tonsils
- Elevated WBC count in CSF (cerebrospinal fluid)
- Cultures positive for meningococcus

Treatment

- IV antibiotics for bacterial meningitis
- Alleviation of symptoms

Follow-up

- History of meningitis, w/ CSF infection
- Defective CH_{50} test (test for the complement-mediated hemolysis)
- Lack of C8

Treatment

- Meningococcal vaccine

Deficiency of the C8 Complement Component

What is wrong with the patient?

- Failure of the formation of the membrane-attack complex
  - Neisseria meningitides infection is preferentially cleared through the attack-complex pathway

Deficiency of the C8 Complement Component

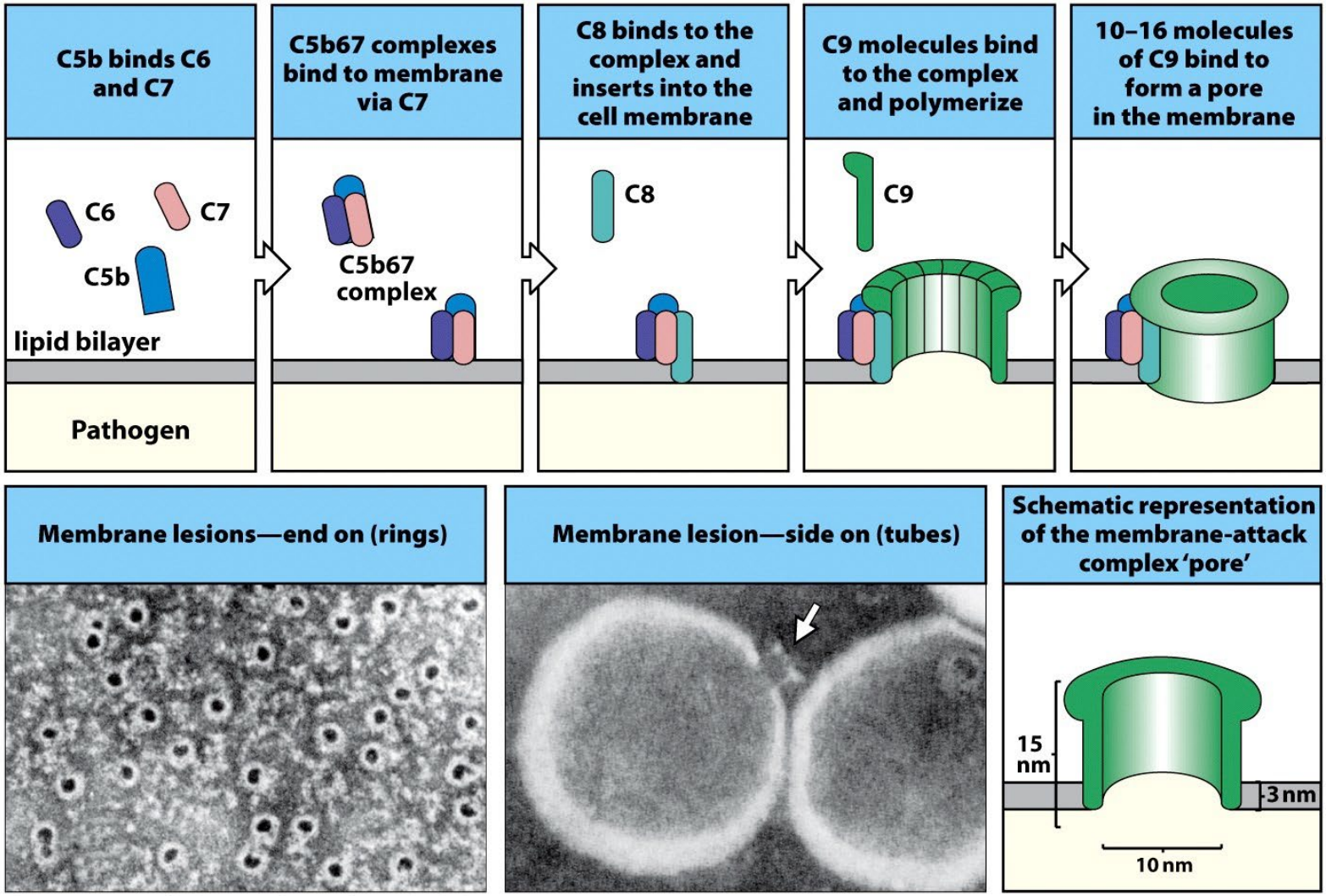


Figure 6-2 Case Studies in Immunology, 5ed. (© Garland Science 2008)