The Complement System

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Learning Objectives

By the end of this lecture you will be able to:

① Recognize the biological functions of the complement cascade

② Identify the components of the complement system

③ Describe the three pathways of complement activation

The Complement System

- A family of more than 20 plasma proteins that include enzymes, proenzymes (**zymogens**), enzyme inhibitors, and glycoproteins

- They interact in cascade and assist in resolution of microbial infection

- The name was coined because they were thought to "complement" the antibacterial activity of antibody

Complement Functions

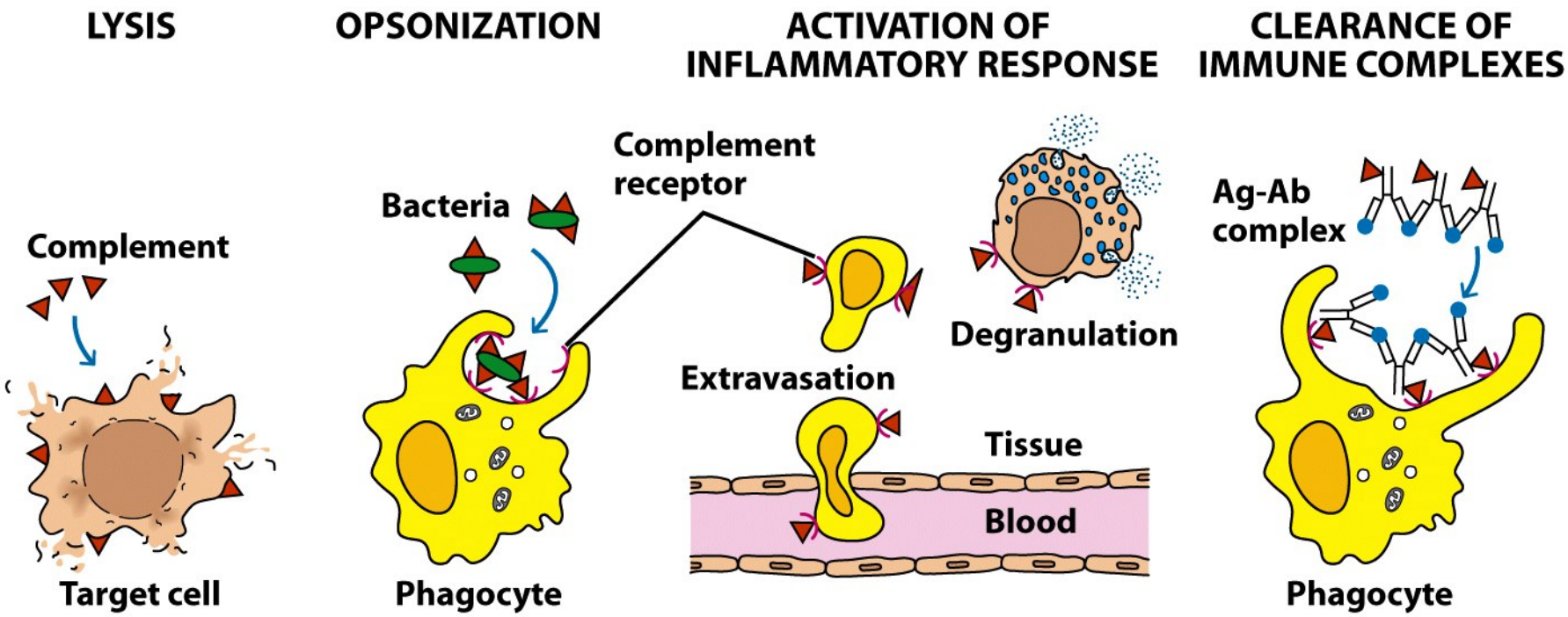


Figure 7-1
Kuby IMMUNOLOGY, Sixth Edition

The Complement System

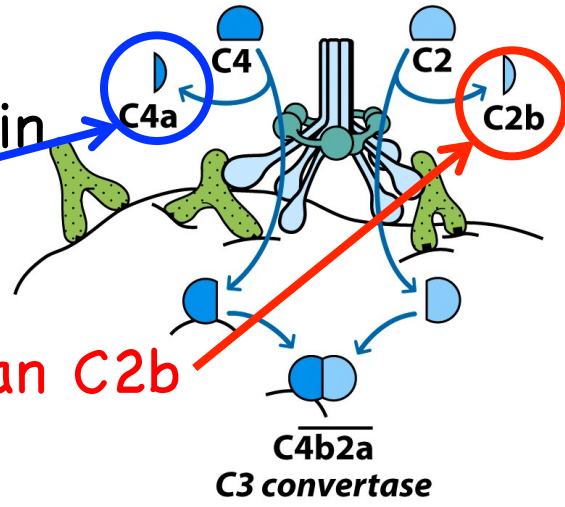
- Synthesized mainly by liver hepatocytes and other cell types (monocyte, macrophage, GI epithelial cells)
- Circulate as inactive proenzymes
- Proteolytic cleavage removes inhibitory fragment and exposes the active site of the complement molecule

Complement Nomenclature

① Designated by numerals **(C1-C9)**, letter symbols **(factor D)**, or trivial names **(homologus restriction factor)**

② Peptide fragments made by activation of a component are denoted:

- For example, activation of C4 results in
  - "a" for smaller fragment – C4a
  - "b" for larger fragment – C4b
- Exception: C2a fragment is larger than C2b

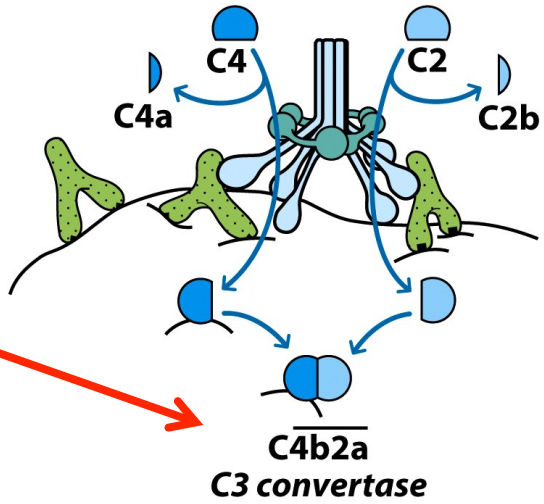


Complement Nomenclature

- Larger fragments bind to the target near the site of activation, while smaller fragments diffuse from the site of activation and can initiate localized inflammatory response

③ Complexes with enzymatic activity have bar over the number or symbol

$\overline{C4b2a}$



Complement Activation

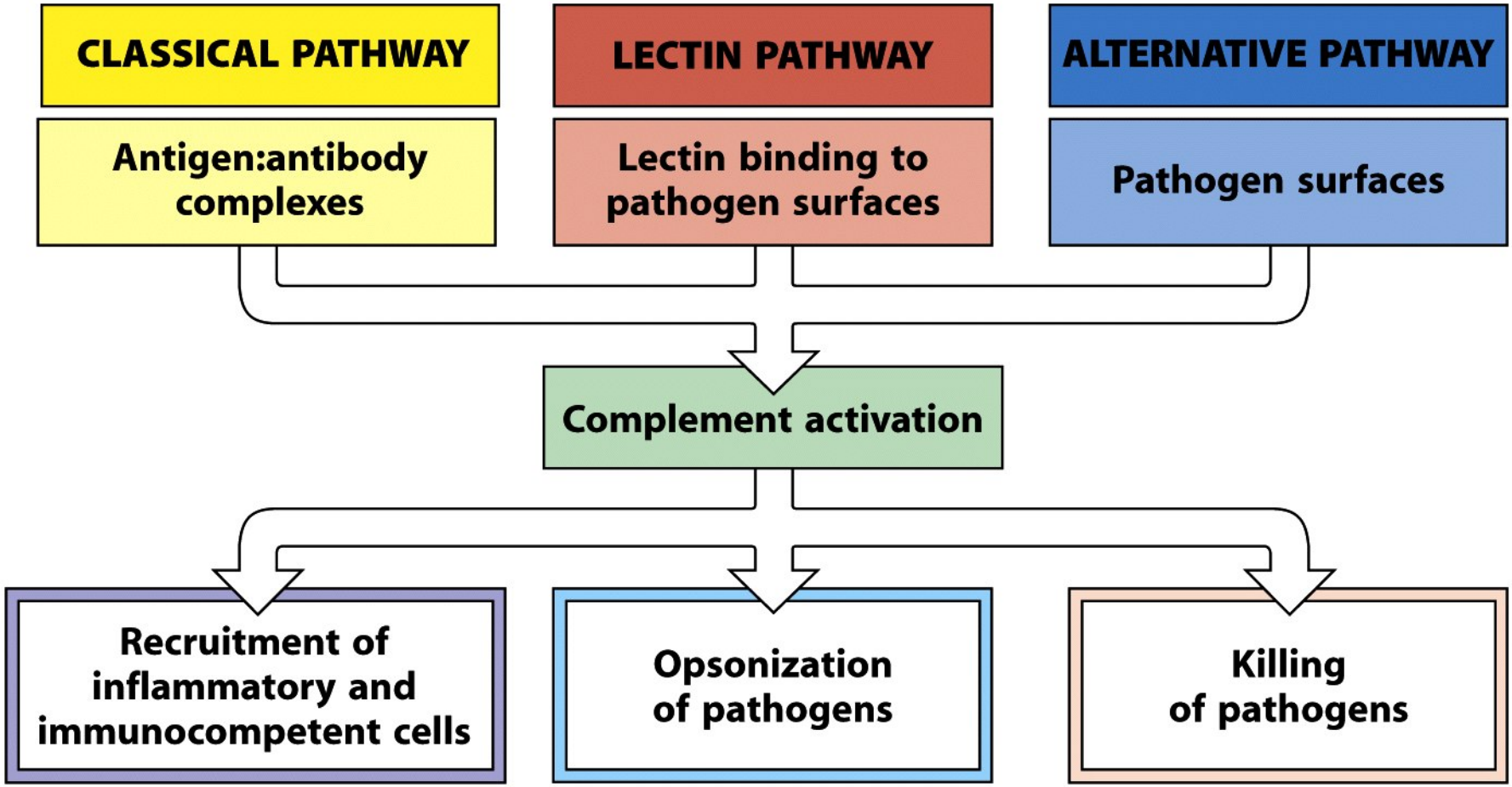


Figure 2-24 Immunobiology, 7ed. (© Garland Science 2008)

The Classical Pathway

- Begins with the formation of antigen-antibody complex (immune complex) or by binding of Ab on bacterial surface
- IgM and IgG can activate the classical complement pathway
- Early stage involves C1, C4, C2, and C3

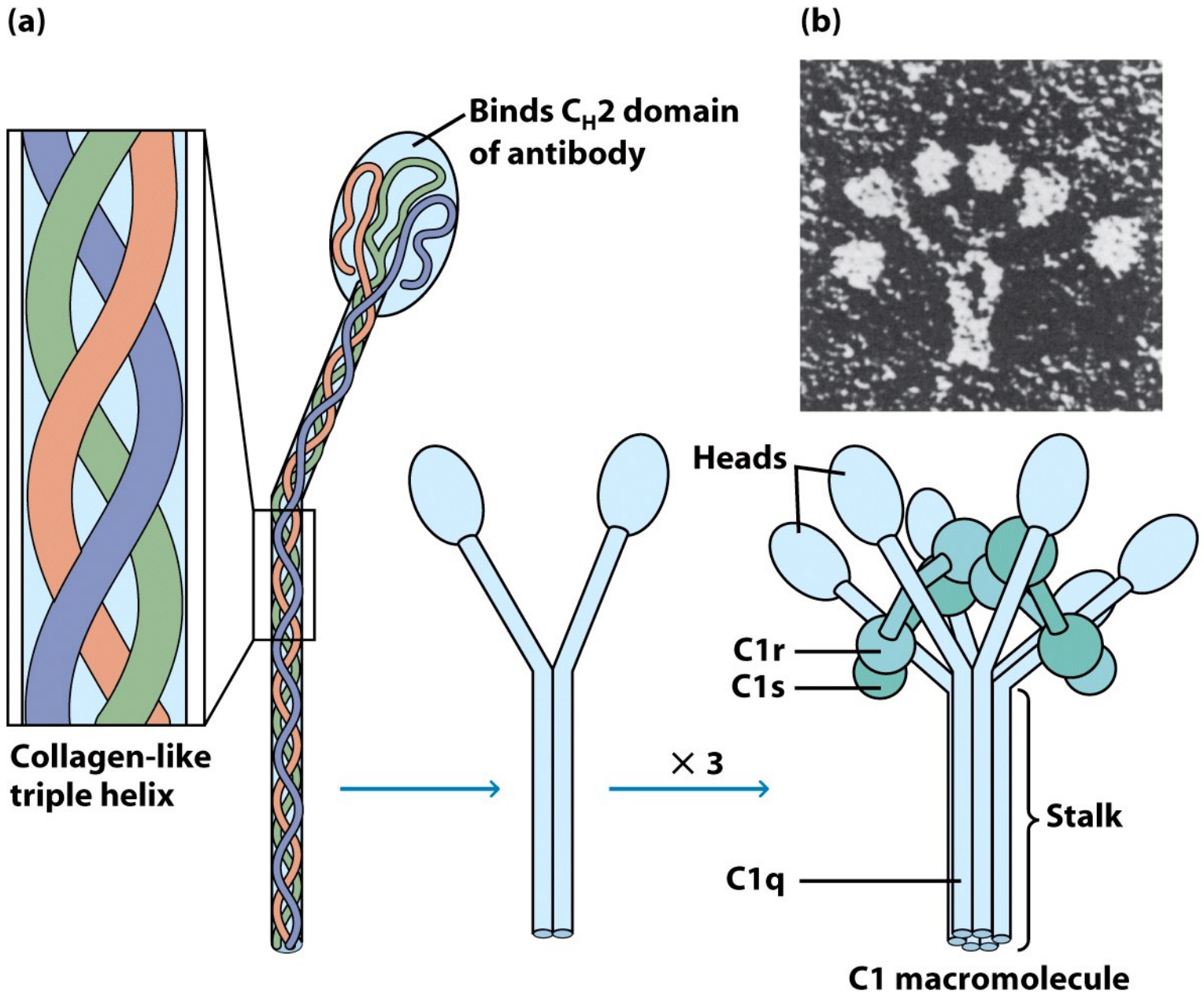


Figure 7-3
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The Classical Pathway

1

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

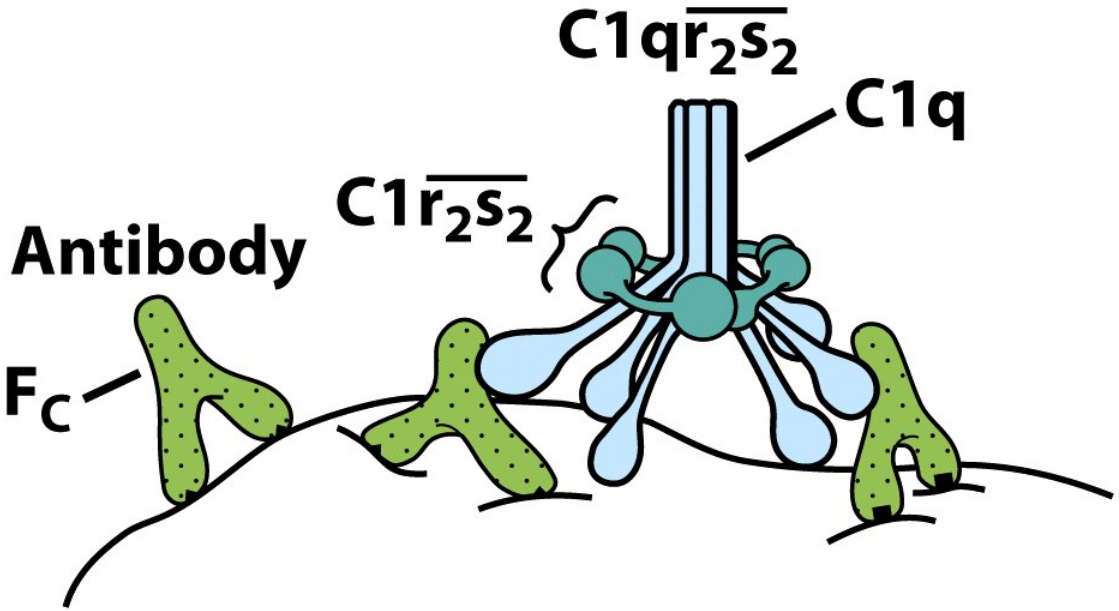

Figure 7-5 part 1
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The Classical Pathway

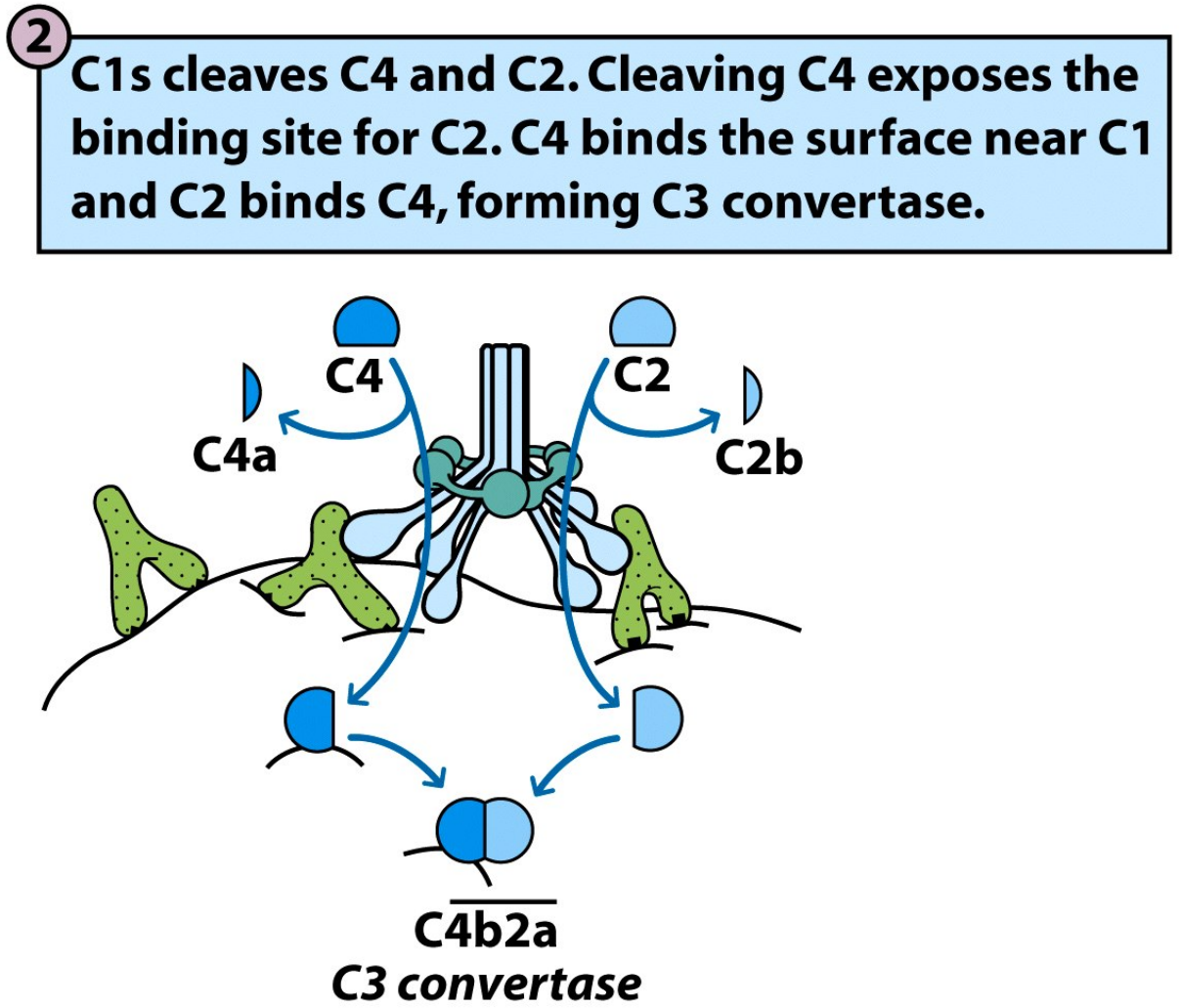

Figure 7-5 part 2
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The Classical Pathway

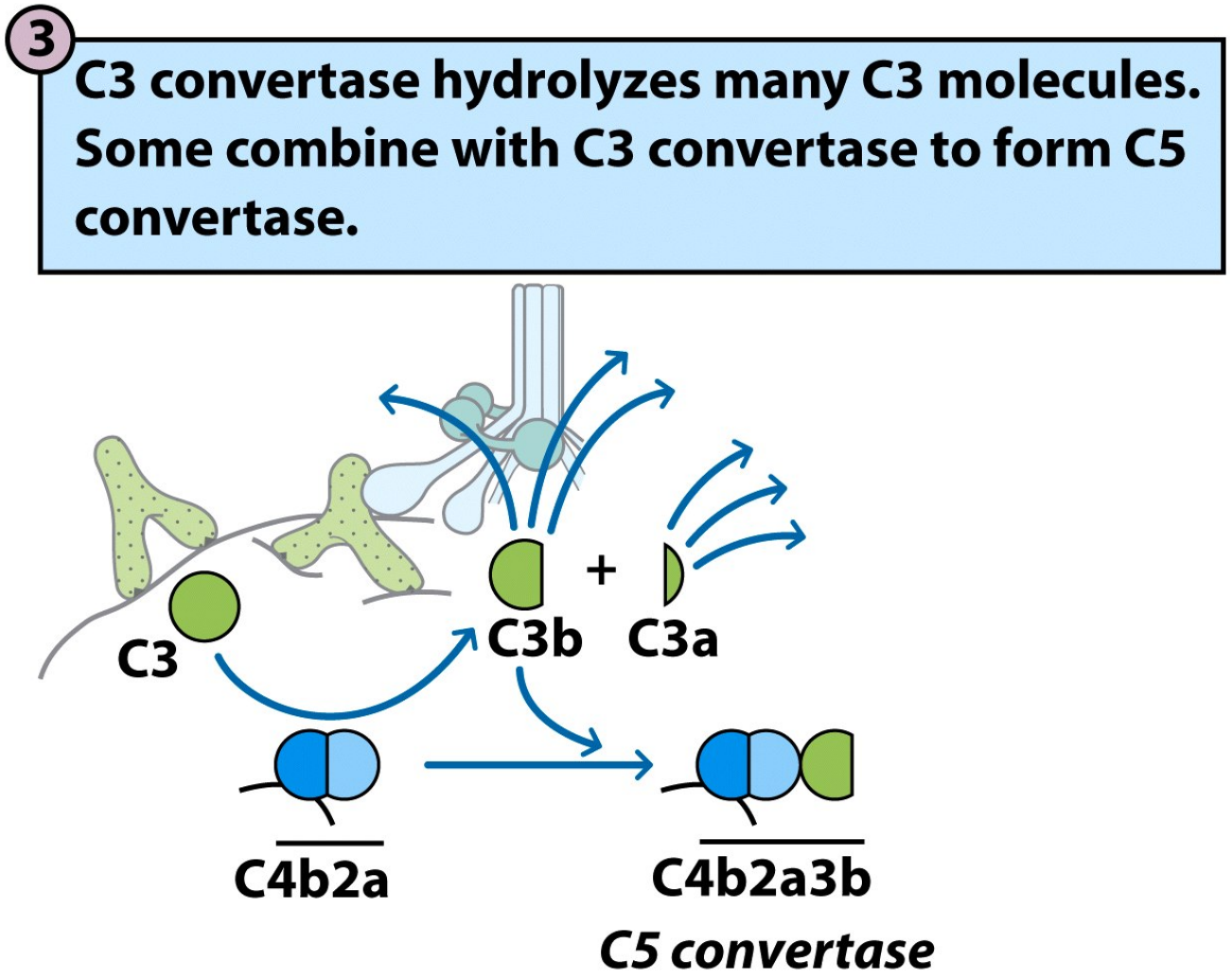

Figure 7-5 part 3
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The Classical Pathway

4 **The C3b component of C5 convertase binds C5, permitting $\overline{C4b2a}$ to cleave C5.**

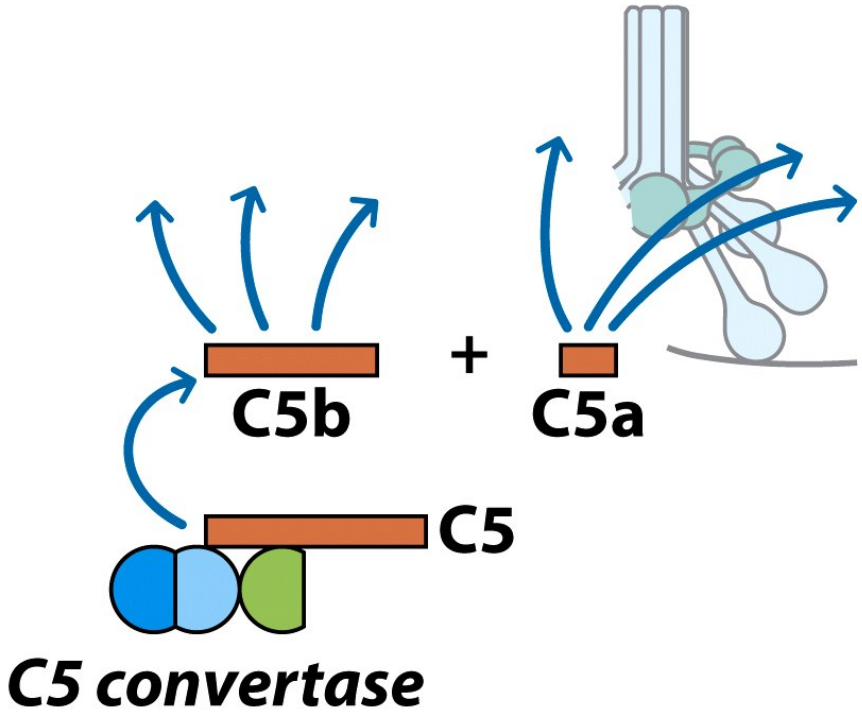

Figure 7-5 part 4
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The Classical Pathway

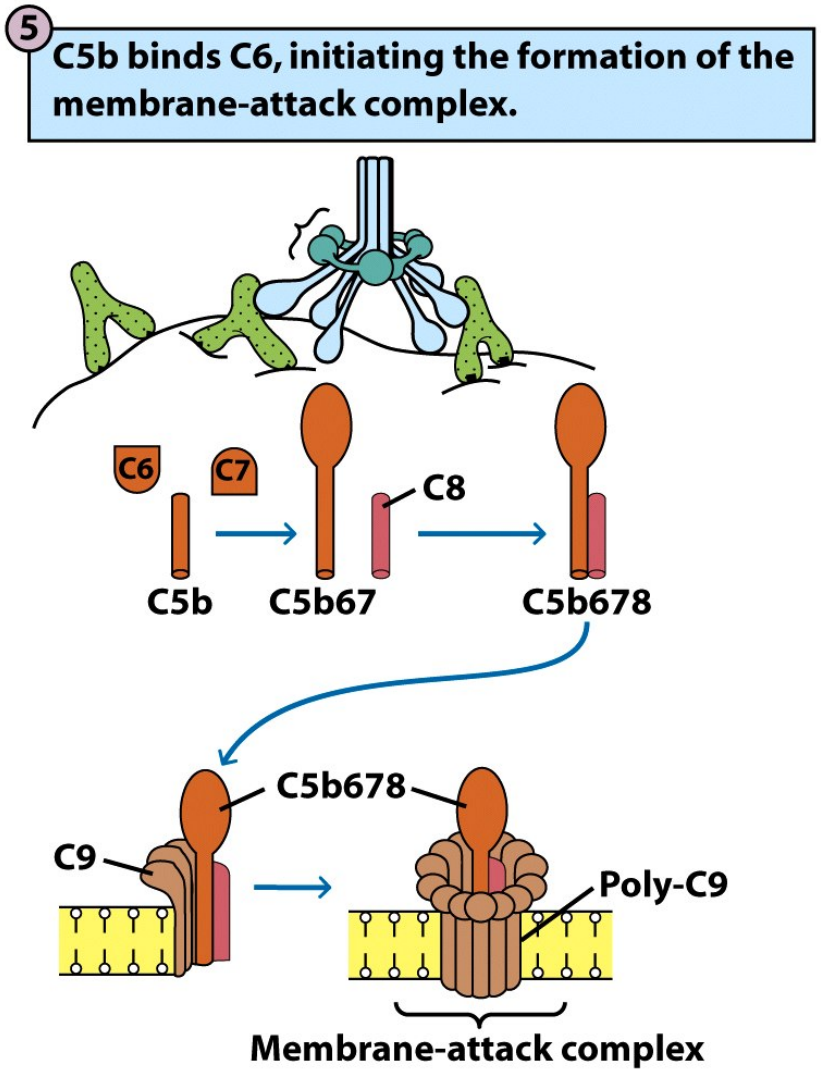

Figure 7-5 part 5
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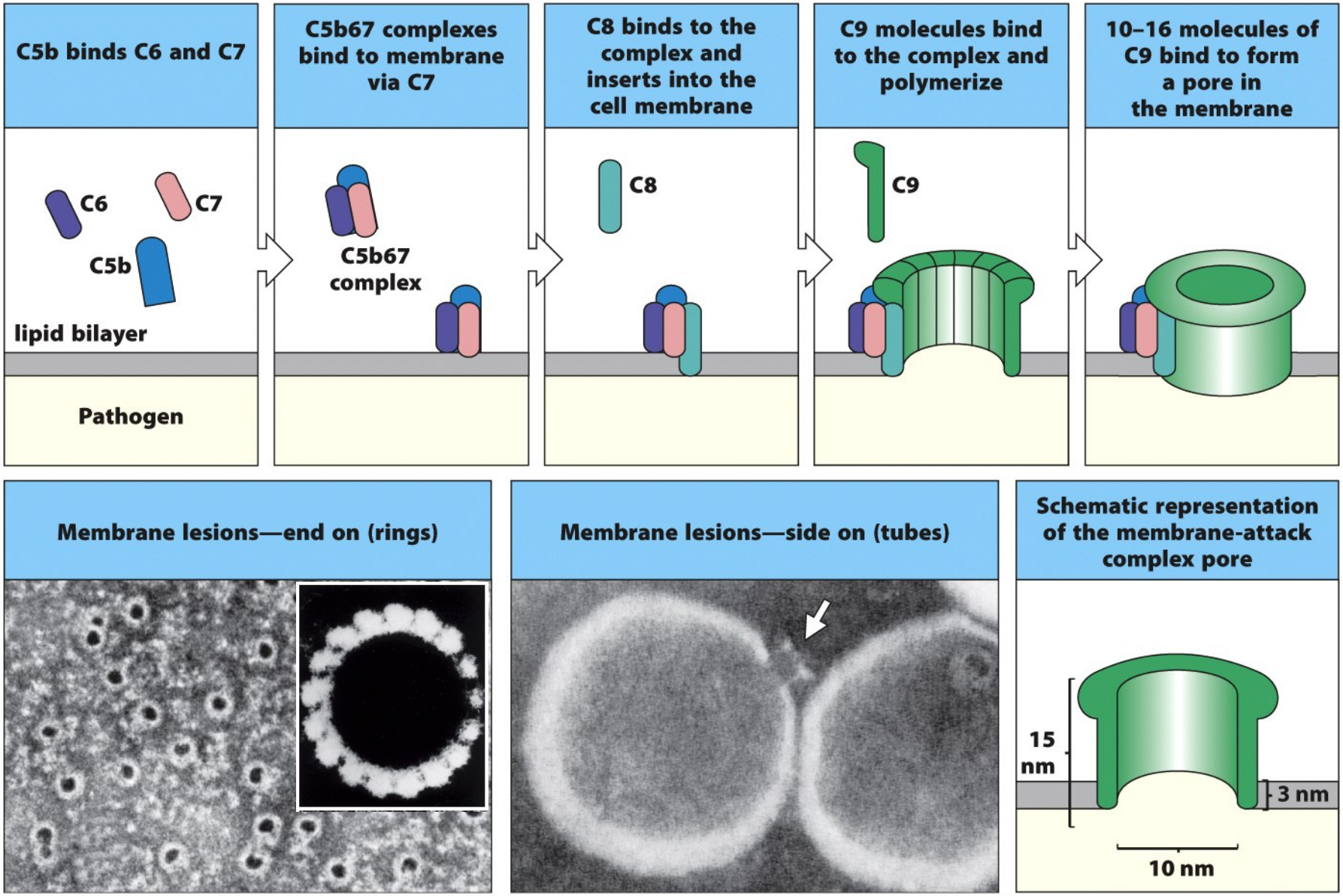
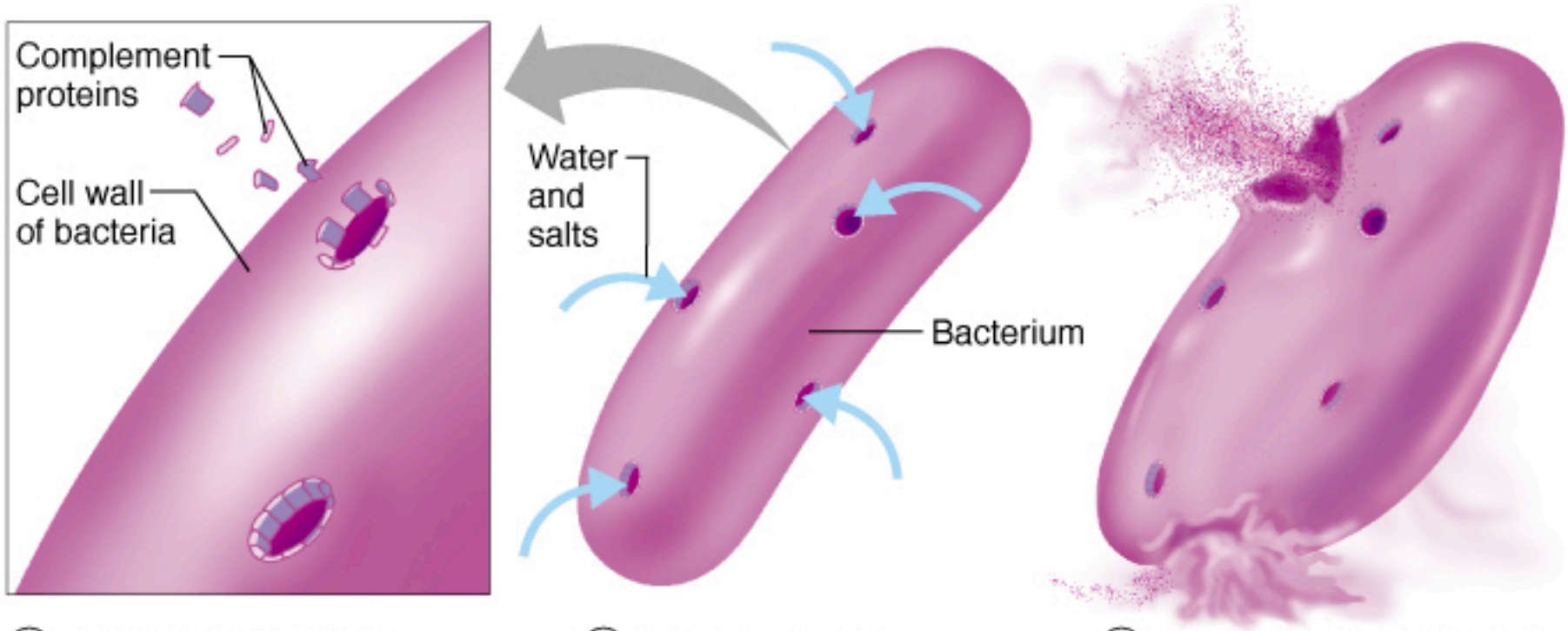


Figure 2.31 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Membrane Attack Complex (MAC)



① Activated complement proteins form complexes of proteins that create holes in the bacterial cell wall.

② Water and salts diffuse into the bacterium through the holes.

③ The bacterium swells and eventually bursts.

The Lectin Pathway

- Lectins such as mannose-binding lectin (MBL) binds to mannose residues on the surface of microorgnisms
- Early stage involve MASP1, MASP2, MBL, C2, C4, and C3
- Sugars recognized by MBL in human cells are covered with sialic acid

The Lectin Pathway

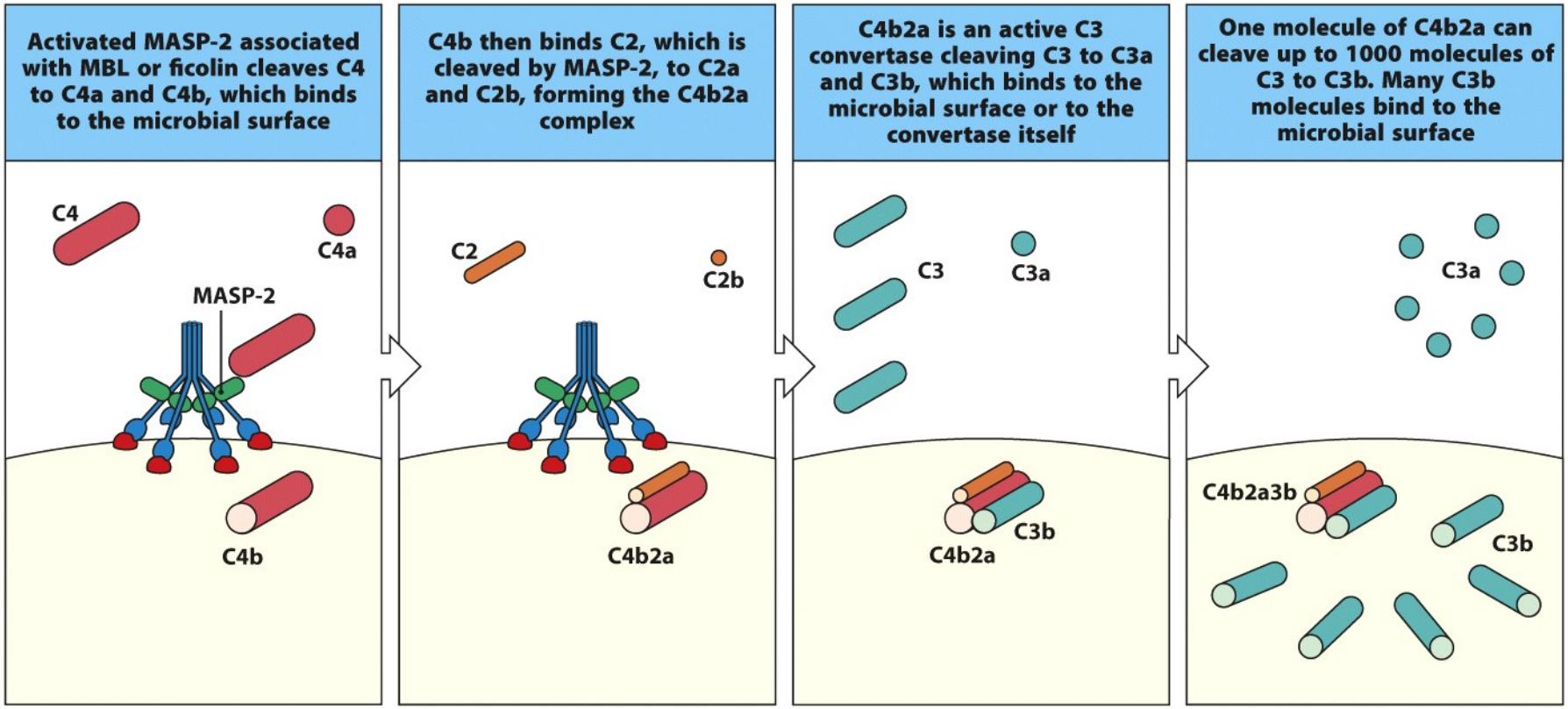


Figure 2.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

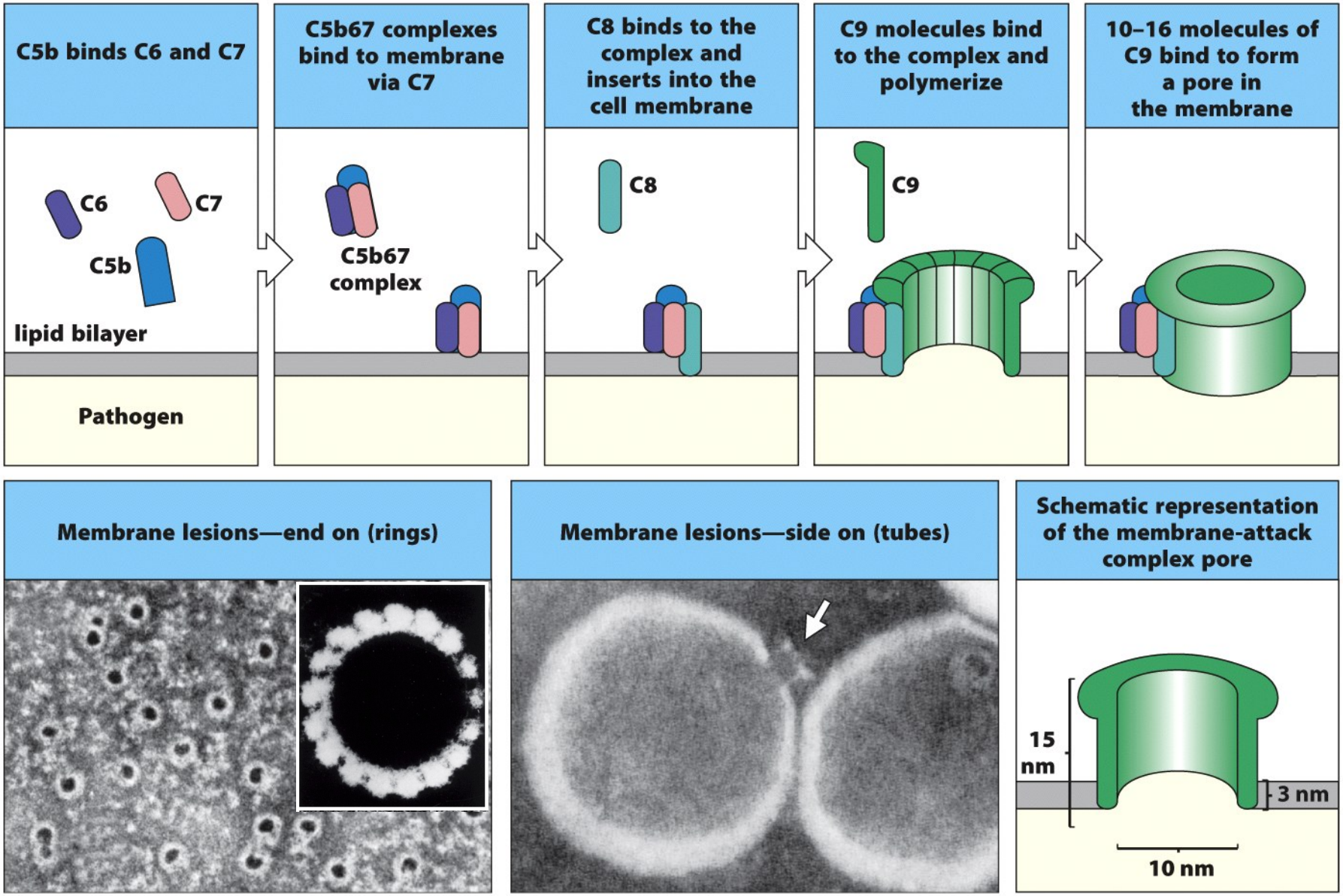
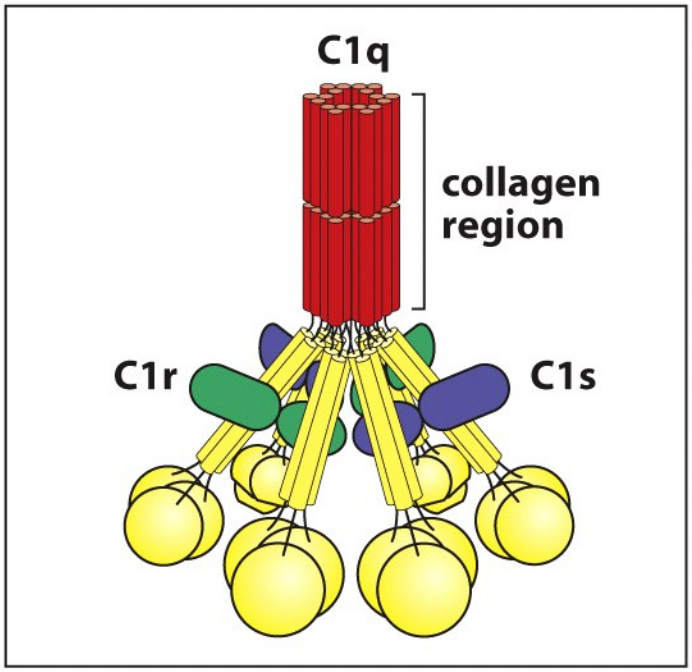
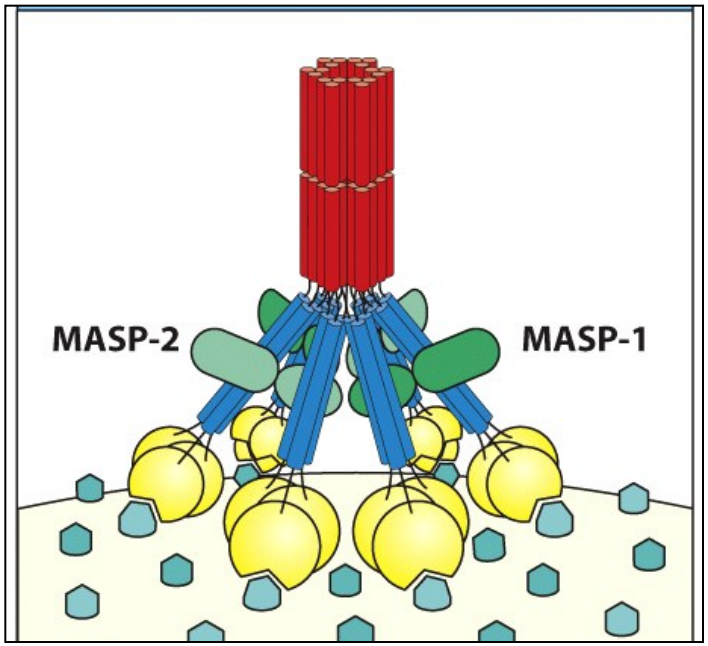


Figure 2.31 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

C1



MBL



The Alternative Pathway

- It generates active products similar to those of the classical pathway but without antigen-antibody complex
- Early stage involve C3, factor B, factor D, and properdin
- Gram negative and gram positive bacterial cell wall can activate the alternative pathway

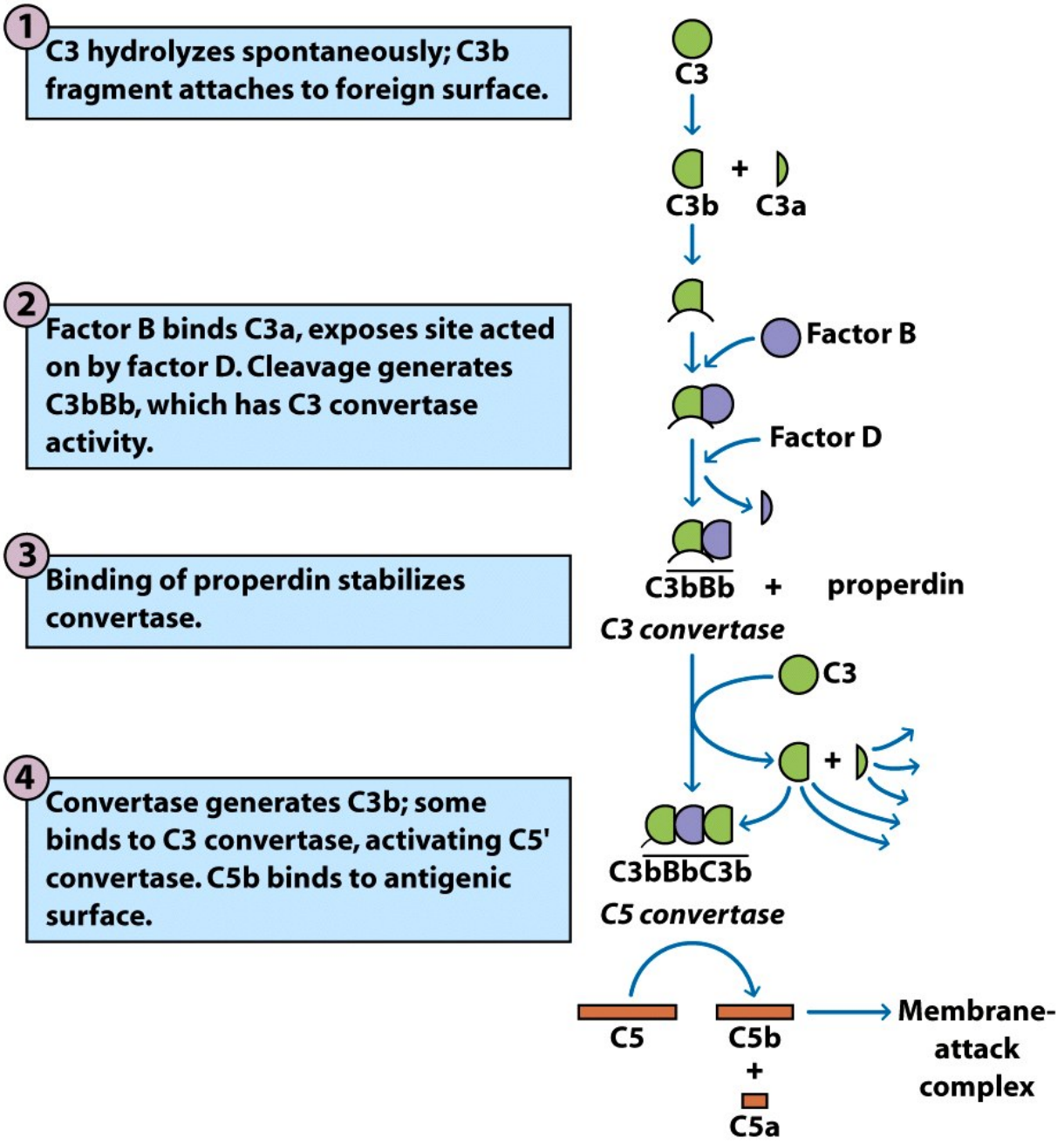


Figure 7-7
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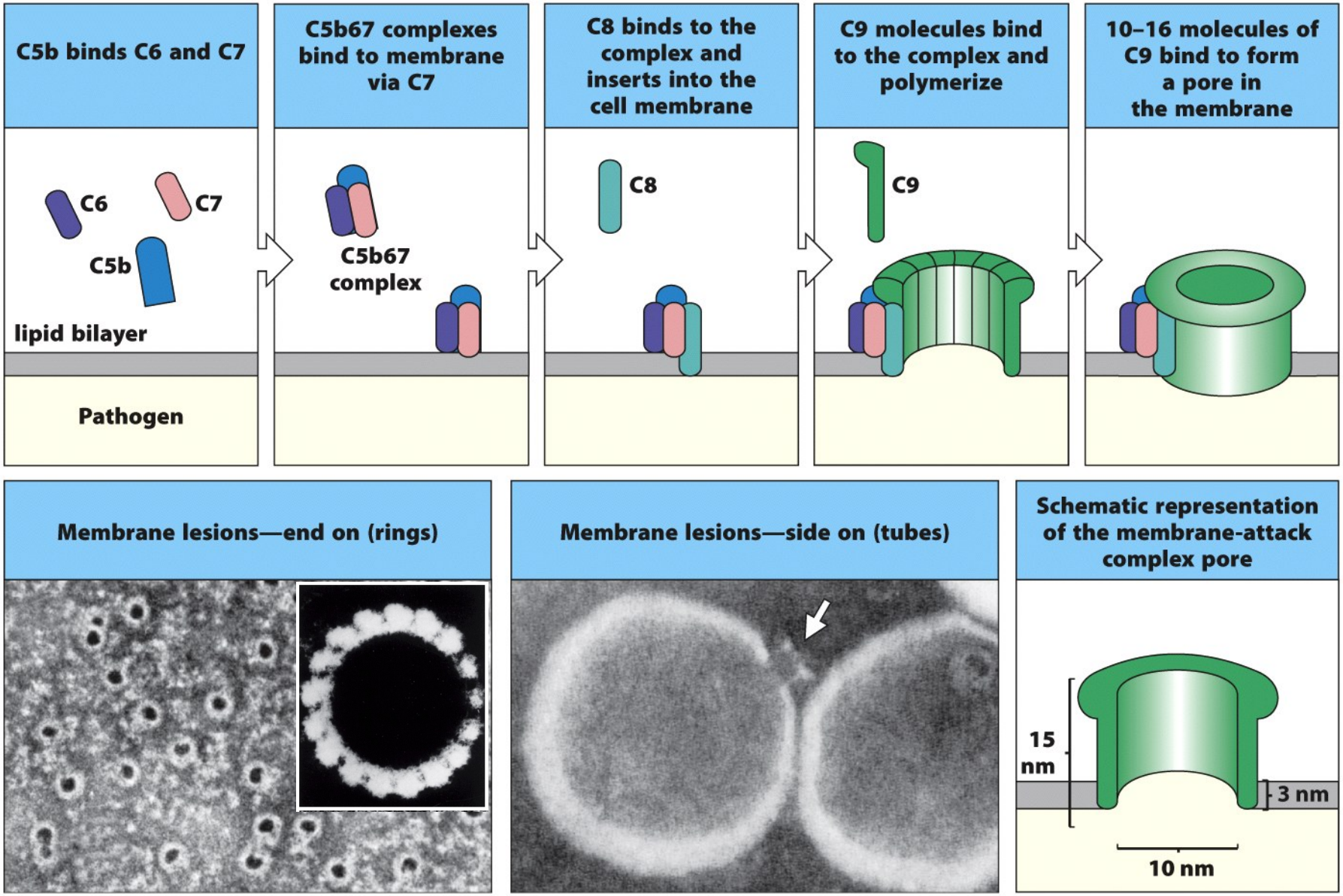

Figure 2.31 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

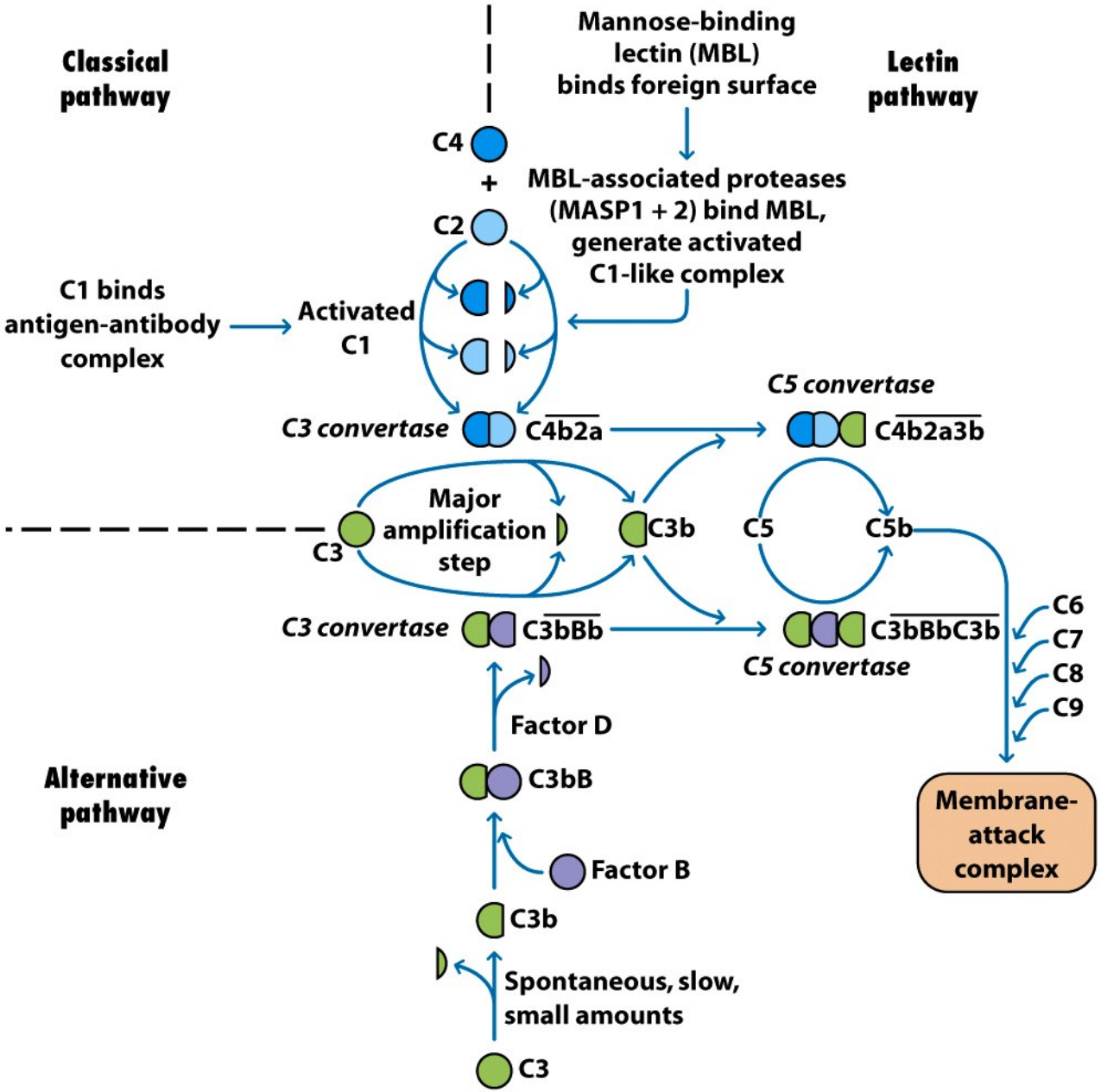

Figure 7-9
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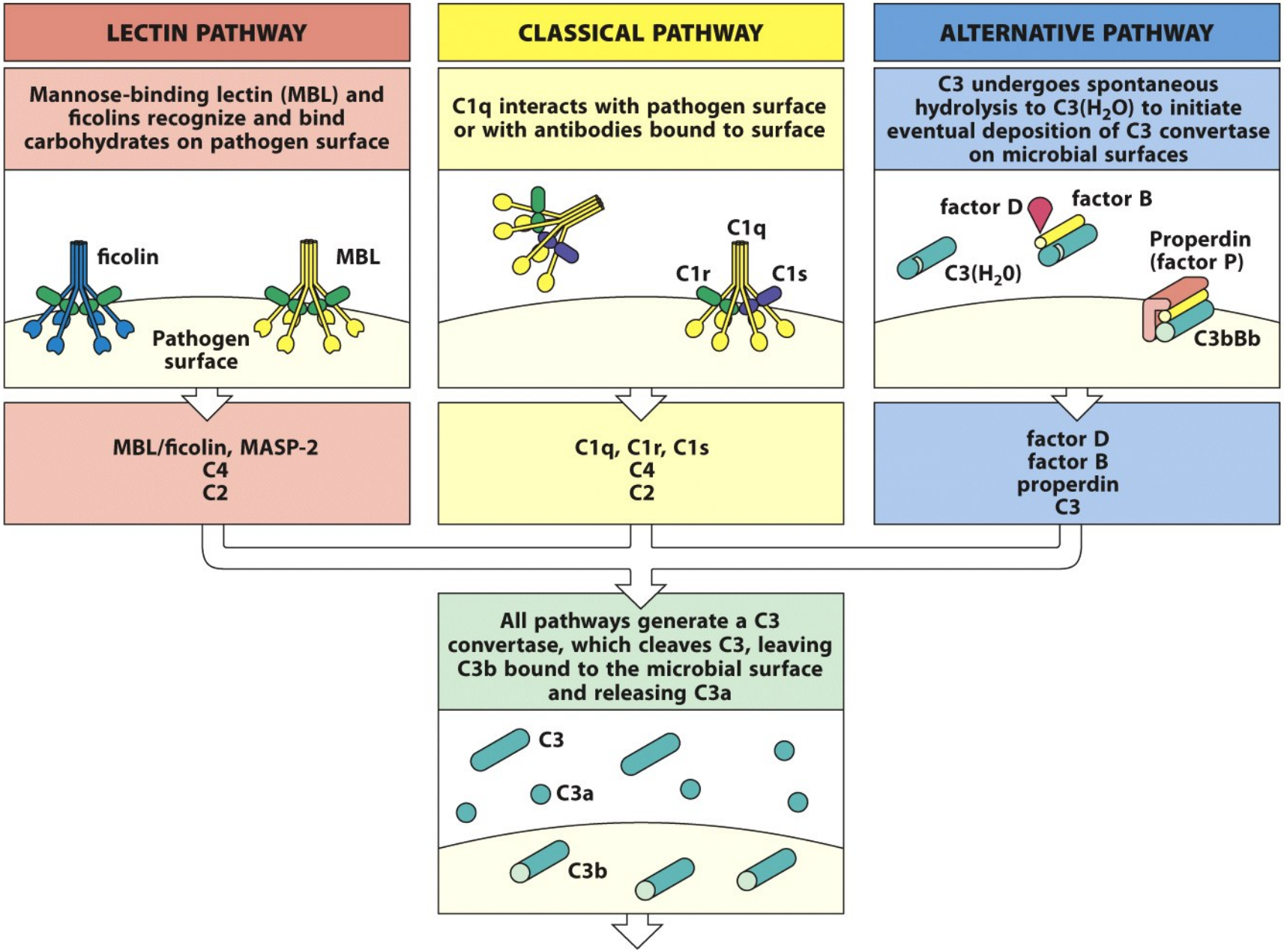

Figure 2.12 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

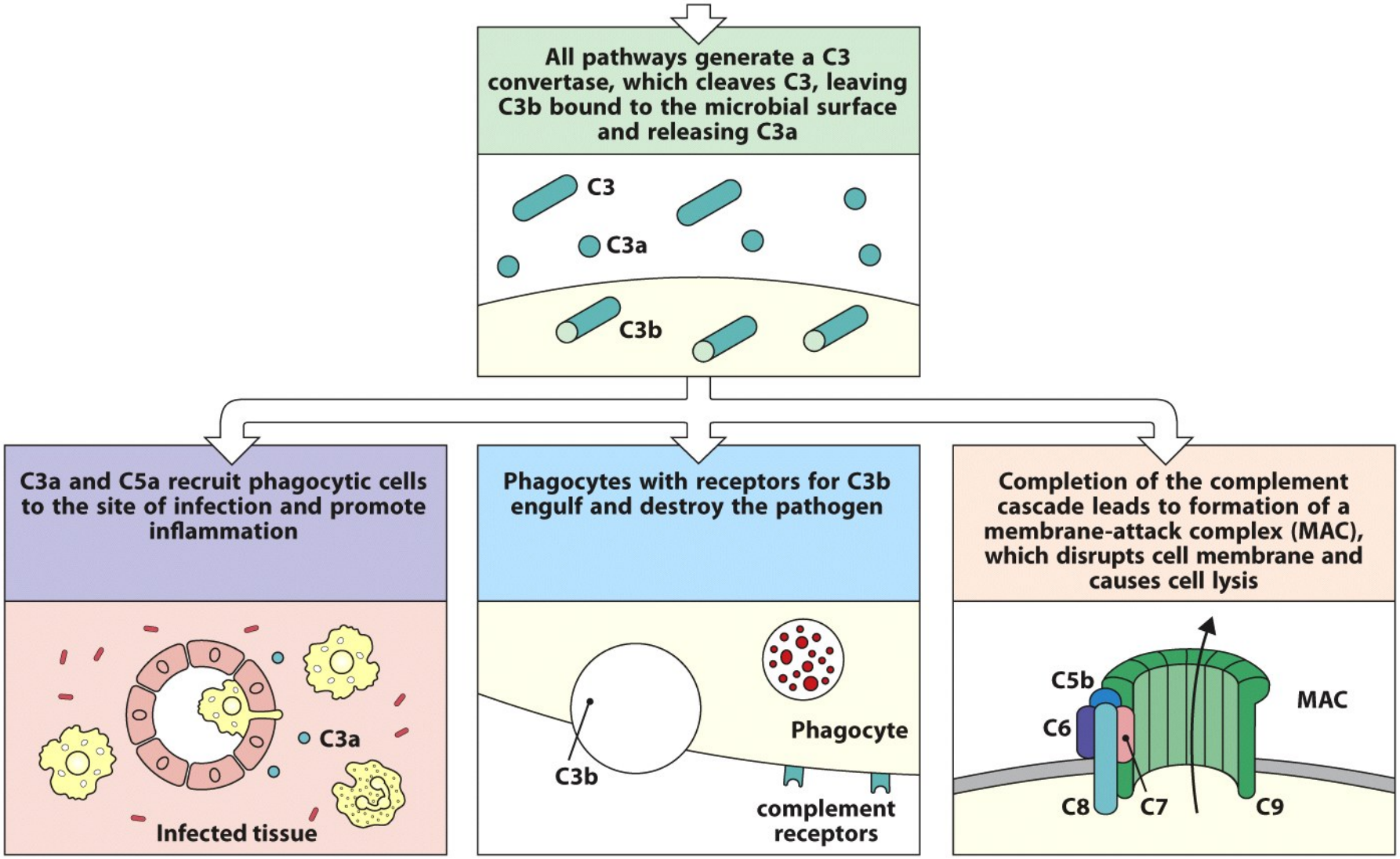

Figure 2.12 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Activation Consequences

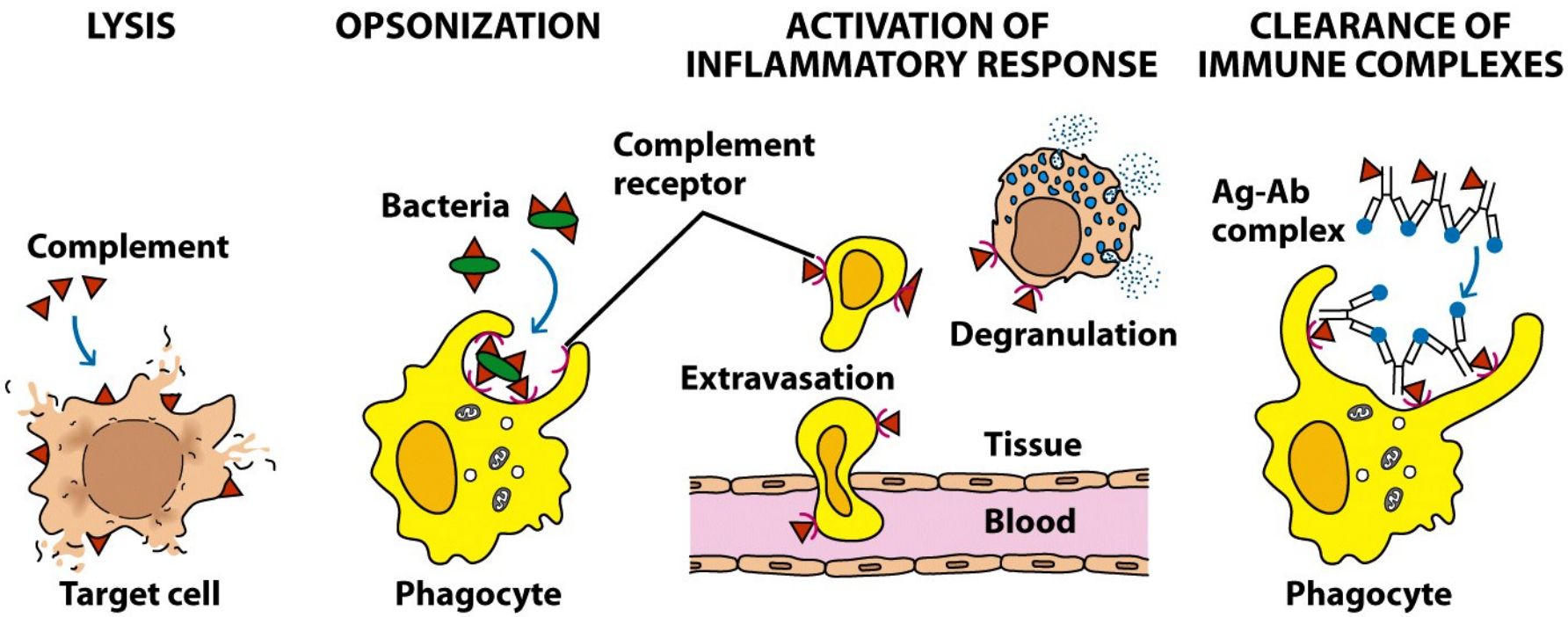

Figure 7-1
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Lysis

- MAC can lyse broad spectrum of cells
- Gram positive bacteria are generally more resistant to MAC because of their thick peptidoglycan layer
- Some cells have developed ways to evade MAC such as cancer cells

Lysis

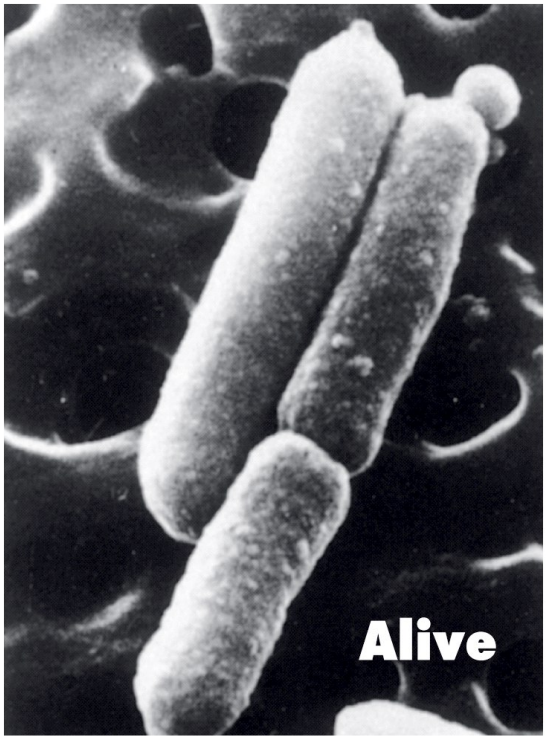

Figure 7-12a
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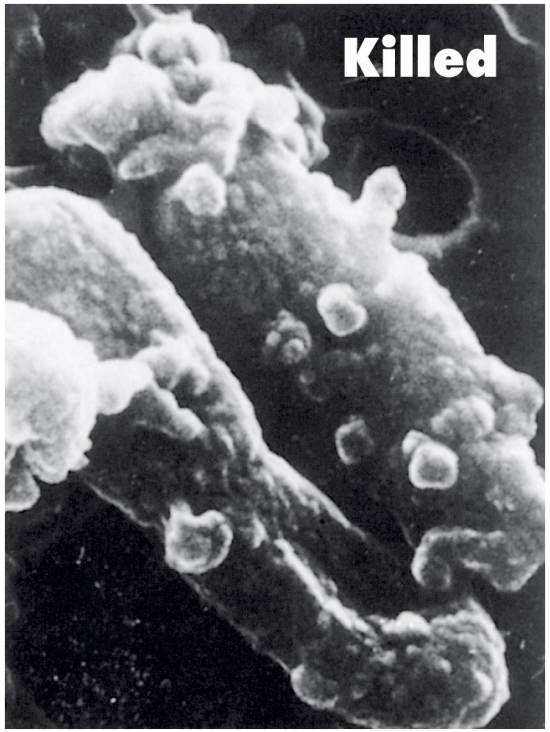

Figure 7-12b
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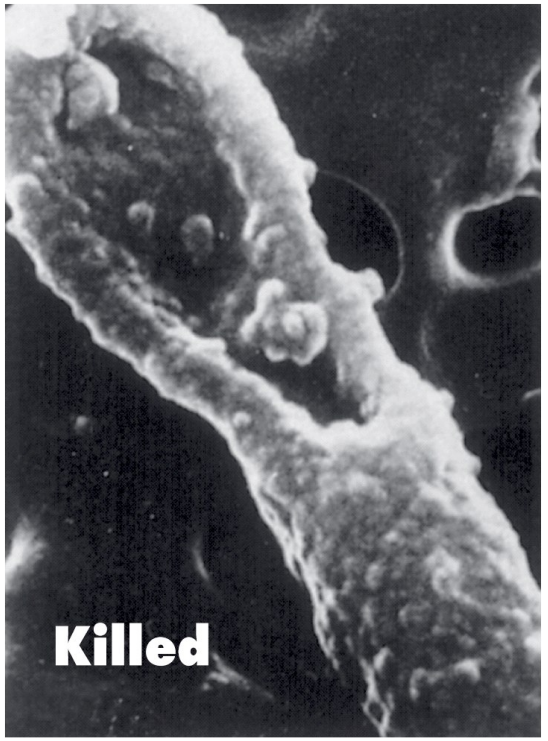

Figure 7-12c
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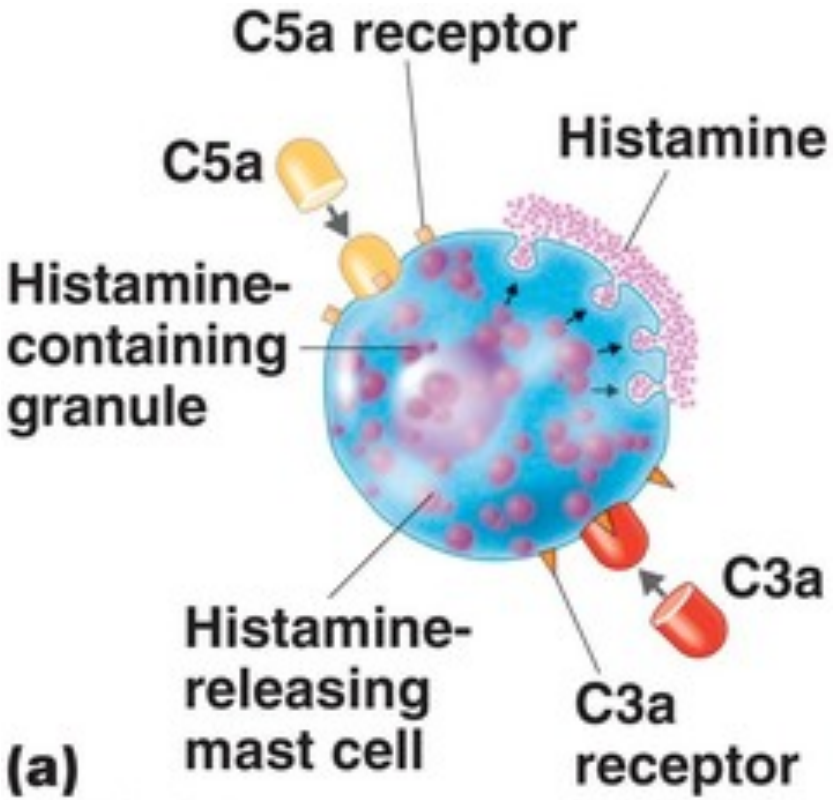
Scanning electron micrograph of *E. coli* before and after complement lysis

Some microbes develop mechanisms to evade complement lysis

Inflammatory Response

- C3a and C5a (**anaphylatoxins**) bind to basophils and mast cells



Inflammatory Response

- C3a and C5a increase vascular permeability

- C3a and C5a mediate **chemotaxis** by inducing monocytes and neutrophils to adhere to vascular endothelium, extravasation, and migration to the site of complement activation in the tissue i.e. inflammation

Opsonization

- C3b and C4b binding facilitates phagocytosis
- Phagocytic cells express complement receptors CR1, CR3, and CR4
- Activation of phagocytic cells increase the number of expressed complement receptors

Opsonization

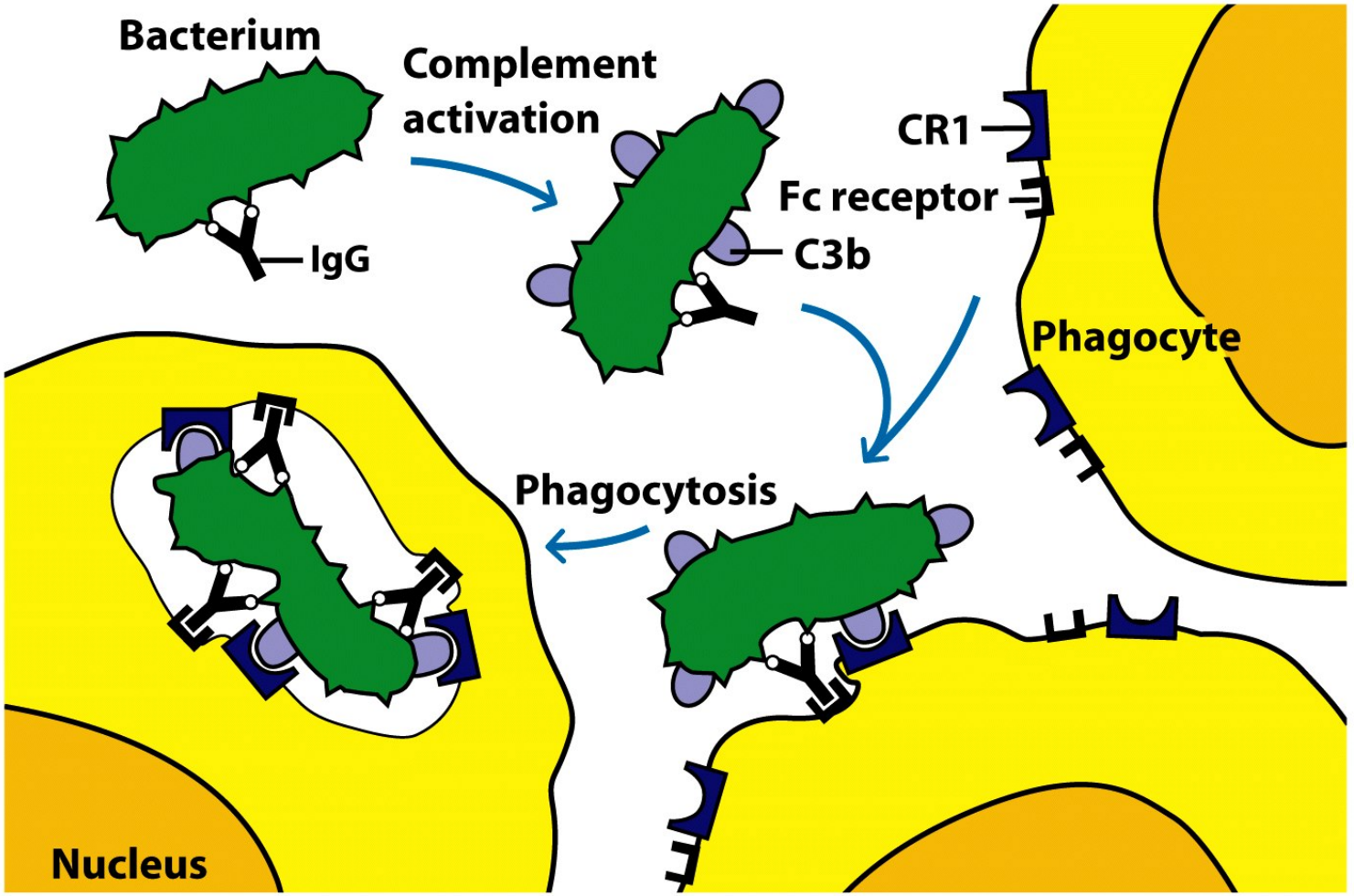


Figure 7-13a
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Virus Neutralization

- Binding of Ab to viral structures causes:
  - Complement fixation (classical, alternative, and lectin pathways)
  - Viral neutralization and aggregation by complement components e.g. C3b
  - Formation of thick protein coat around the virus
- These mechanisms blocks attachment to susceptible host cells

Clearing Immune Complexes

- Immune complexes can damage tissues
- C3b coats immune complexes
- RBC have capability of binding C3b coated complexes and carrying them to liver and spleen to be cleared

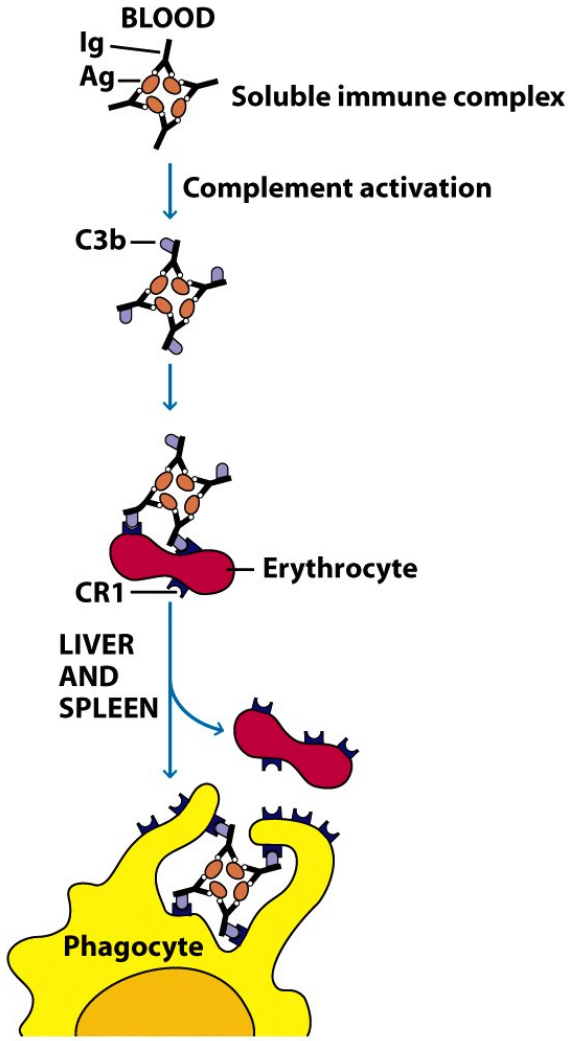

Figure 7-15
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Activated Complement Regulation

- Activated complement components are able to harm normal tissues. Therefore, they get spontaneously inactivated if they are not stabilized by other components

- C3 convertase is a central amplification step in all pathways. Regulatory proteins control C3 convertase activity

Regulation of the Complement System

(a) Before assembly of convertase activity

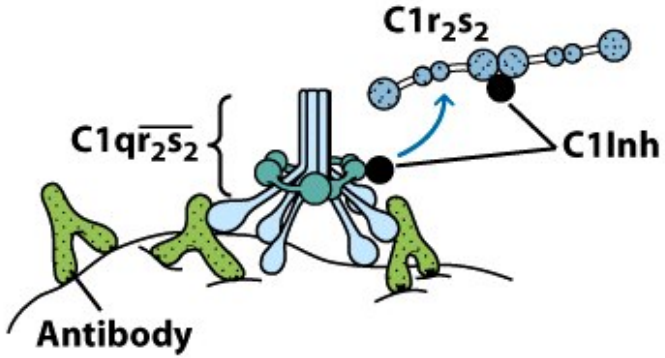
1. C1 inhibitor (C1Inh) binds $C1r_2s_2$, causing dissociation from C1q.

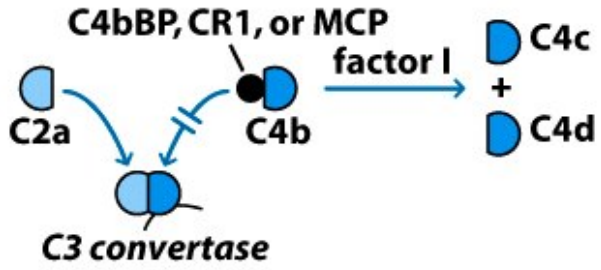
2. Association of C4b and C2a is blocked by binding C4b-binding protein (C4bBP), complement receptor type I, or membrane cofactor protein (MCP).

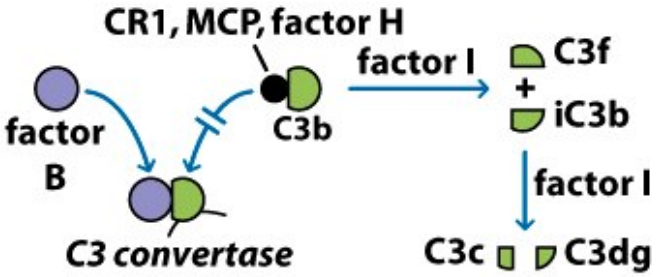
3. Inhibitor-bound C4b is cleaved by factor I.

4. In alternative pathway, CR1, MCP, or factor H prevents binding of C3b and factor B.

5. Inhibitor-bound C3b is cleaved by factor I.

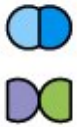






(b) After assembly of convertase

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



C4bBP, CR1, factor H, DAF → Dissociation of convertase; remaining C4b or C3b cleaved by factor I.

(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) or membrane inhibitor of reactive lysis (MIRL or CD59) bind C5b678, preventing assembly of poly-C9 and blocking formation of MAC.

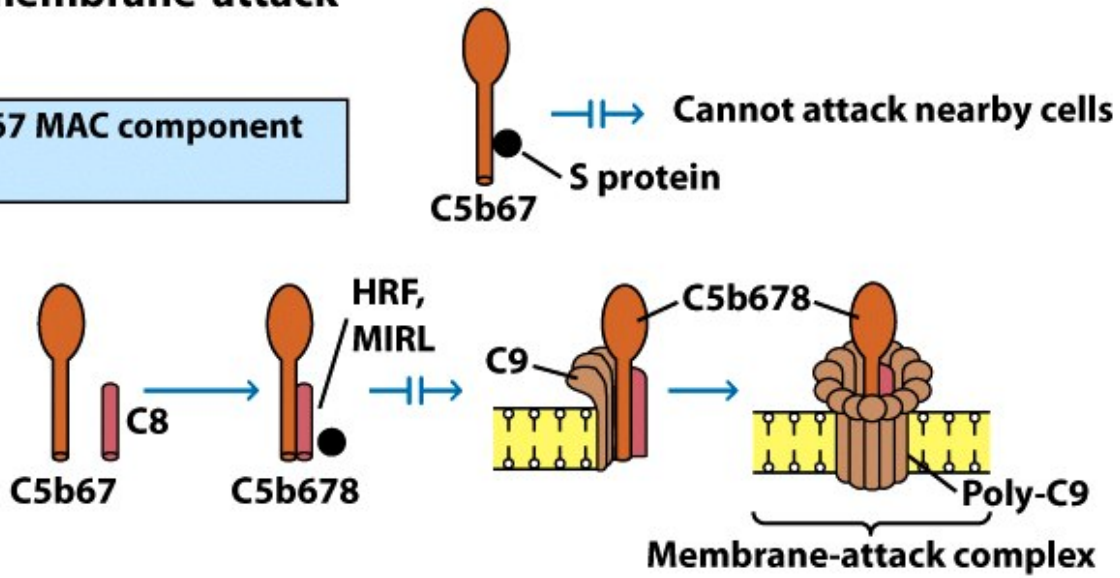


Figure 7-10
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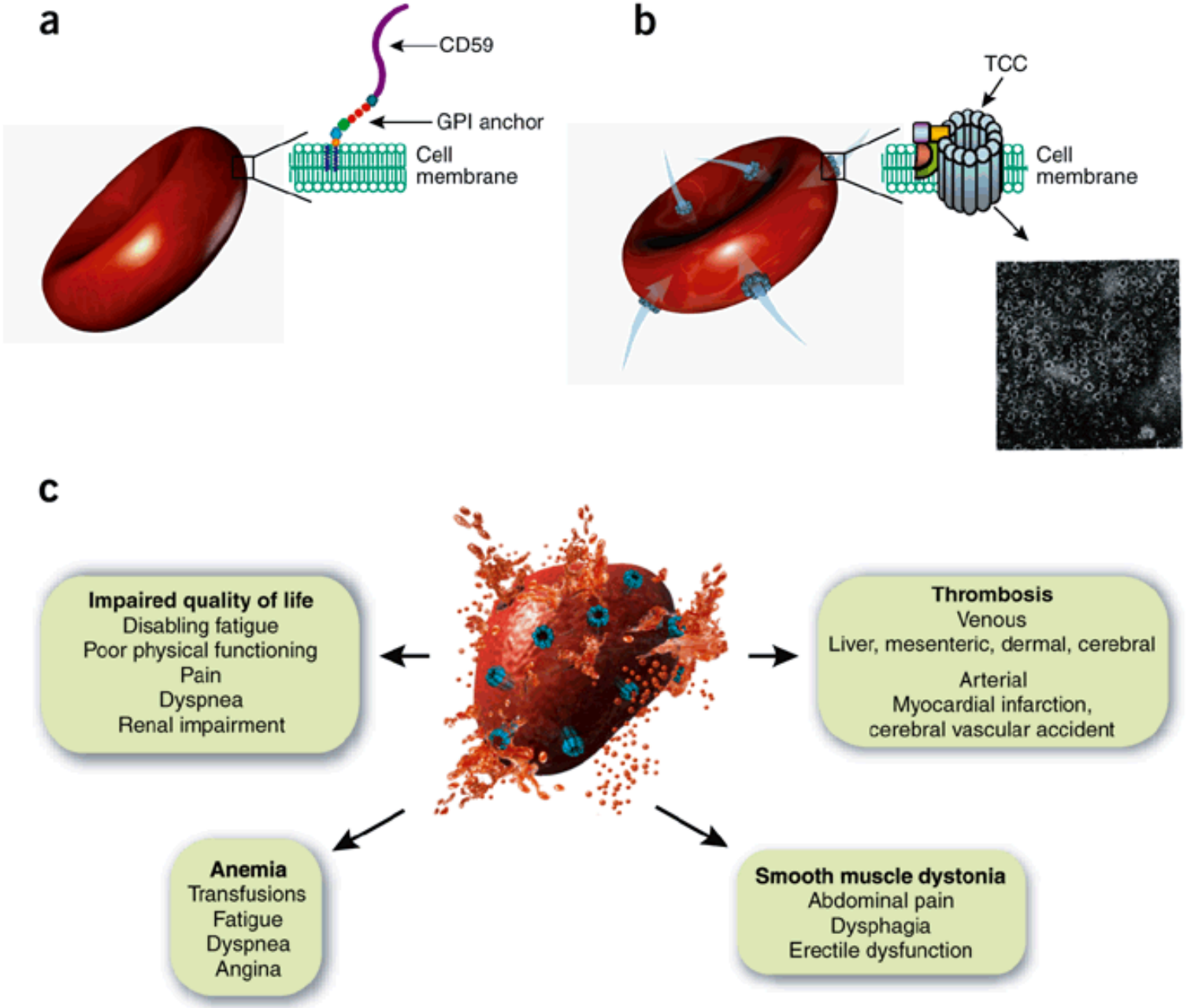
Complement Deficiencies

- **Paroxysmal Nocturnal Hemoglobinuria (PNH)**
  - Somatic mutation in the pig-A gene that synthesizes GPI proteins
  - Mutated GPI cannot bind to DAF and CD59
  - This results in hemolytic anemia, iron deficiency, and thrombosis


a
CD59
GPI anchor
Cell membrane
b
TCC
Cell membrane
c
Impaired quality of life
Disabling fatigue
Poor physical functioning
Pain
Dyspnea
Renal impairment
Thrombosis
Venous
Liver, mesenteric, dermal, cerebral
Arterial
Myocardial infarction, cerebral vascular accident
Anemia
Transfusions
Fatigue
Dyspnea
Angina
Smooth muscle dystonia
Abdominal pain
Dysphagia
Erectile dysfunction

Complement Deficiencies

- **Paroxysmal Nocturnal Hemoglobinuria (PNH) - Treatment**

Problem	Management
Lack of RBC	RBC transfusion
Deficient erythropoietin	Recombinant erythropoietin
Increased thrombosis	Heparin and anticoagulants
Loss of iron	Iron supplementation
Persistent complement activation	Eculizumab to block C5

You are now able to:

- ✓ Recognize the biological functions of the complement cascade
- ✓ Identify the components of the complement system
- ✓ Describe the three pathways of complement activation