COMPLEMENT SYSTEM

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What is an immune response?

Entry of pathogen

First line of defense - Innate Immunity

Second line of defense - Adaptive Immunity

INNATE IMMUNE SYSTEM

EARLY DEFENSE AGAINST INFECTIONS

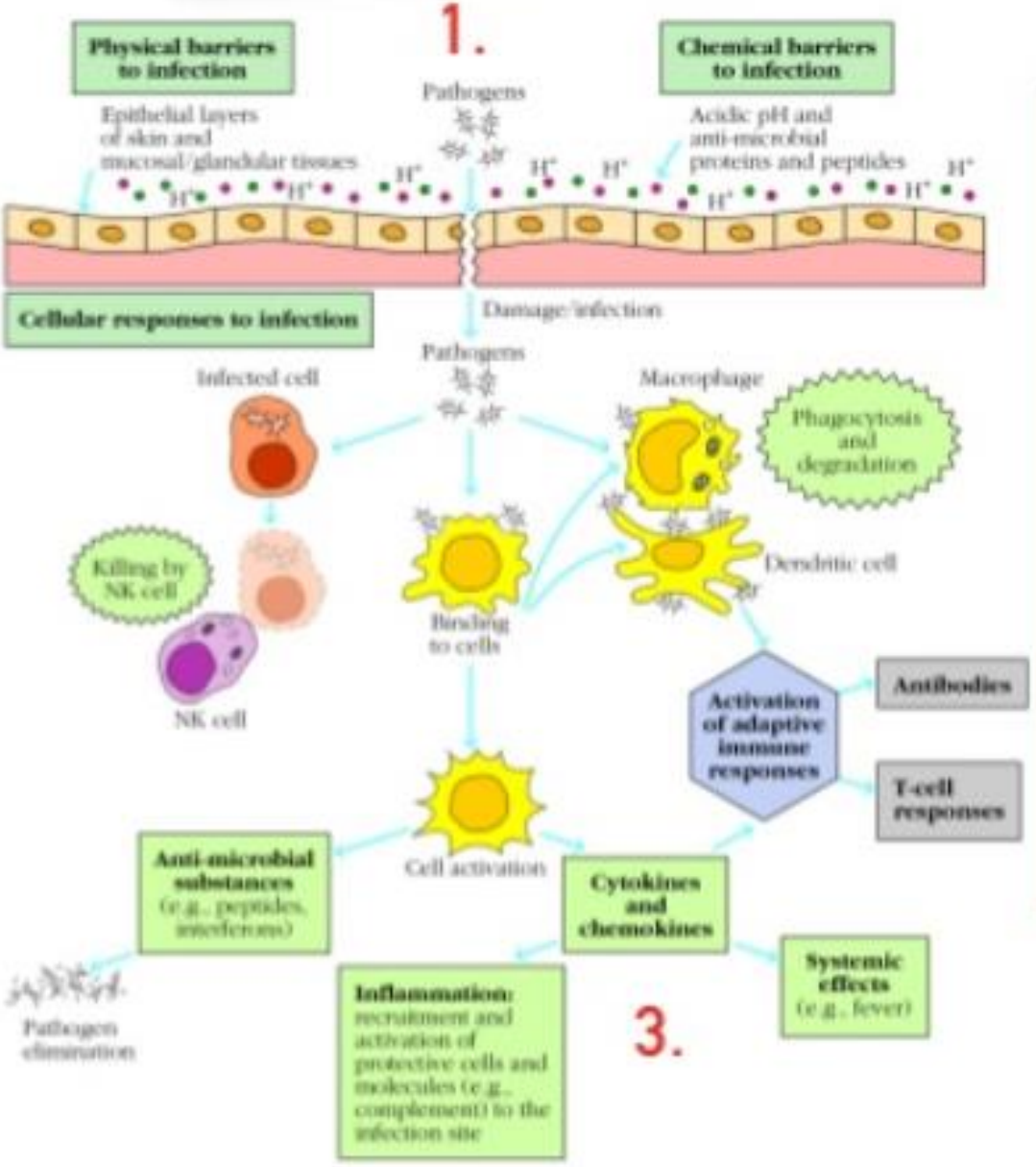
Components of the IIS

- Epithelia – barrier to infection
- Cells (in circulation and tissues)
- Proteins

  APP

  Complement

Component of innate immunity



1. Anatomical barrier
   - Physical barriers
   - Chemical barriers
2. Cell
   - Phagocytic cells
   - Dendritic cell
   - NK cells, ILC
3. Soluble proteins
   - Complement
   - Cytokines, Chemokines
   - Anti-microbial substances

Complement

- Complement is a collection of **soluble proteins** present in **blood** and other **body fluids**

- **Heat-labile** component of normal plasma that **augmented** the **opsonization** and killing of bacteria

Complement…..

- The complement system is composed of more than **30 different plasma proteins**, which are produced mainly by the **liver**

- In the absence of infection, these proteins circulate in an **inactive form**

- In the presence of pathogens or of antibody bound to pathogens, the complement system becomes '**activated**.'

Complement…..

- Particular complement proteins **interact** with each other to form several different pathways of complement activation

- Final outcome is **killing of the pathogen**, either directly or by facilitating its **phagocytosis**, and **inducing inflammatory responses** that help to fight infection

Complement…..

- Many of the complement proteins are **proteases** that successively **cleave and activate one another**

- The proteases of the complement system are **synthesized as** inactive **pro-enzymes**, which only become enzymatically **active** after **proteolytic cleavage**, usually by another complement protein

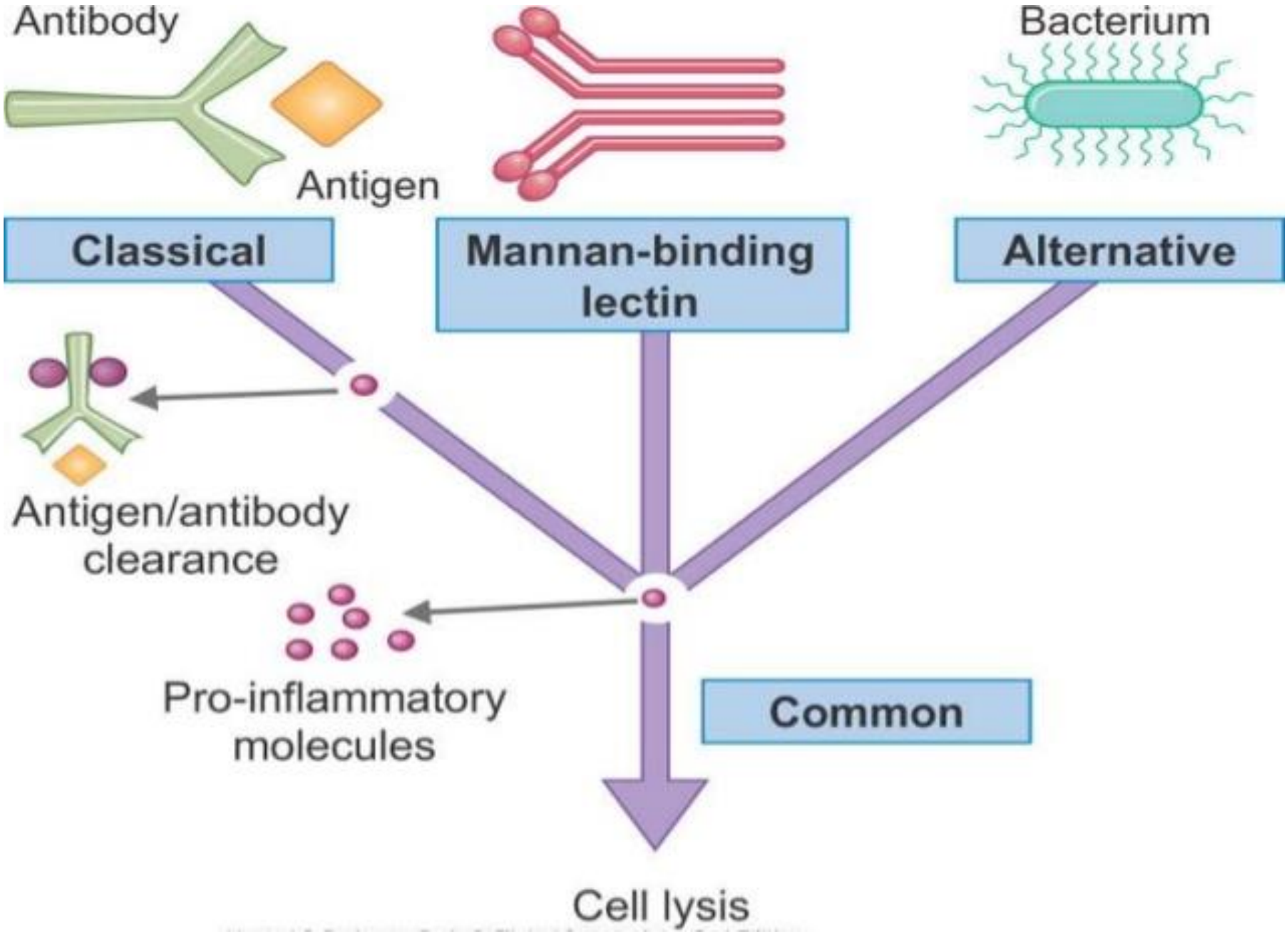
Complement…..

- These **proteolytic cascades** finally generate the **effector complement** components that aid the **removal of the pathogen**.

Complement Activation

- There are three pathways of complement activation

1. Classical
2. Lectin
3. Alternative


Antibody
Antigen
Bacterium
Classical
Mannan-binding lectin
Alternative
Antigen/antibody clearance
Pro-inflammatory molecules
Common
Cell lysis

Complement proteins

- **First** proteins discovered belong to the **classical pathway**, and are designated by the letter **C** followed by a number.

- The **native complement** proteins have a simple number designation, for example **C1** and **C2**

- The **reaction sequence** in the classical pathway, for example, is **C1, C4, C2, C3, C5, C6, C7, C8, and C9**

Complement proteins….

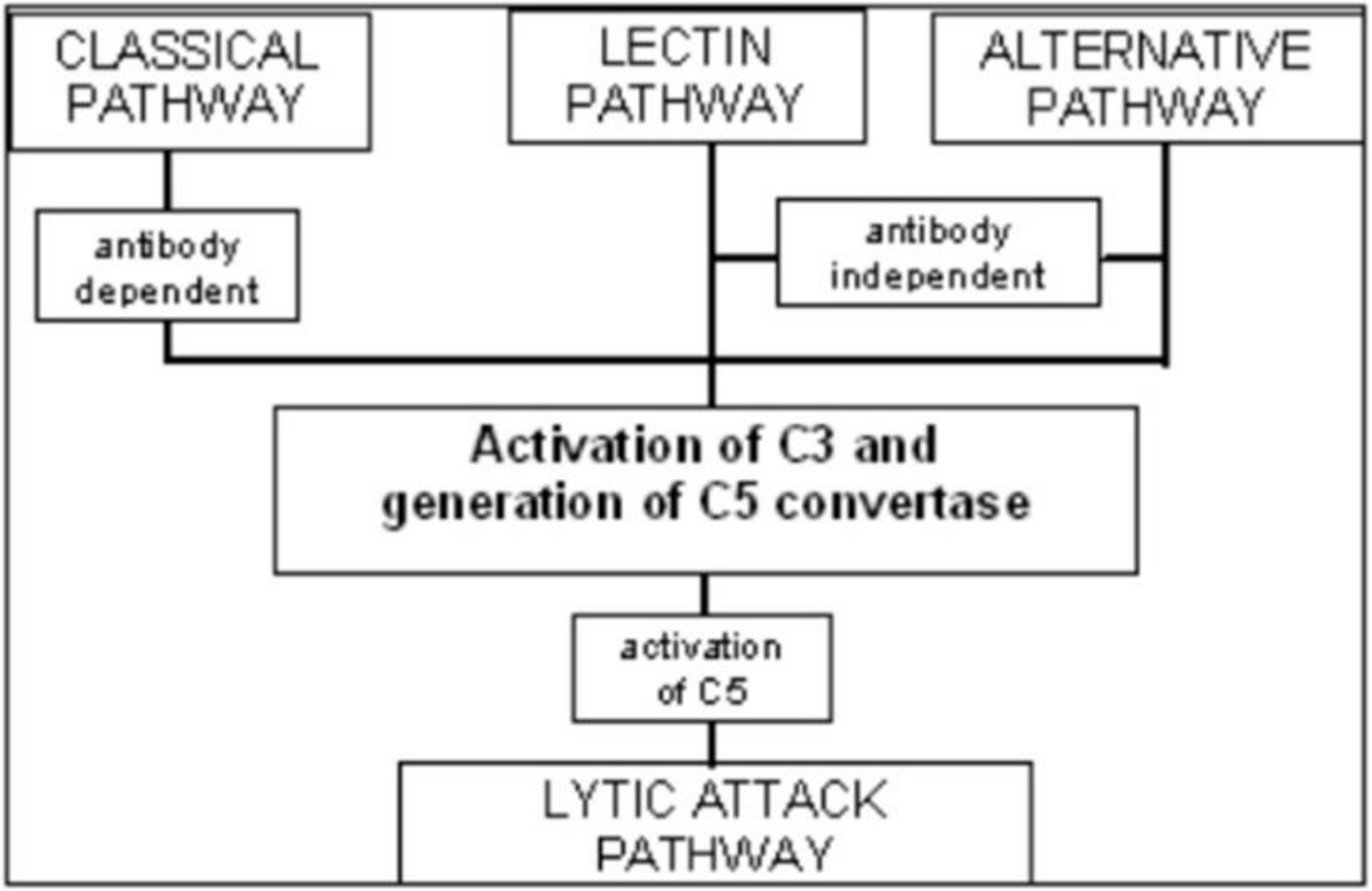
- The proteins of **the alternative pathway** were discovered later and are designated by different capital letters, for example **factor B and factor D.**

- Their **cleavage products** are also designated by the addition of **lower-case a and b**: thus, the large fragment of B is called Bb and the small fragment Ba.

Complement activation

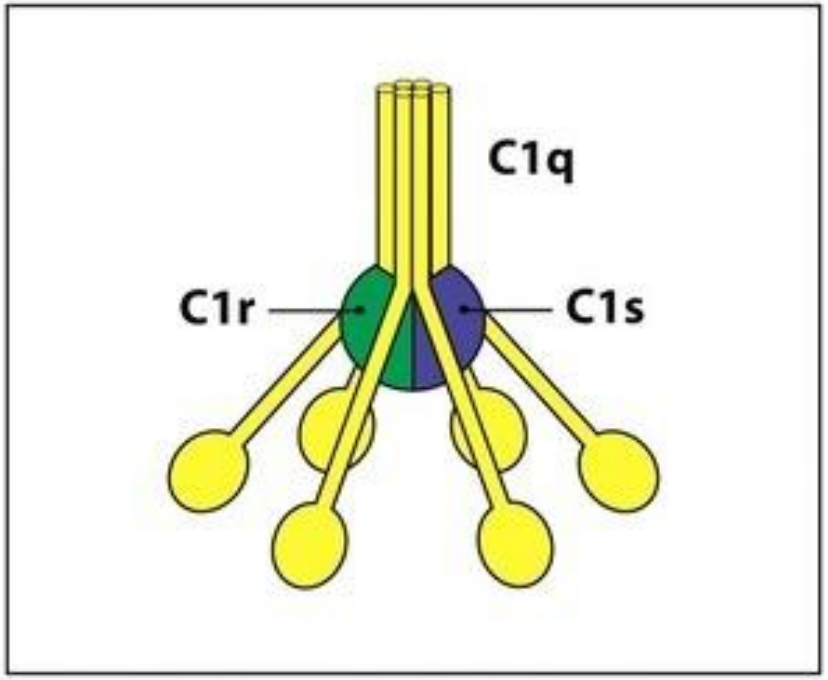
- The three pathways of complement activation are initiated in different ways.

Pathways of complement activation



Classical pathway

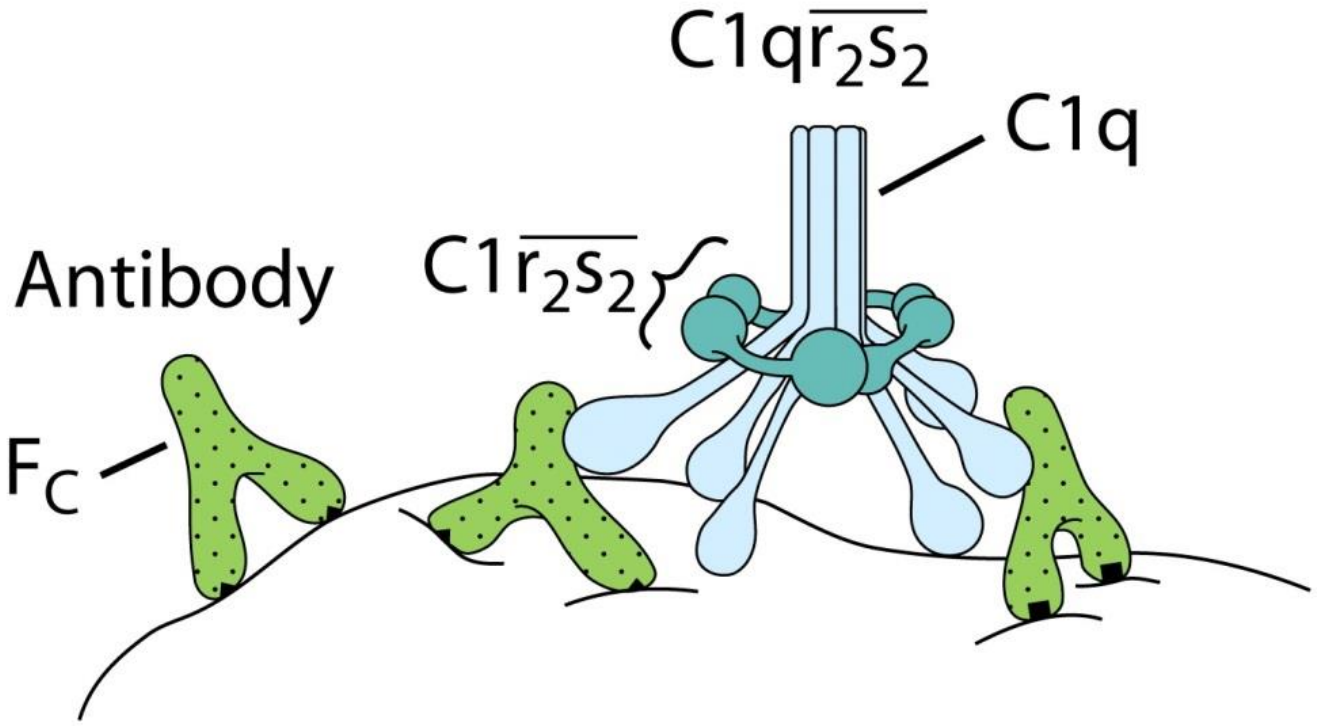
- The classical pathway is initiated by activation of the C1 complex

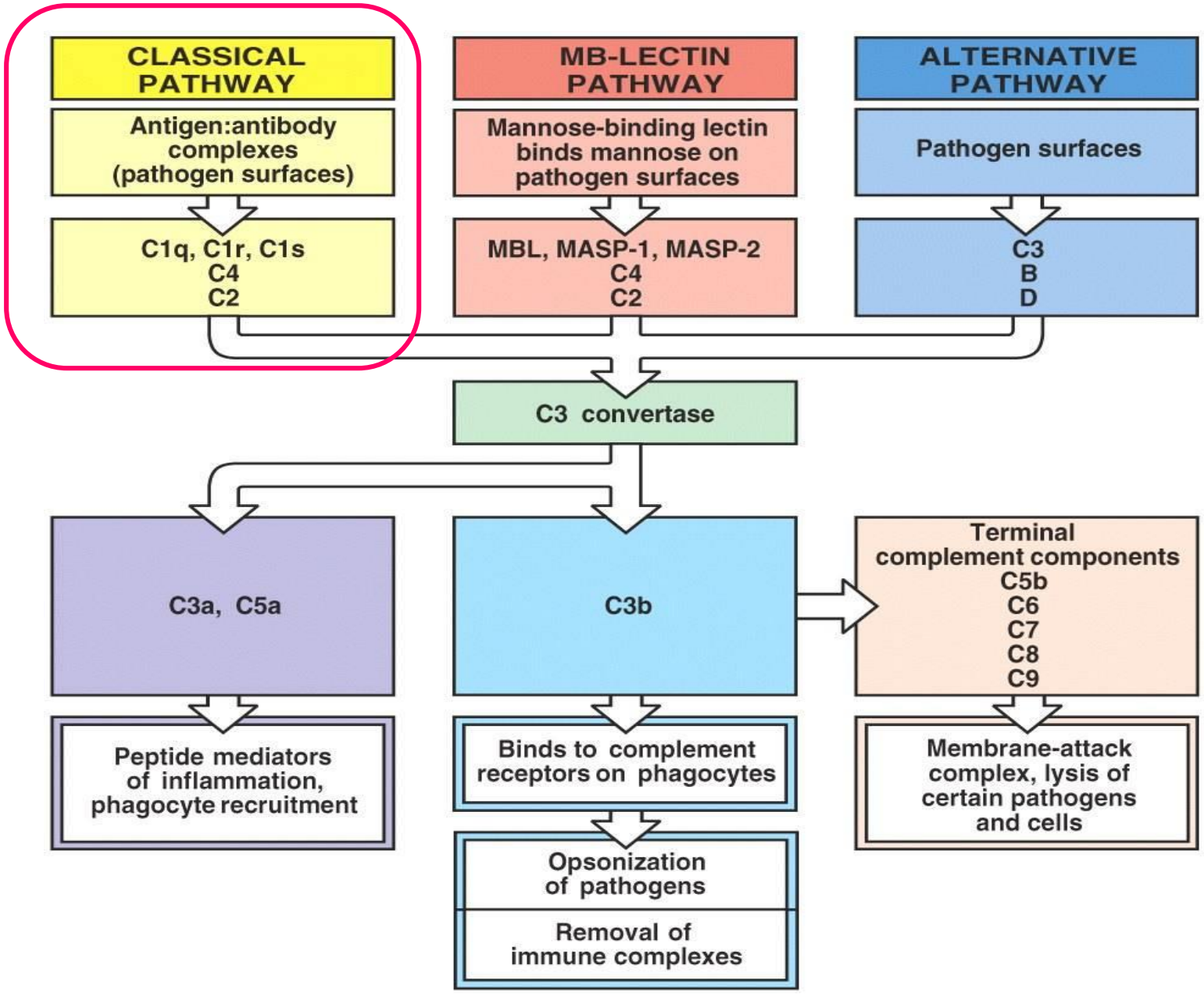


Distinct proteins that together comprise C1.

Classical pathway…

Classical pathway begins with ag-ab binding



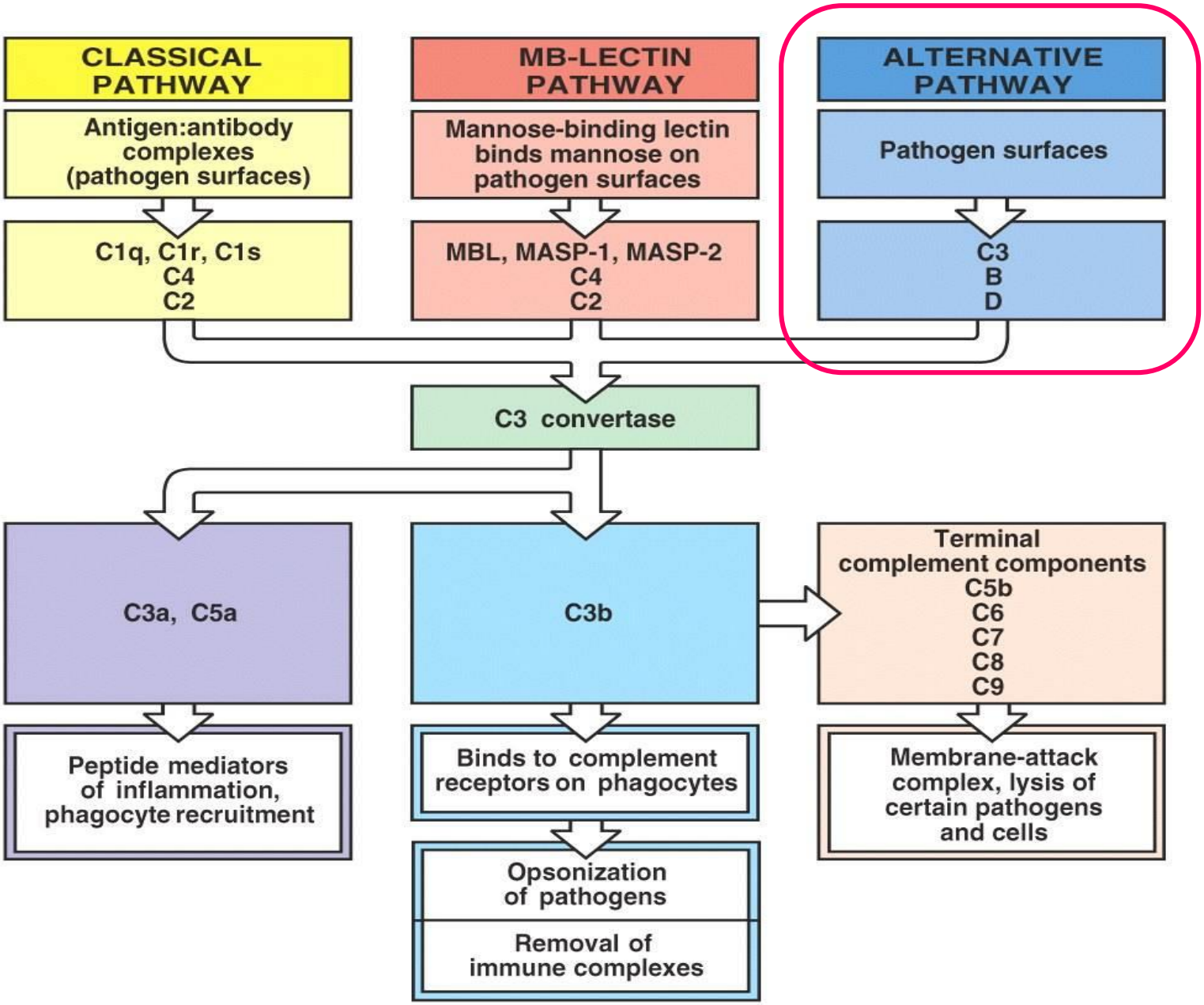

CLASSICAL PATHWAY
Antigen:antibody complexes (pathogen surfaces)
C1q, C1r, C1s
C4
C2
MB-LECTIN PATHWAY
Mannose-binding lectin binds mannose on pathogen surfaces
MBL, MASP-1, MASP-2
C4
C2
ALTERNATIVE PATHWAY
Pathogen surfaces
C3
B
D
C3 convertase
C3a, C5a
Peptide mediators of inflammation, phagocyte recruitment
C3b
Binds to complement receptors on phagocytes
Opsonization of pathogens
Removal of immune complexes
Terminal complement components
C5b
C6
C7
C8
C9
Membrane-attack complex, lysis of certain pathogens and cells

Alternative pathway

- **Doesn't need Ab**

- It is **initiated by cell-surface constituents** that are foreign to the host, e.g., bacterial cell wall.
- C1, C4 and C2 are not involved

- Four serum proteins, **C3, factor B, factor D, and properdin,** are involved in this pathway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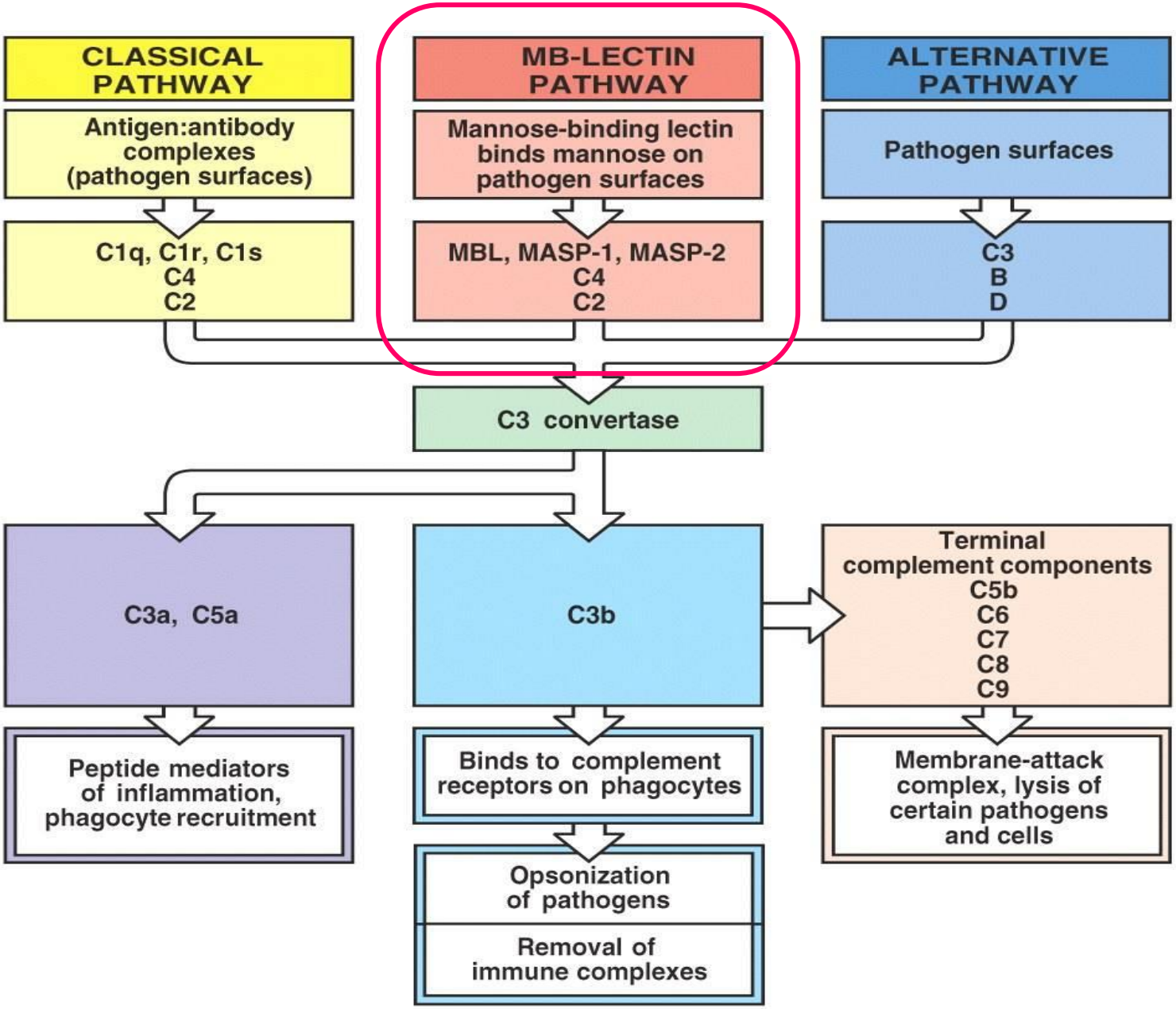
Lectin pathway

- The lectin pathway is initiated by **soluble carbohydrate-binding proteins—mannose-binding lectin** that bind to particular carbohydrate structures on microbial surfaces.

- Proteases associated with these recognition proteins **then trigger the cleavage** of complement proteins and activation of the pathway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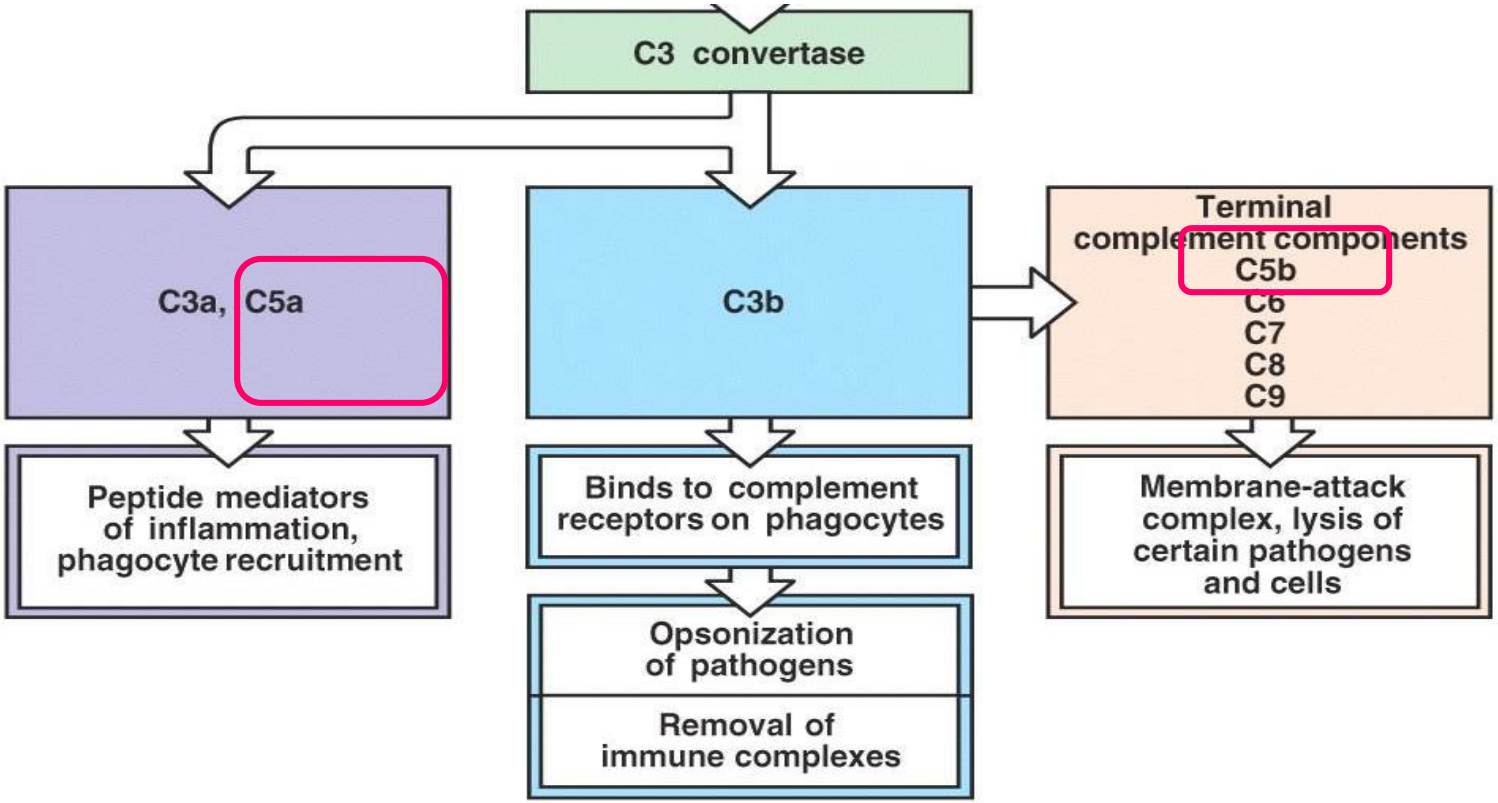
Membrane-attack complex, lysis of certain pathogens and cells

Complement activation

- **C3b** can also bind to the **C3 convertases** formed
- by the classical and lectin pathways, forming another multisubunit enzyme, a **C5 convertase**

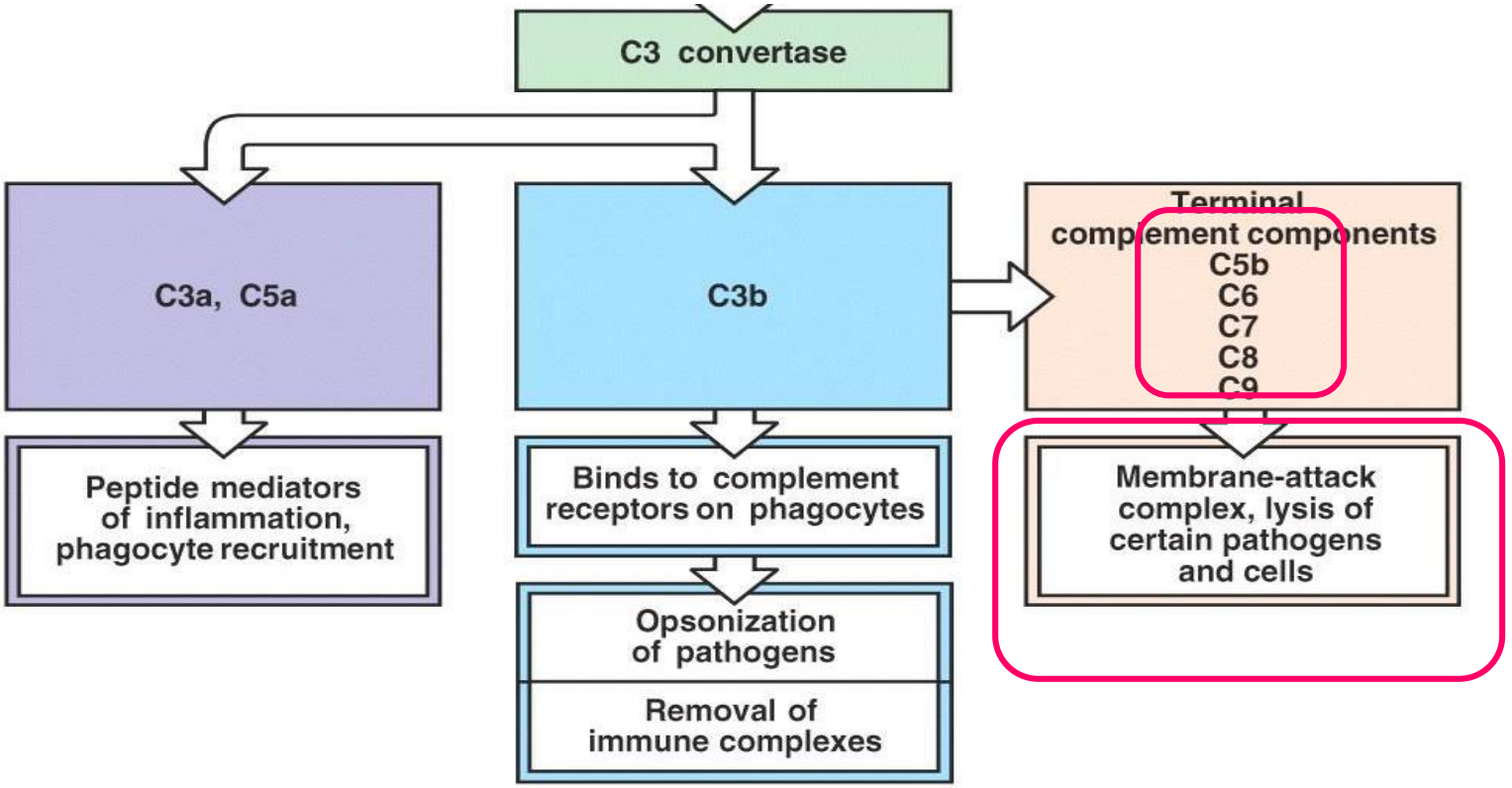
Complement activation

- C5 convertase cleaves C5, liberating the highly inflammatory peptide C5a and generating C5b.



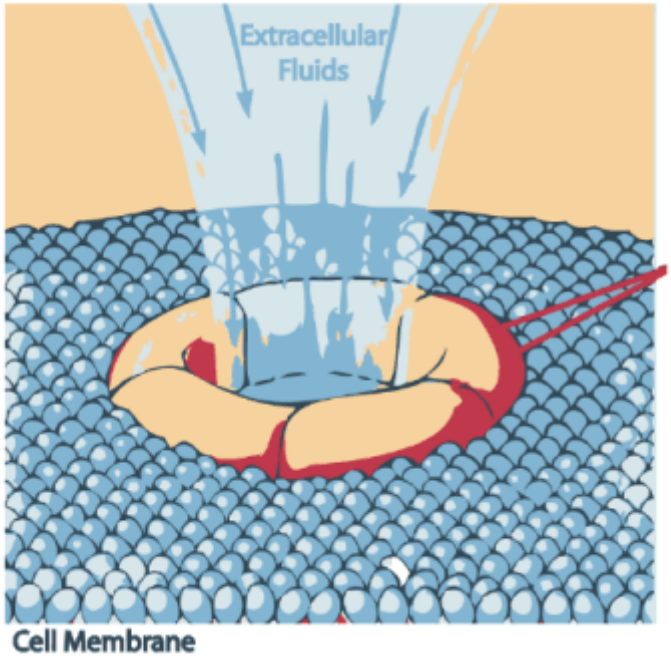
Complement activation

- **C5b** initiates the 'late' **events of complement activation**
- Set of complement proteins interact with C5b to form a membrane-attack complex on the pathogen surface, creating a pore in the cell membrane that leads to cell lysis.



Membrane attack complex

- Requires enzymatic **cleavage of C5**
- **Sequential binding** of C6, C7 (hydrophobic status), C8, C9 (up to 14 monomers)
- Formation of lytic 'plug' – **majority** of damage caused by **C9**



MAC forming pore on cell membrane

Functions of complement system

- Defends against pyogenic bacterial infections
- Bridges both the innate and adaptive immunity systems
- Assists in disposing of immune complexes etc
- C3b binds covalently to the microbial surface and acts as an opsonin

Functions of complement system

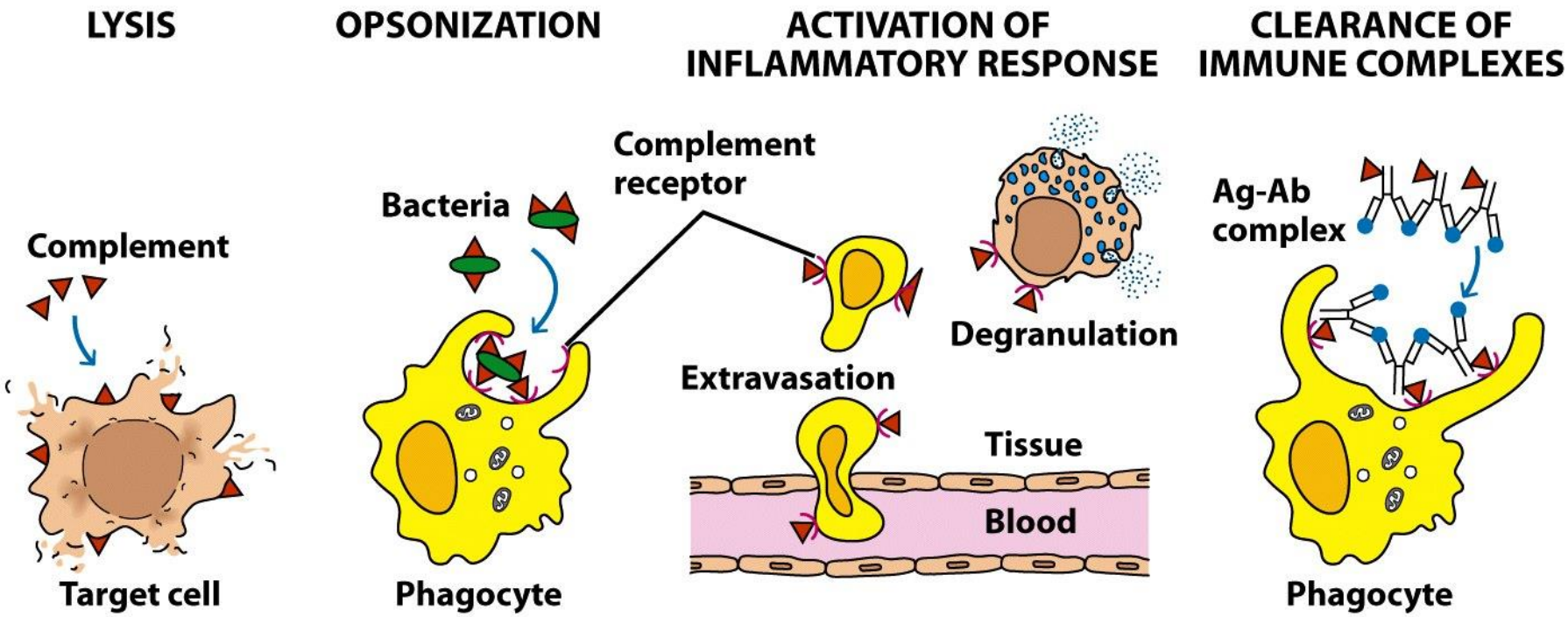


Figure 7-1
Kuby IMMUNOLOGY, Sixth Edition

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, and to activated MASP-2, removing it from MBL
C4-binding protein (C4BP)	Binds C4b, displacing C2a; cofactor for C4b cleavage by I
Complement receptor 1 (CR1)	Binds C4b, displacing C2a, 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 C2a 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 allogeneic cells. Widely expressed on membranes

Complement disorders

1. **Deficiency of early complement components** (C1, C4, C2) results in a symptom complex resembling collagen vascular disorders (e.g., systemic lupus erythematosus (SLE)] and increased susceptibility to pyogenic infections.

2. C3 deficiency results in **severe pyogenic infections**. Several patients have also had SLE and glomerulonephritis.

Complement disorders

3. **Deficiency of late complement components** (C5, C6, C7, C8) results in systemic Neisseria infections such as meningococcal sepsis and meningitis, and disseminated gonococcal infections.

4. **Abnormalities of the control proteins of the alternative pathway** (factor H, factor I, properdin) may result in recurrent infections.

5. **Deficiency of complement inhibitors** (C1 esterase inhibitor, carboxypeptidase N) leads to recurrent angioedema.

Assess the complement system

- CH50
- AH50