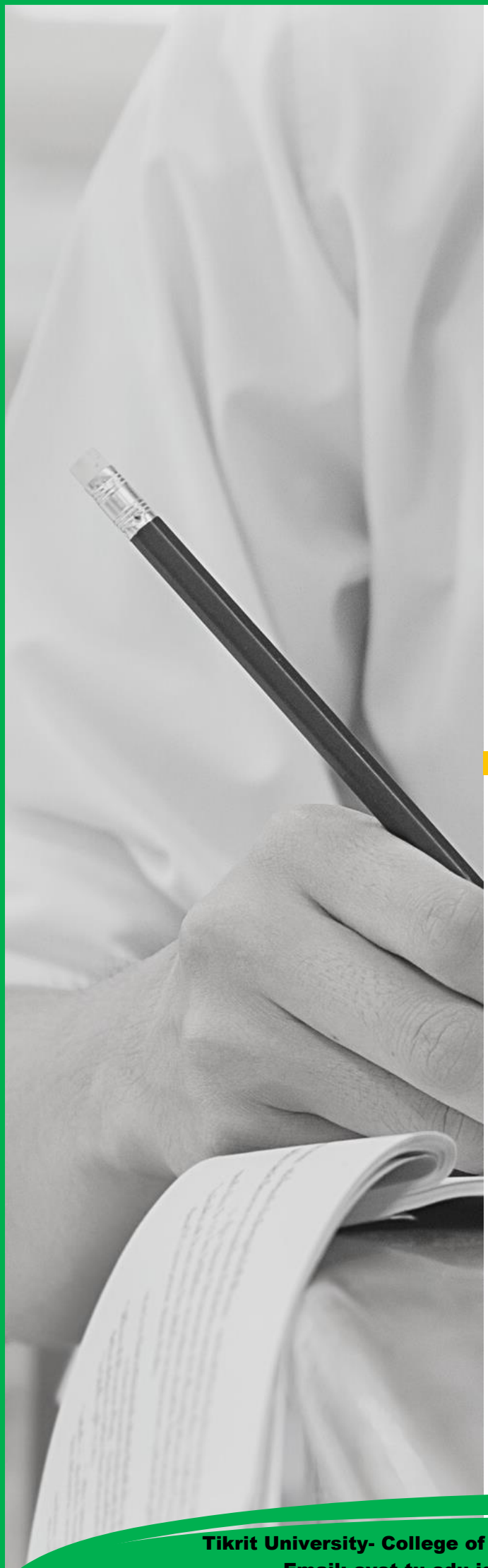

Tikrit University
College of Veterinary Medicine

Lecture 6: Humoral Factors: The Complement System

Subject name: Immunology (Theoretical)
Subject year: Third Stage / 3rd Year
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Lecturers link

Humoral Factors: The Complement System

1. The **complement system** is a major effector mechanism of **humoral immunity** and also plays an essential role in **innate immunity**. It consists of a group of **heat-labile plasma proteins** (inactivated at 56°C for 30 minutes) that circulate in the blood in an **inactive (zymogen / proenzyme) form** and become activated in response to microbial infection.
2. Most complement proteins are produced in the **liver**, and they account for about **10% of the serum globulin fraction**. The complement system includes **over 30 proteins**, identified either by numbers (C1–C9) or by letters (B, D, P, etc.).

Once activated, complement proteins undergo **sequential enzymatic cleavage**, generating fragments:

- Larger fragments are labeled with **"b"** (e.g., **C3b**) and usually bind to microbial surfaces.
- Smaller fragments are labeled with **"a"** (e.g., **C3a**) and often act as inflammatory mediators.

Activated complement leads to:

- **Opsonization** (enhanced phagocytosis)
- **Chemotaxis** of immune cells
- **Membrane attack and lysis of microbes**

Pathways of Complement Activation

There are **three main pathways** by which complement can be activated:

1. Classical Pathway

Triggered when **antibodies (IgG or IgM)** bind to antigens on a pathogen surface.

Steps:

1. **Activation Trigger**

   The classical complement pathway is activated when **specific antibodies (IgG or IgM)** bind to antigens on the surface of a pathogen
2. **C1 Complex Composition**

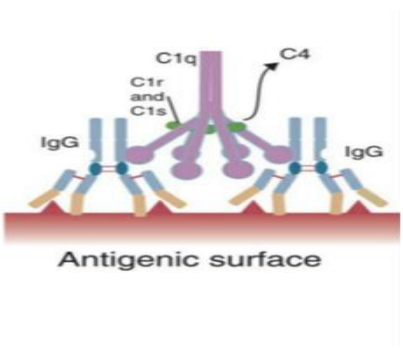
   The first component involved is the **C1 complex**, which consists of **three subunits**:

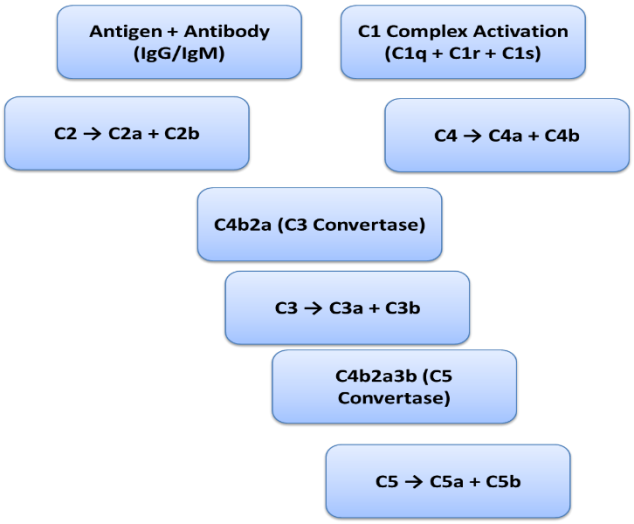
   C1q, C1r, and C1s.
3. **Role of C1q**

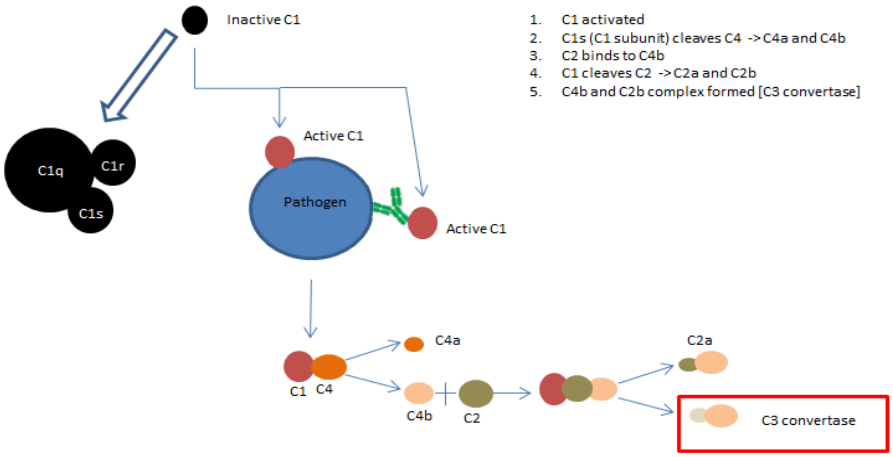
   C1q has a structure resembling an **umbrella**, with **six globular head regions** attached to a central stalk.

   These globular heads **bind to the Fc region** of **IgG or IgM** antibodies once they are attached to an antigen.
4. **C1r and C1s are serine esterases containing two molecules of each and located between C1q strands.**
5. **5. Binding of C1q to two or more Fc regions leads to enzymatic activation of C1r that cleaves and activates C1s**
6. This binding activates **C1r** and **C1s**, initiating the classical pathway cascade.
7. Activated C1s cleaves **C4 → C4a + C4b**.

   C4b binds to the surface and then binds **C2**.
8. C2 is cleaved forming **C4b2a**, the **C3 Convertase**.
9. C3 Convertase cleaves **C3 → C3a + C3b**.
10. C3b associates with C4b2a to form **C5 Convertase (C4b2a3b)**.
11. **C5 is cleaved and the pathway proceeds to membrane attack complex formation**.







2. Alternative Pathway

Spontaneous Activation of C3 (Alternative Pathway Initiation)

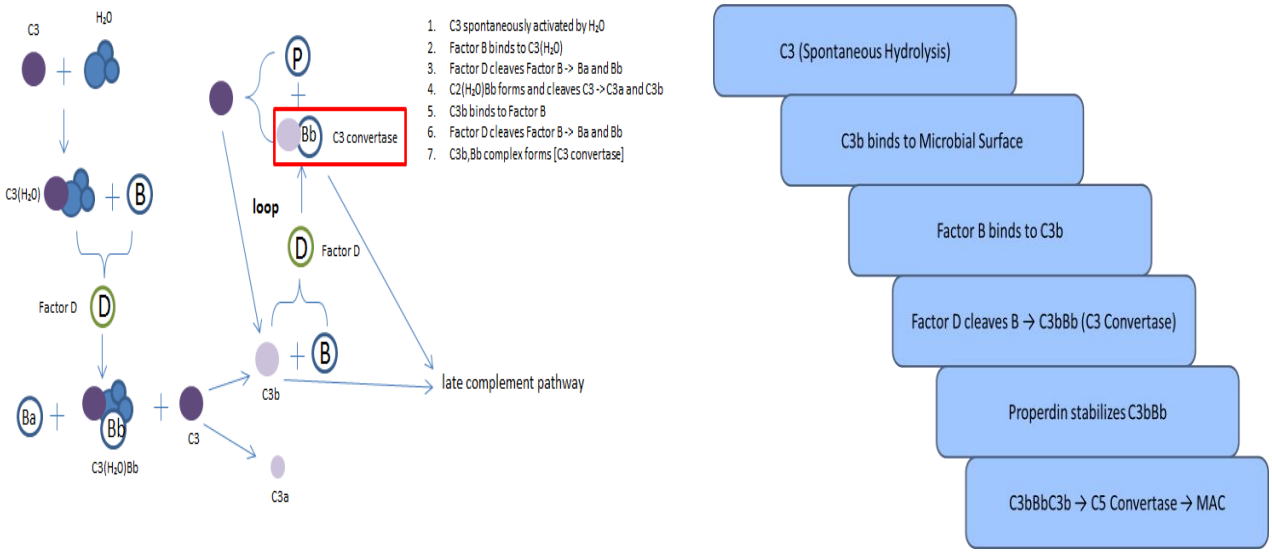
1. This pathway **does not require antibodies**.
2. It is activated **directly by** nearby **foreign surfaces**
3. **Main Components:** C3b, Factor B, Factor D, Properdin.

- Under normal physiological conditions, a small amount of **C3** undergoes **spontaneous hydrolysis**, producing **C3a** and **C3b**.
- The newly formed **C3b** contains a **reactive thioester bond**, enabling it to **covalently attach** to **nearby foreign surfaces** (e.g., bacterial and fungal polysaccharides, LPS, viral particles, aggregated IgA, toxins).

- This attachment occurs **without the need for receptors**.
- Once bound to a foreign surface, **C3b becomes stabilized** and **initiates of the Alternative Pathway**.
- **C3b that binds to host cells** is rapidly **inactivated by regulatory proteins**, preventing **self-tissue damage**.

Steps of the Alternative Pathway

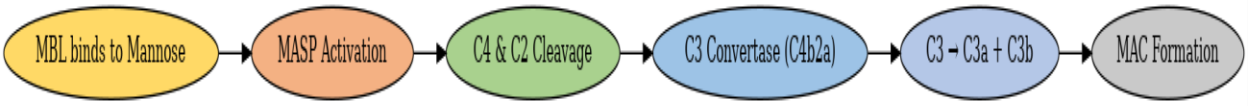
1. **Spontaneous cleavage** of C3 → **C3a + C3b**.
2. **C3b binds** to nearby **foreign surfaces**.
3. **Factor B** binds to C3b and is **cleaved by Factor D → C3bBb (C3 Convertase) has a half-life of only 5 minutes**
4. **Properdin** binds and **stabilizes C3bBb**, enhancing activity.
5. Addition of another **C3b** forms **C3bBbC3b (C5 Convertase) → initiates MAC formation**.

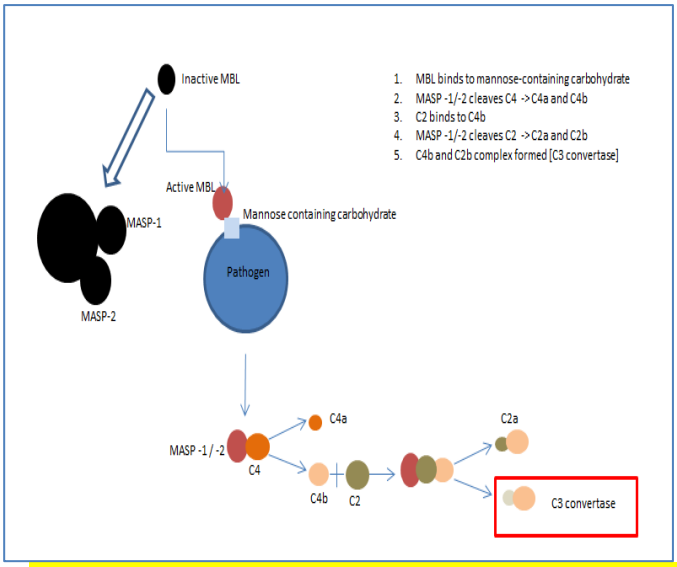


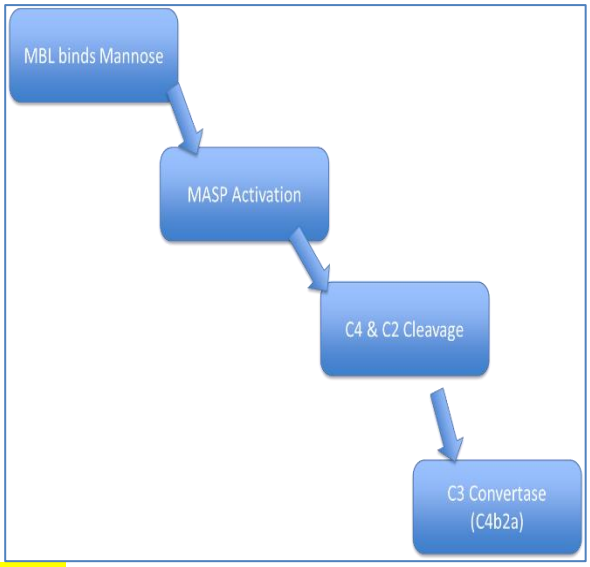
3. Lectin Pathway

- The lectin pathway is activated by lectins, which are proteins that recognize and bind to specific carbohydrate structures on microbial surfaces.

- A key lectin involved in this pathway is **Mannose-Binding Lectin (MBL), which functions similarly to C1q in the classical pathway**.
- When MBL binds to mannose residues on the pathogen surface, it activates enzymes called MBL-Associated Serine Proteases (MASP). These MASP enzymes act like scissors
- MASP enzymes cleave:
    - C4 → C4a + C4b
    - C2 → C2a + C2b
- C4b and C2a combine to form the C3 convertase (C4b2a), the same enzyme formed in the classical pathway.
- The pathway then proceeds to generate C5 convertase and ultimately forms the Membrane Attack Complex (MAC), similar to both the classical and alternative pathways.





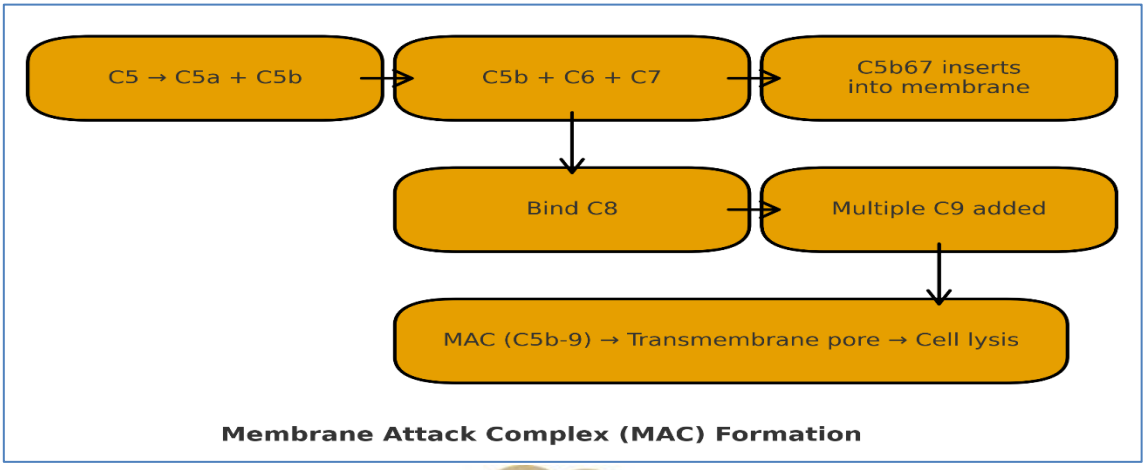


Membrane Attack Complex (MAC) Formation

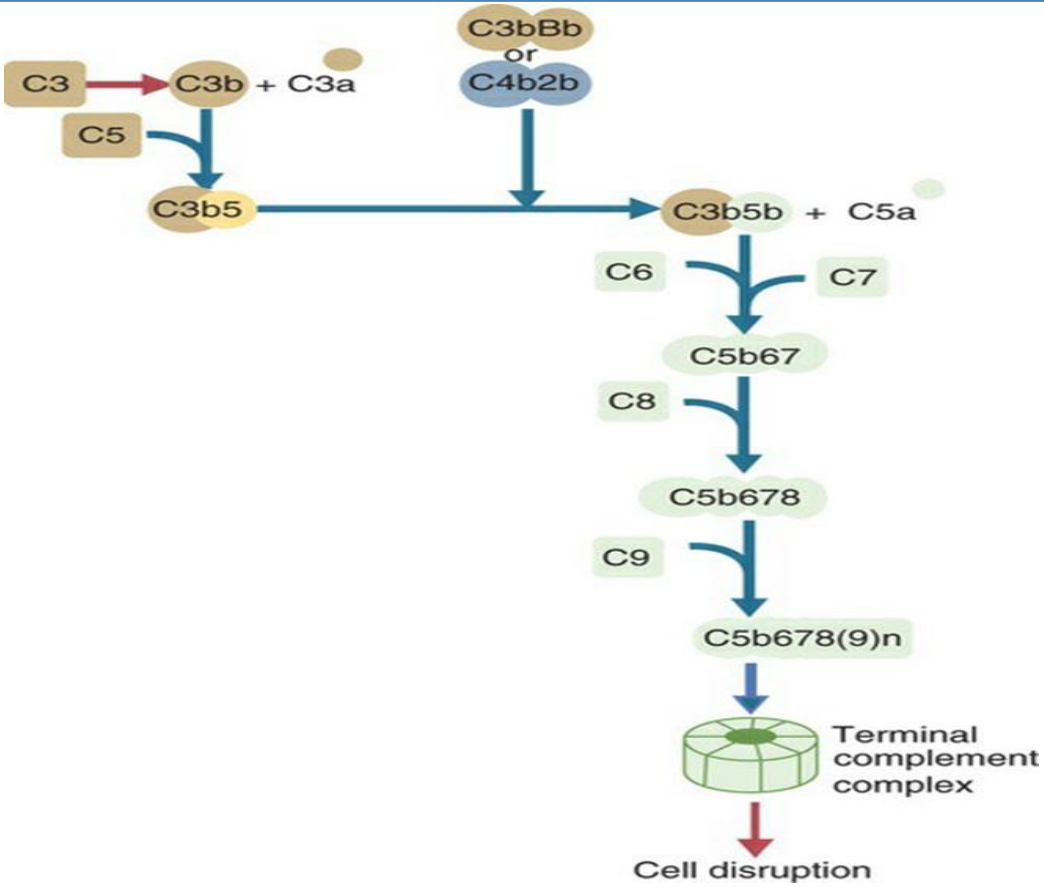
The final stage of all pathways leads to **cell lysis**.

- **C5 Convertase** (from any pathway: Classical **C4b2aC3b**, Alternative **C3bBbC3b**, or Lectin **C4b2aC3b**) cleaves **C5** into **C5a** and **C5b**.
- **C5a** is released and acts as a **potent inflammatory mediator** (anaphylatoxin & chemotactic factor).
- **C5b** remains and binds sequentially to **C6** and **C7**, forming the **C5b67 complex**.
- **C5b67** separates from C3b and **inserts into the lipid bilayer** of the target cell membrane.
- Once embedded, it binds **C8**, which initiates membrane penetration.
- Multiple **C9 molecules** (≈12–18) polymerize around the complex to form **C5b-9**, known as the **Membrane Attack Complex (MAC)**.

- **MAC** forms a **transmembrane pore**, causing **loss of osmotic balance → water influx → cell lysis** and death of the target microbe.



Membrane Attack Complex (MAC) Formation



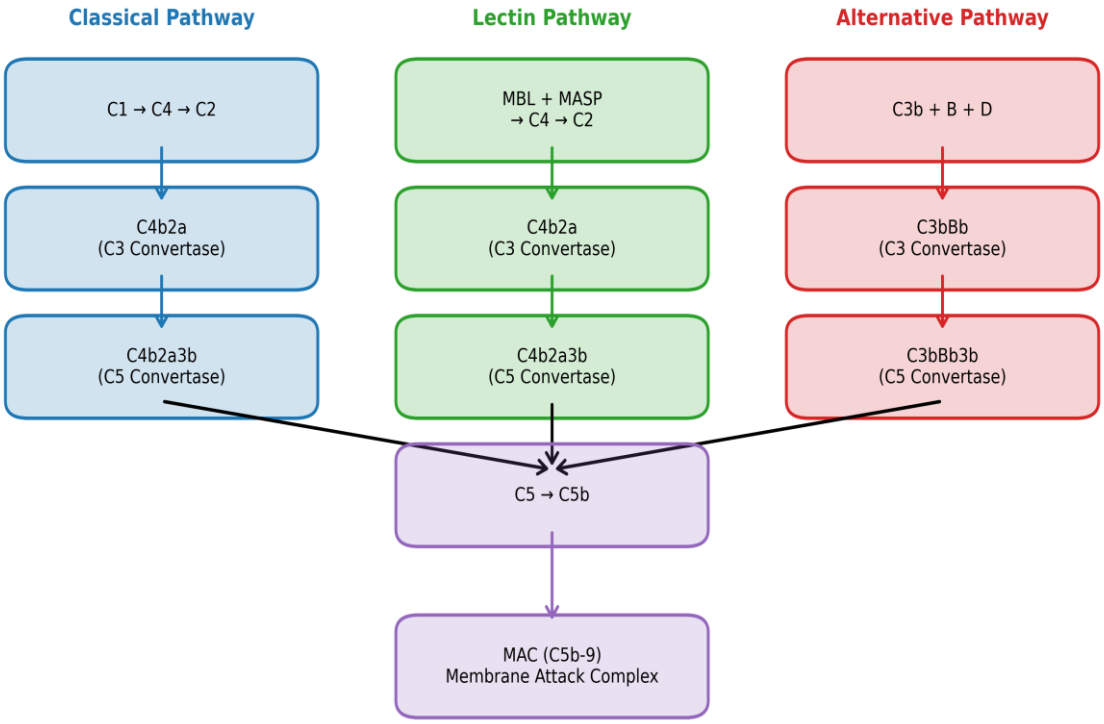
Major Functions of the Complement System

Function	Key Component(s)	Effect

Chemotaxis	C5a	Attracts neutrophils and macrophages to infection sites.
Inflammation	**C3a, C4a, C5a**	Induce mast cell degranulation → histamine release → vasodilation.
Opsonization	**C3b**	Enhances phagocytosis by binding microbes and interacting with receptors on phagocytes.
Cytolysis	**MAC (C5b-9)**	Creates membrane pores → cell lysis (especially bacteria).
Enhanced Antibody Response	**C3b on B-cell receptors**	Increases B-cell activation and antibody production.

Summary Comparison of Pathways

Feature	Classical	Alternative	Lectin
Trigger	Antigen–antibody complex	Microbial surface molecules	Mannose residues on pathogens
First Key Component	C1q	C3b + Factor B	MBL + MASPs
C3 Convertase Formed	C4b2a	C3bBb	C4b2a
Antibody Required?	Yes	No	No



- **Classical Pathway** starts with *antibody binding (C1 activation)*
- **Lectin Pathway** starts with *MBL binding to mannose (MASP activation)*
- **Alternative Pathway** starts with *spontaneous C3 hydrolysis + Factor B & D*
- All three generate **C3 Convertases**, then **C5 Convertases**, and finally lead to:
- **→ C5b-9 = MAC → Microbial Cell Lysis**