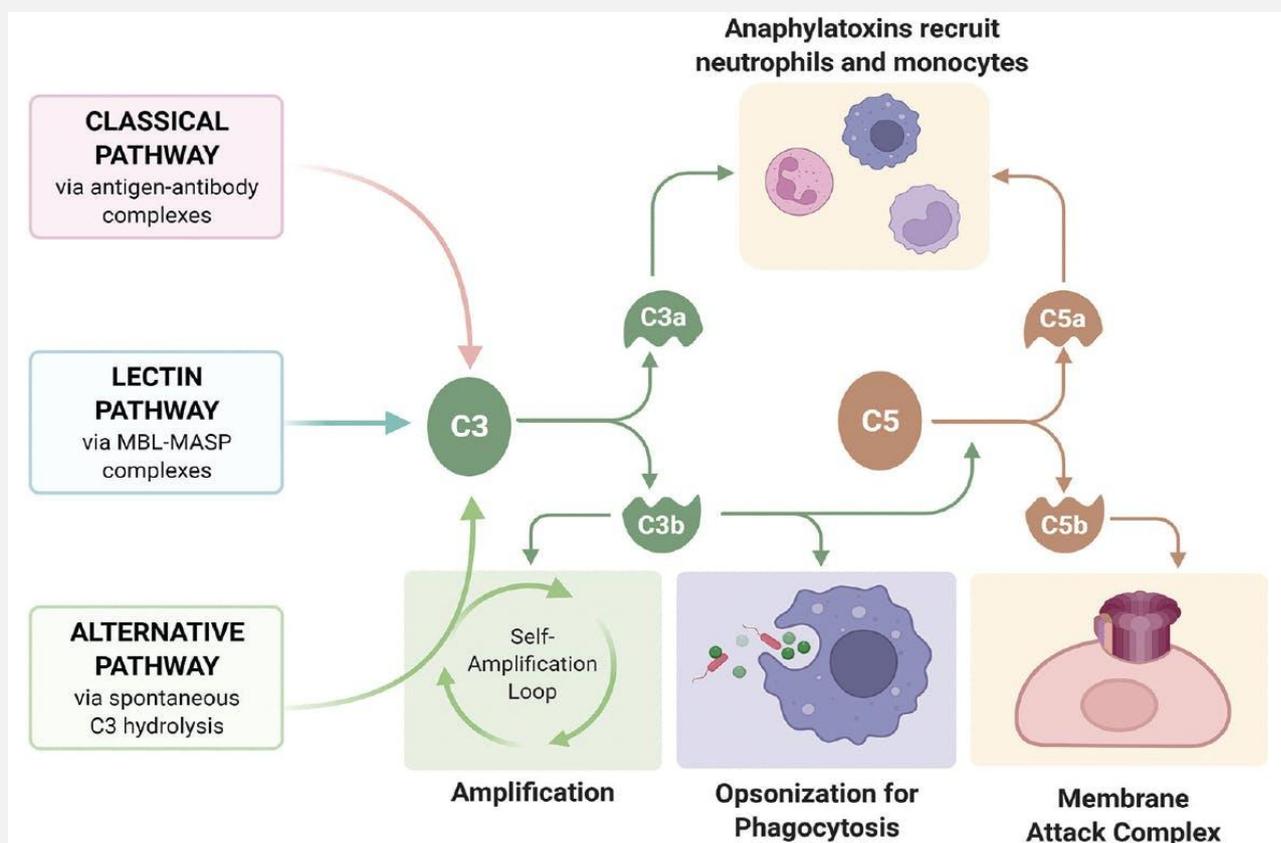


COMPLEMENT SYSTEM

- The complement system is a part of the innate immune system that enhances the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism.
- It consists of a series of blood proteins that are activated in a cascade, which can lead to the inflammation of tissues, the opsonization of pathogens, and the direct lysis of pathogens by forming a membrane attack complex.
- The system is crucial for immune defense and is involved in both innate and adaptive immunity

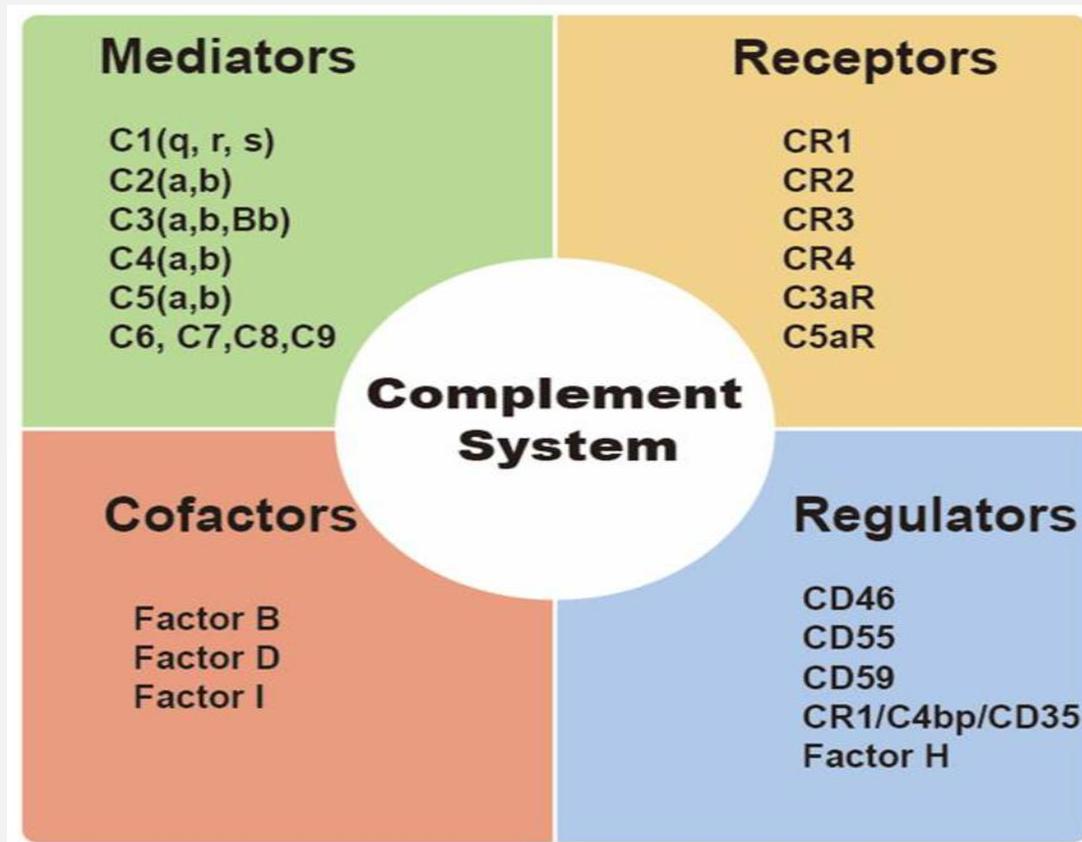


◆ Definition

- The **complement system** is a complex network of **plasma proteins** that enhances (complements) the ability of antibodies and phagocytic cells to clear pathogens.
- It forms an essential part of **innate immunity** and bridges to **adaptive immunity**.

Components

- Over **30 proteins** in plasma and on cell surfaces.
- Most are **zymogens (inactive precursors)** synthesized mainly in the **liver**.
- Key components: **C1–C9**, along with **regulatory and receptor proteins**.

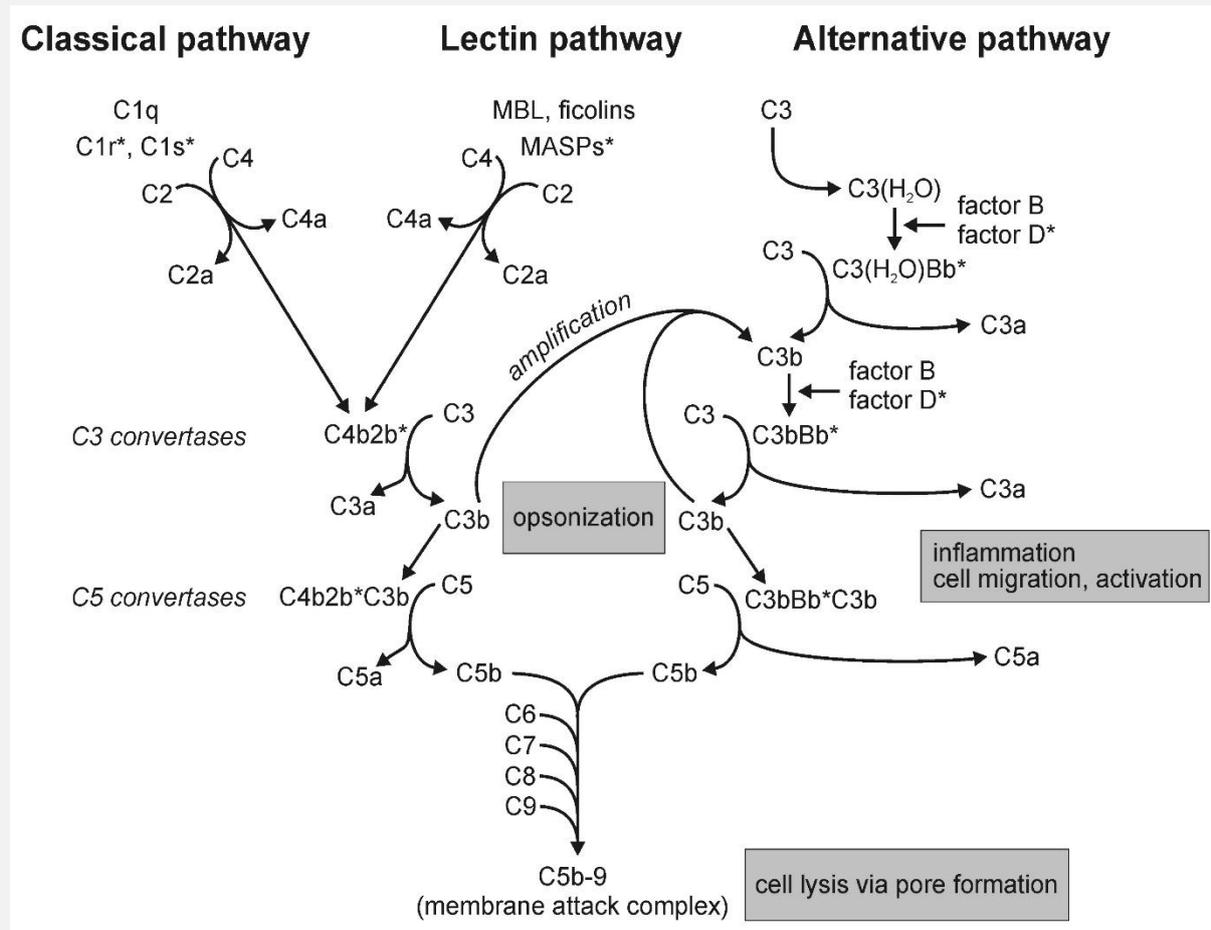


Major Functions

1. **Opsonization** → Enhances phagocytosis (C3b coats microbes).
2. **Chemotaxis** → Attracts immune cells to infection site (C5a).
3. **Cell Lysis** → Destroys pathogens by forming the **Membrane Attack Complex (MAC)**.
4. **Inflammation** → Promotes inflammatory response (C3a, C5a = anaphylatoxins).
5. **Clearance** → Removes immune complexes and apoptotic cells.

Pathways of Activation

There are **three main pathways** leading to complement activation, all converging at **C3 activation**.



1. Classical Pathway

- Trigger: **Antigen–antibody complexes** (IgG or IgM).
- **Steps:**
 1. **C1 complex** (C1q + C1r + C1s) binds to Fc region of antibody on antigen.
 2. Activation of **C1r and C1s** → cleavage of **C4** and **C2**.
 3. **C4b + C2a** form **C4b2a = Classical C3 convertase**.
 4. **C3 convertase** cleaves C3 → C3a + C3b.
 5. **C3b** joins C4b2a → forms **C4b2a3b = C5 convertase**.

2. Alternative Pathway

- Trigger: **Direct activation** on microbial surfaces (no antibody needed).
- **Steps:**
 1. **C3** undergoes spontaneous hydrolysis → **C3(H₂O)**.
 2. **Factor B** binds; **Factor D** cleaves B → **Bb** fragment remains bound.
 3. **C3(H₂O)Bb** = fluid-phase **C3 convertase** → generates more C3b.
 4. On pathogen surface, **C3b + Factor B + Factor D** → **C3bBb** (stabilized by **Properdin**).
 5. **C3bBb** = **Alternative pathway C3 convertase**.
 6. **C3bBbC3b** = **C5 convertase**.

3. Lectin Pathway

- Trigger: **Mannose residues** on microbial surfaces.
- **Steps:**
 1. **Mannose-binding lectin (MBL)** or **ficolins** bind to microbial carbohydrates.
 2. MBL-associated serine proteases (**MASP-1, MASP-2**) activate.
 3. Cleavage of **C4** and **C2** → forms **C4b2a** (same as in classical pathway).
 4. Follows the same downstream steps as the classical pathway.

Terminal (Lytic) Pathway

After formation of **C5 convertase** (from any pathway):

1. **C5** cleaved → **C5a** (inflammatory mediator) + **C5b**.
2. **C5b** binds sequentially to **C6, C7, C8**, and multiple **C9** molecules.
3. Forms **Membrane Attack Complex (MAC) = C5b–C9**.
4. MAC creates pores in the pathogen membrane → **osmotic lysis**.

Biological Effects of Complement Components

Component	Function
C3b	Opsonization – promotes phagocytosis.
C3a, C5a	Anaphylatoxins – increase vascular permeability, cause smooth muscle contraction.
C5a	Potent chemotactic factor for neutrophils and monocytes.
C3d	B-cell activation (binds to CR2 receptor).
MAC (C5b–C9)	Lysis of target cells (especially Gram-negative bacteria).

Regulation of the Complement System

Uncontrolled activation can cause host tissue damage.

Hence, **regulatory proteins** keep the system in check:

Regulator	Function
C1 esterase inhibitor (C1-INH)	Inhibits C1r and C1s → stops classical pathway initiation.
Factor H & Factor I	Inactivate C3b (alternative pathway).
Decay Accelerating Factor (DAF/CD55)	Dissociates C3 convertase on host cells.
CD59 (Protectin)	Prevents formation of MAC on host cells.
C4-binding protein (C4BP)	Inhibits classical pathway C3 convertase.