# Immunology Presentation: Complement system

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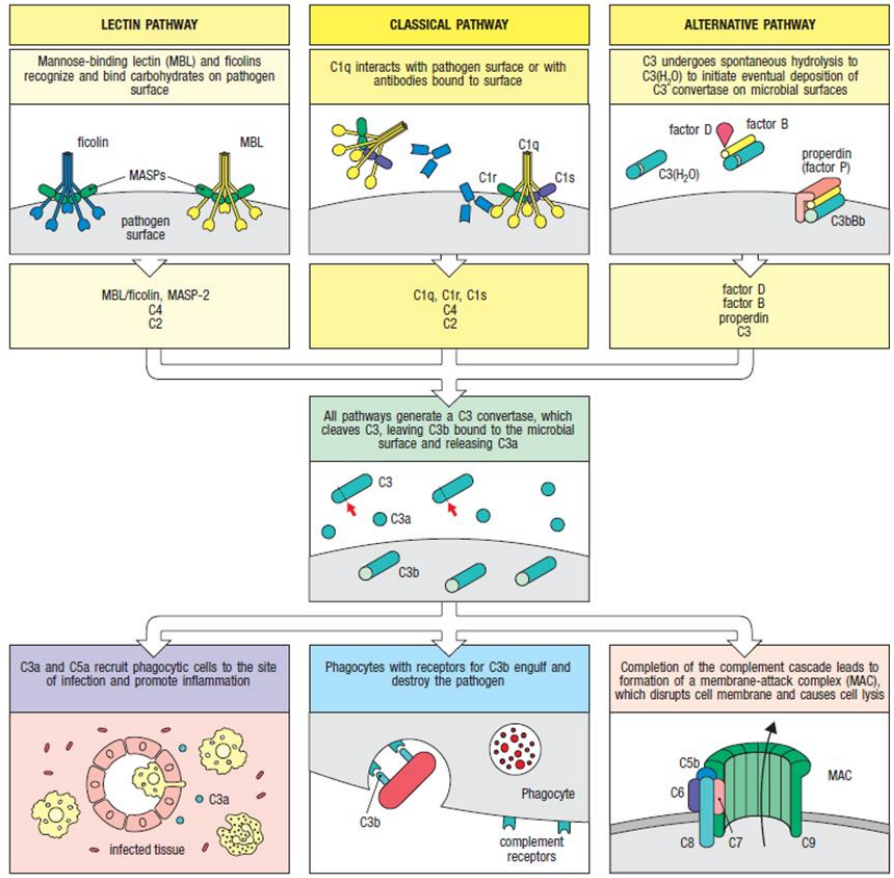
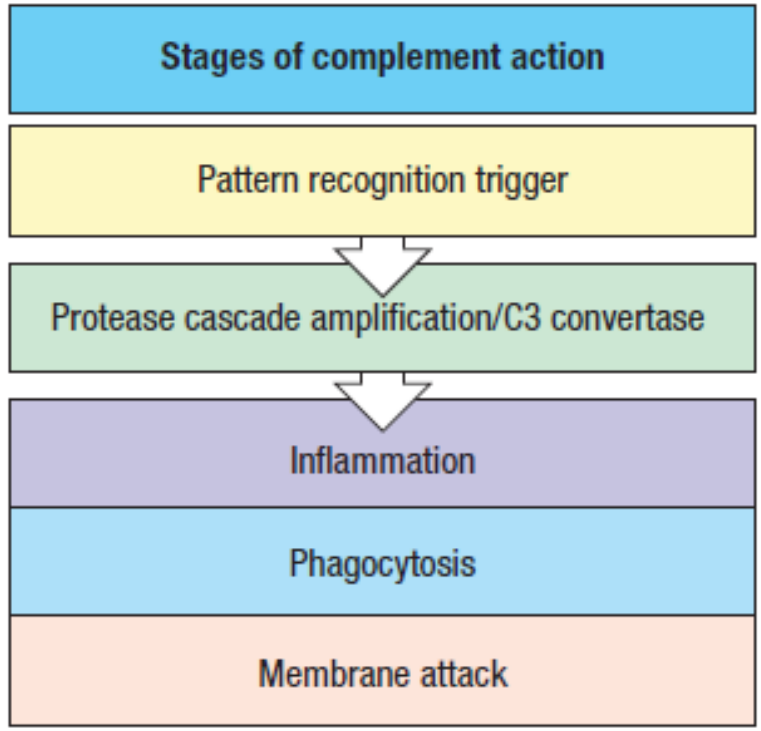
# Overview

- Complement system
- Initiation phase
    1) Classical
    2) Lectin
    3) Alternative
- Formation of C3/C5 convertase
- Terminal cascade
- Membrane attacking complex
- Complement components C3a and C5a
- Regulated activation of complement system



# Complement system - overview

- Part of the innate immune system
  - Activates when pathogen breaches host's epithelial barriers and initial antimicrobial
- Complement = collection of soluble proteins
  - present in blood and other body fluids
  - Proteins interact with each other
    - form different pathways

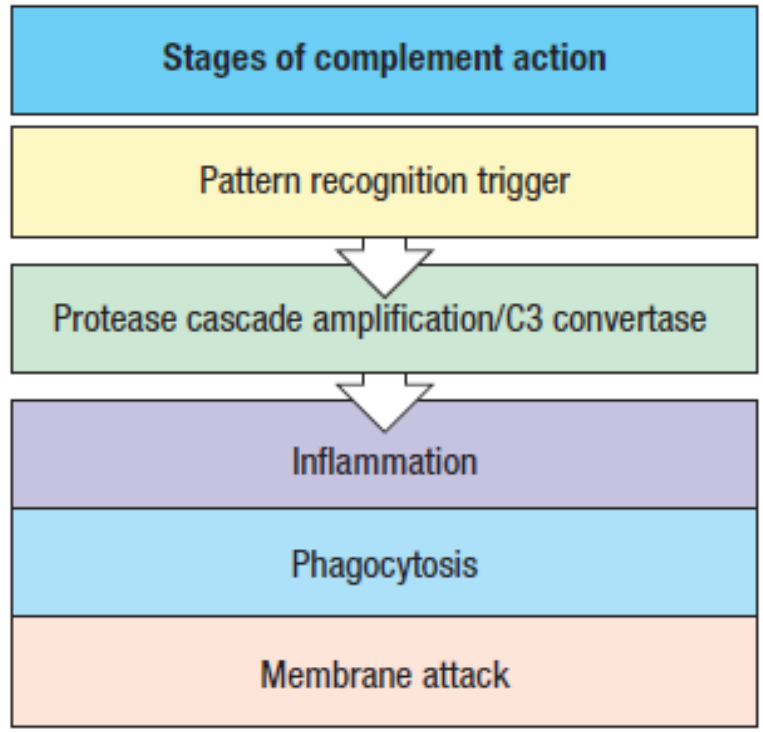


# Complement system - overview

- Complement Goal:

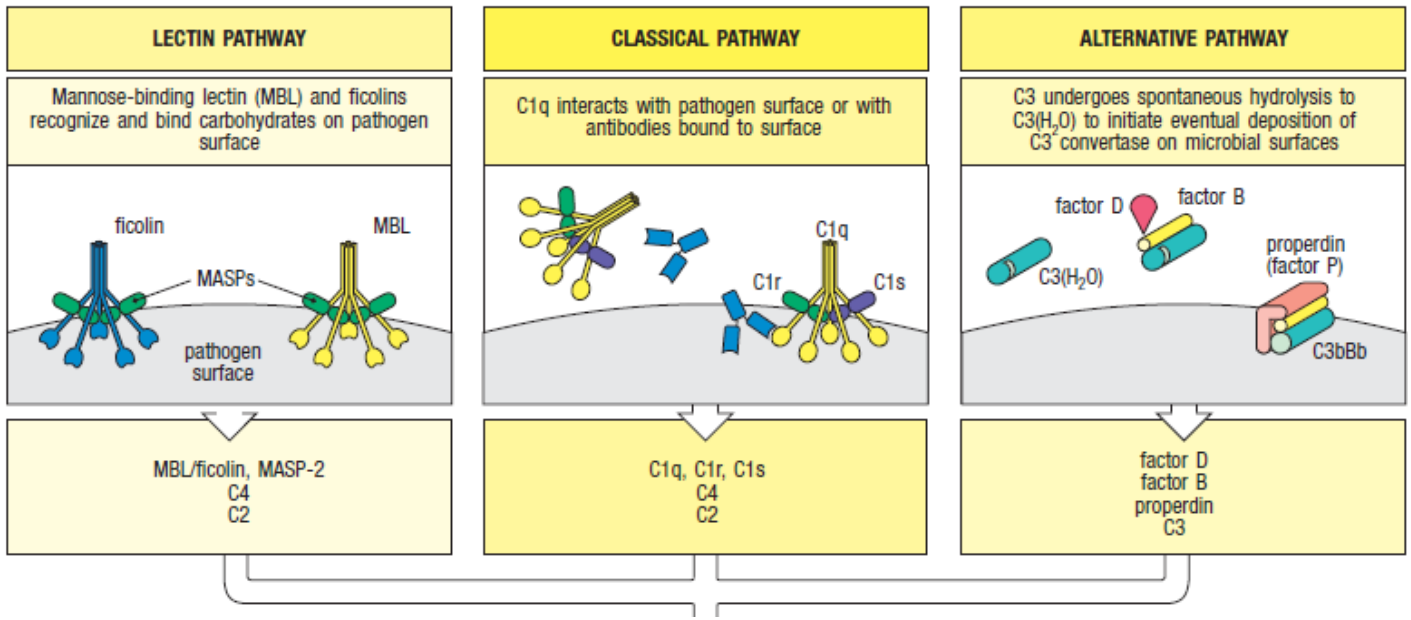
➢ activation of 3 distinct effector pathways

1) Inflammation
2) Phagocytosis
3) Membrane attack
    - ➢ helps eliminate pathogens



# Initiation phase

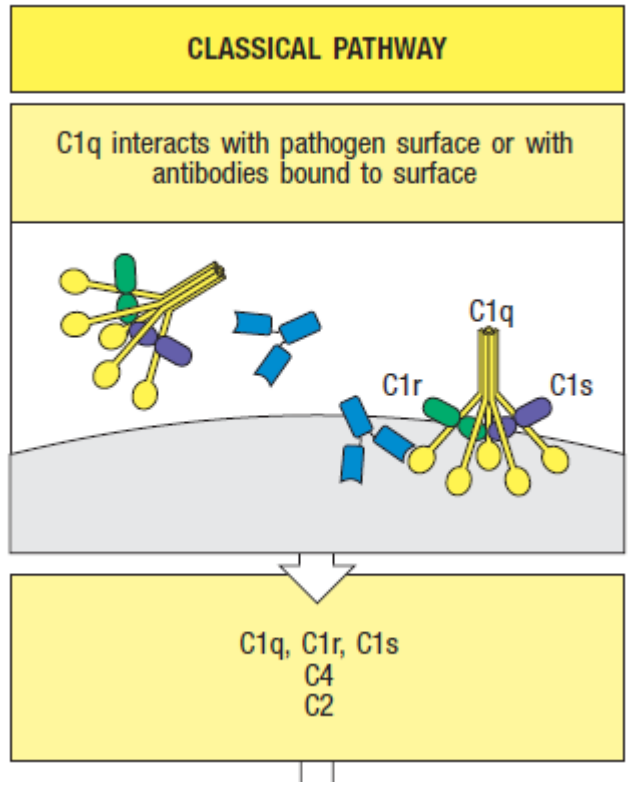
- Initiation phase of the complement system
  - ➢ 3 ways of activation
    1. Classical Pathway
    2. Lectin Pathway
    3. Alternative Pathway



# Initiation phase - Classical

1) Classical Pathway:

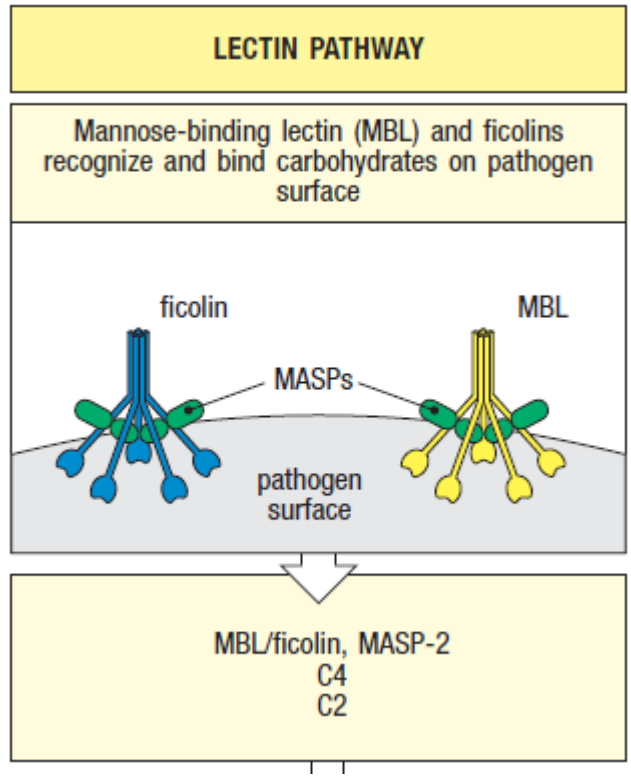
- triggered by binding of C1 complex to antibodies (IgG or IgM)
  - ➢ Antibodies bound to antigens on surface of pathogen
  - ➢ C1 complex consisting of C1q, C1r and C1s
- C1q recognizes the immune complexes
  - ➢ activates C1r and C1s
    - ➢ leads to cleavage of C4 and C2
      - ➢ C4b and C2a form C3 convertase C4b2a



# Initiation phase - Lectin

2) Lectin Pathway:

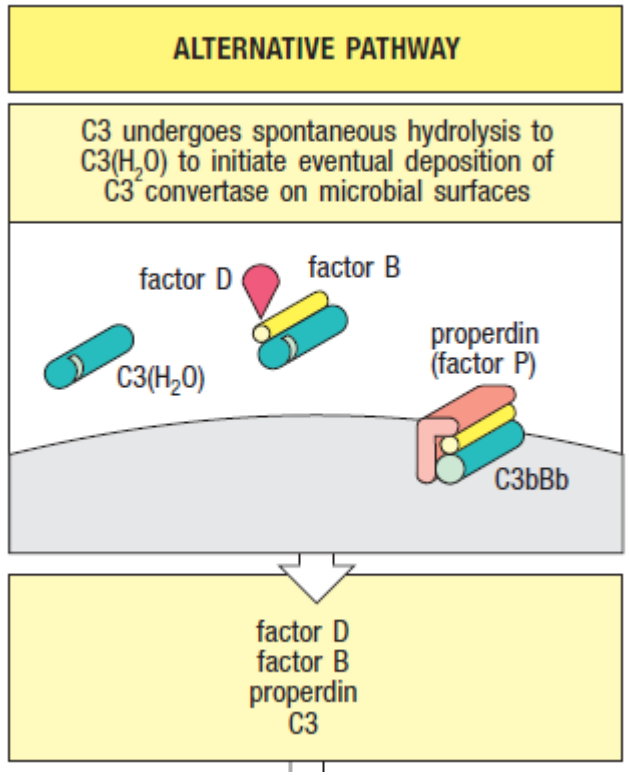
- Start: mannose-binding lectin (MBL) or ficolins
  - ➢ recognizes sugar structures on pathogen surface
- Lectins connected to MASP (MBL-associated serine proteases)
  - ➢ After recognition of pathogen
    - ➢ MASPs activates C4 and C2
      - ➢ formation of C3 convertase C4b2a



# Initiation phase - Alternative

3) Alternative Pathway:

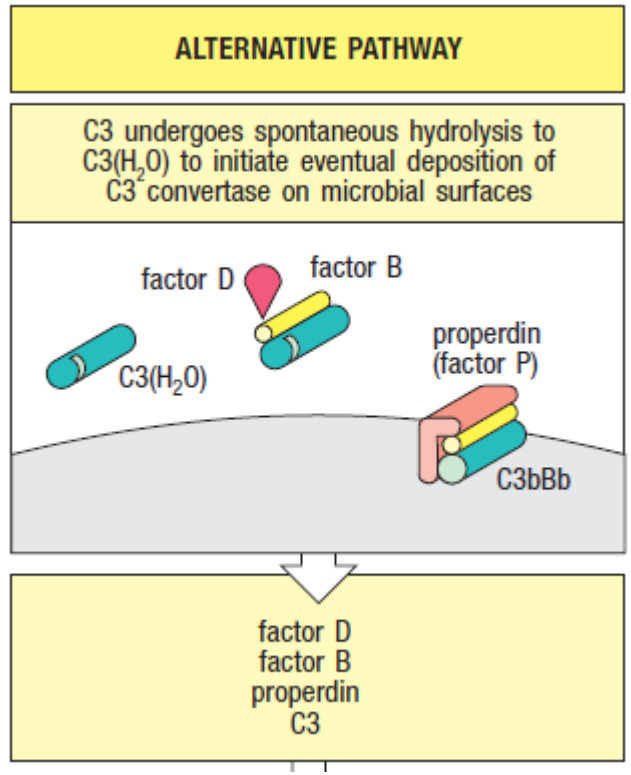
- Trigger: spontaneous hydrolysis of C3 in plasma
  - = “tickover”
  - Result: $C3(H_2O)$ can bind factor B
    - cleaved to Bb by factor D
      - $C3(H_2O)Bb$ formed
        - soluble C3 convertase



# Initiation phase

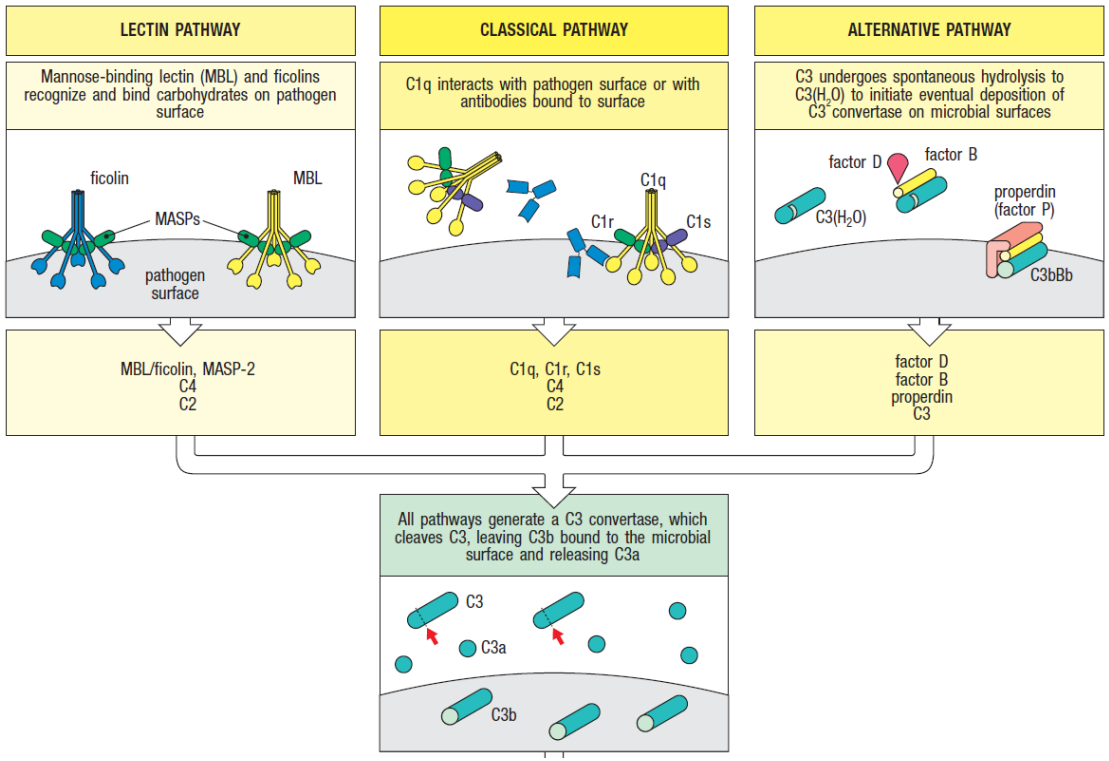
3) Alternative Pathway:

- C3b bound to pathogen surfaces
  - ➢ binds factor B
    - ➢ cleavage by D
      - ➢ formation of C3 convertase C3bBb



# Formation of C3 convertase

- All pathways lead to formation of C3 convertase
  - Classical & lectin pathway: C4b2a
  - Alternative pathway: C3bBb
- Goal: cleave C3 into C3a (Inflammation) and C3b (Opsonin)

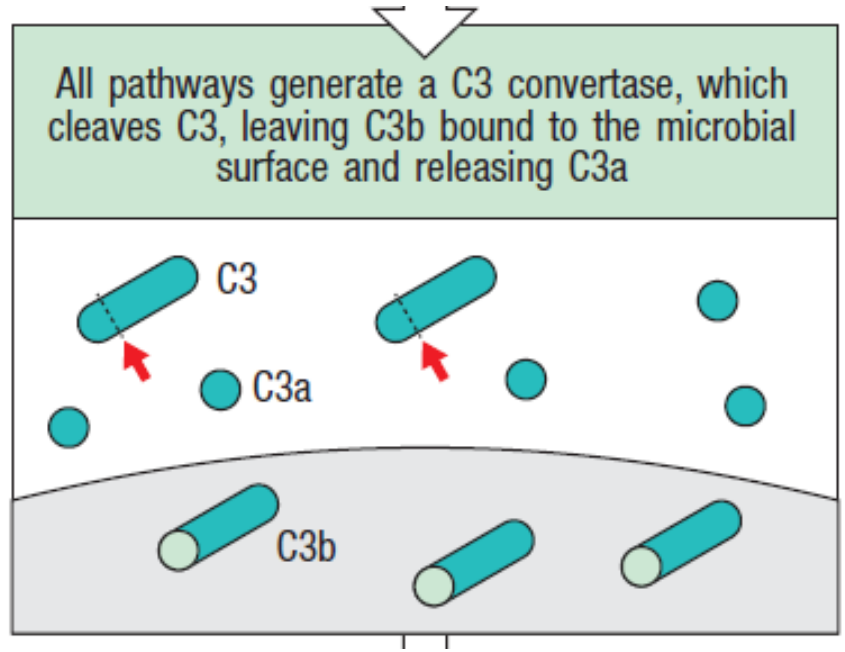



| C3 convertase | |
|---|---|
| Lectin pathway | C4b2a |
| Classical pathway | C4b2a |
| Alternative pathway | C3bBb |
| Fluid phase | $C3(H_2O)Bb$ |

# Formation of C5 convertase

- C3b is covalently bound to the pathogen surface
  - ➢ enhances opsonization
- C3b itself can also bind to C3 convertases
  - ➢ generates C5 convertase
    - ➢ C4b2a3b or $C3b_2Bb$
    - ➢ cleaves C5 to C5a and C5b

| C5 convertase | |
|---|---|
| Lectin pathway | C4b2a3b |
| Classical pathway | C4b2a3b |
| Alternative pathway | $C3b_2Bb$ |

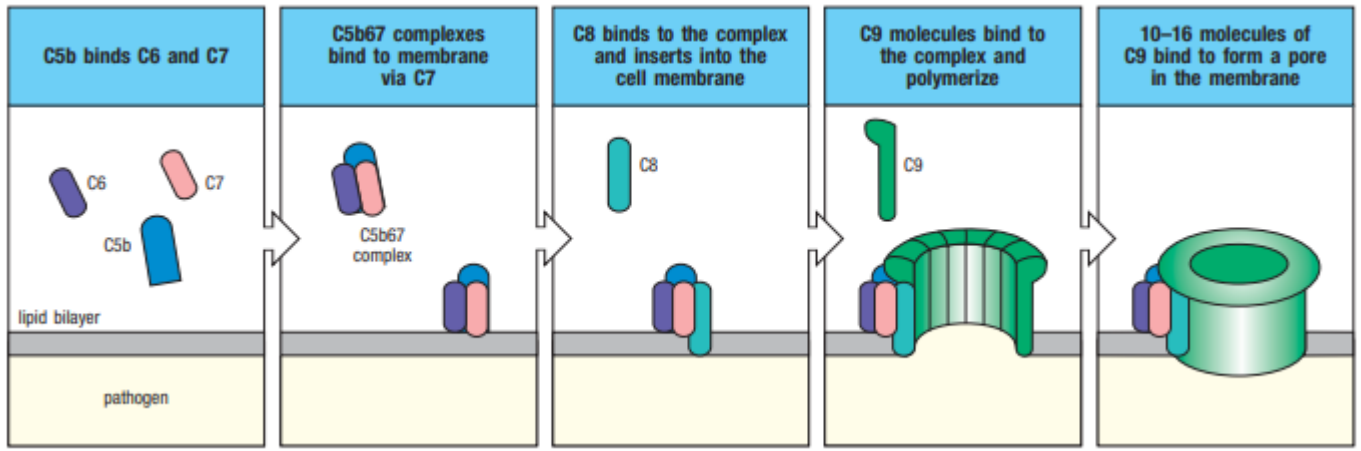


# Terminal cascade

- Terminal cascade: final phase in the activation cascade of the complement system
- Builds a pore-forming structure called <u>membrane-attack complex (MAC)</u>

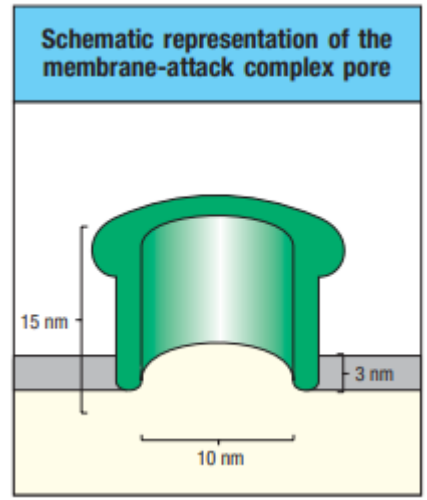
**The terminal complement components that form the membrane-attack complex**

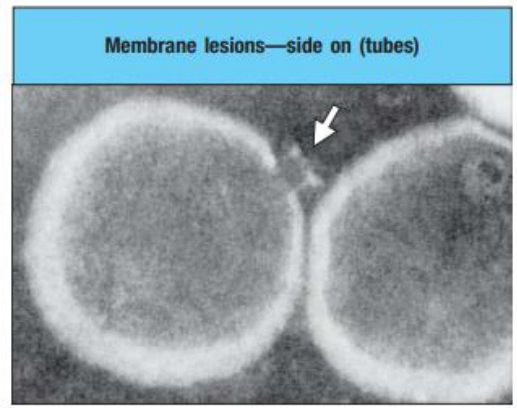
| Native protein | Active component | Function |
|---|---|---|
| C5 | C5a | Small peptide mediator of inflammation (high activity) |
| | C5b | Initiates assembly of the membrane-attack system |
| C6 | C6 | Binds C5b; forms acceptor for C7 |
| C7 | C7 | Binds C5b6; amphiphilic complex inserts into lipid bilayer |
| C8 | C8 | Binds C5b67; initiates C9 polymerization |
| C9 | $C9_n$ | Polymerizes to C5b678 to form a membrane-spanning channel, lysing the cell |



# Membrane-attack complex

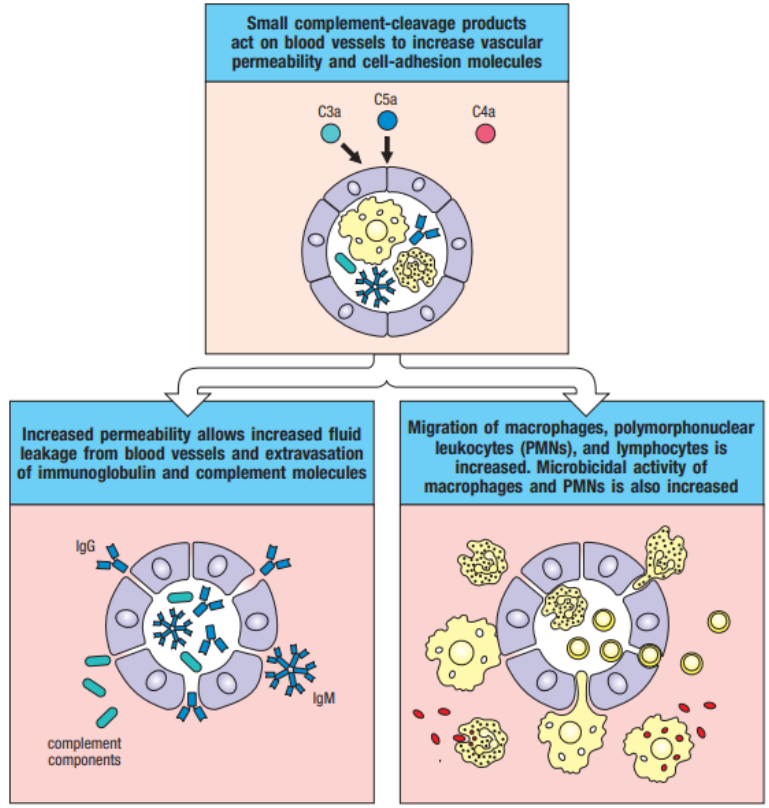
- Leads to:
  - loss of cellular homeostasis
  - disruption of the proton gradient across the membrane
  - penetration of enzymes – such as lysozymes
  - destruction of pathogens
- Impact of MAC may look dramatic but:
  - Real effects are less central
  - People with C5-C9 deficiencies are only more prone to *Neisseria* species



# Complement components C3a and C5a

- Induce local inflammatory response
- Effects on cells and tissues:
  - induce the contraction of smooth muscle
  - increase vascular permeability
  - activation of mast cells → release of:
    - Histamine (promotes inflammation)
    - TNF-α (a cytokine that attracts immune cells)
- High concentration of C3a and C5a
  - circulatory collapse
- Named <u>anaphylatoxins</u>



# Regulated activation of complement system - 1

- Activation of complement system is locally limited
  - largely confined to the surface on which it is initiated
  - Prevents attachment to healthy host cells
- Common for lectin and classical pathway regulation:
  - C3 activation on surface of pathogen, not on host-cell surfaces or in plasma
  - Acquired through C4 catalysation by ficolin or MLB complex
    - C4b cleavage product binds adjacent proteins or carbohydrates on pathogen surface
  - If C4b does not rapidly form bonds:
    - C4b irreversibly inactivated

# Regulated activation of complement system - 2

- Alternative pathway - Regulation:
  - Properdin acts as a positive regulator by stabilizing C3bBb on pathogen or damaged cell surfaces
  - Negative regulatory proteins protect healthy host cells by:
    - preventing formation of the C3 convertase
    - promoting rapid dissociation of existing convertases
  - Decay-accelerating factor (DAF/CD55)
  - Factor I
  - Factor H

**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 (C1q); MASP-2 (MBL) | Displaces C1r/s and MASP-2, inhibiting activation of C1q and MBL | Hereditary angiodema |
| C4-binding protein (C4BP) | C4b | Displaces C2a; cofactor for C4b cleavage by factor I | |
| CPN1 (Carboxypeptidase N) | C3a, C5a | Inactivates C3a and C5a | |
| Factor H | C3b | Displaces Bb, cofactor for factor I | Age-related macular degeneration, atypical hemolytic uremic syndrome |
| Factor I | C3b, C4b | Serine protease, cleaves C3b and C4b | Low C3 levels, hemolytic uremic syndrome |
| Protein S | C5b67 complex | Inhibits MAC formation | |

**Membrane-bound factors regulating complement**

| Name | Ligand/ binding factor | Action | Pathology if defective |
|---|---|---|---|
| CRIg | C3b, iC3b, C3c | 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 protein (MCP, CD46) | C3b, C4b | Cofactor for factor I | Atypical hemolytic anemia |
| Protectin (CD59) | C8 | Inhibits MAC formation | Paroxysmal nocturnal hemoglobinuria |

# Regulated activation of complement system - 3

- Classical pathway - Regulation:
  - C2 cleavage by C1s requires binding to C4b, ensuring activation occurs only on the pathogen surface
  - active C2a serine protease confined to pathogen surface, remains associated with C4b -> forming the C3 convertase C4b2a
  - C3b inactivated by hydrolysis unless a rapid covalent bond is formed with thioester

| Regulatory proteins of the classical and alternative pathways | | | |
|---|---|---|---|
| **Soluble factors regulating complement** | | | |
| **Name** | **Ligand/ binding factor** | **Action** | **Pathology if defective** |
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# Regulated activation of complement system - 4

- Complement activation initiated by antibodies bound to pathogens is specific to the classical pathway
- Antibody that is chemically cross-linked to complement is likely the most efficient trigger for phagocytosis

# References

1. Janeway`s IMMUNOBIOLOGY 9th Edition by Kenneth Murphy & Casey Weaver

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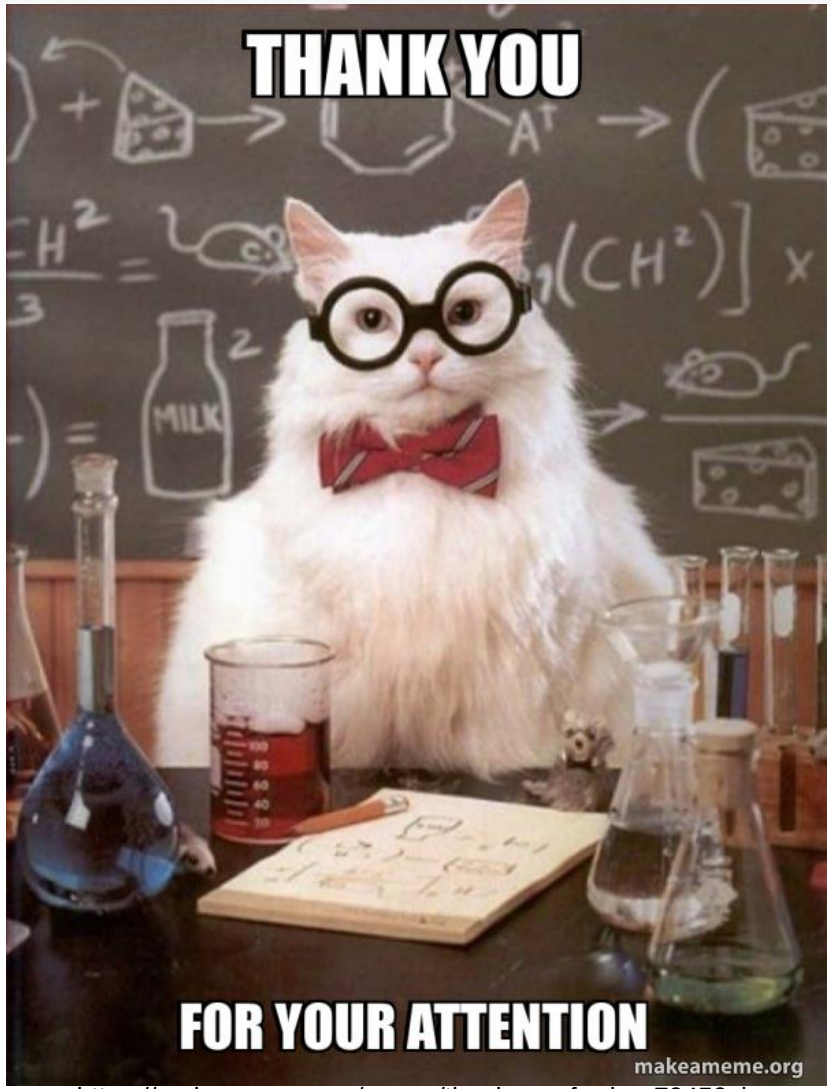


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