

Ministry of Higher Education
and Scientific Research
Tishk International University
Faculty of education
Department of Biology



Complement System

Lecture-9-

By

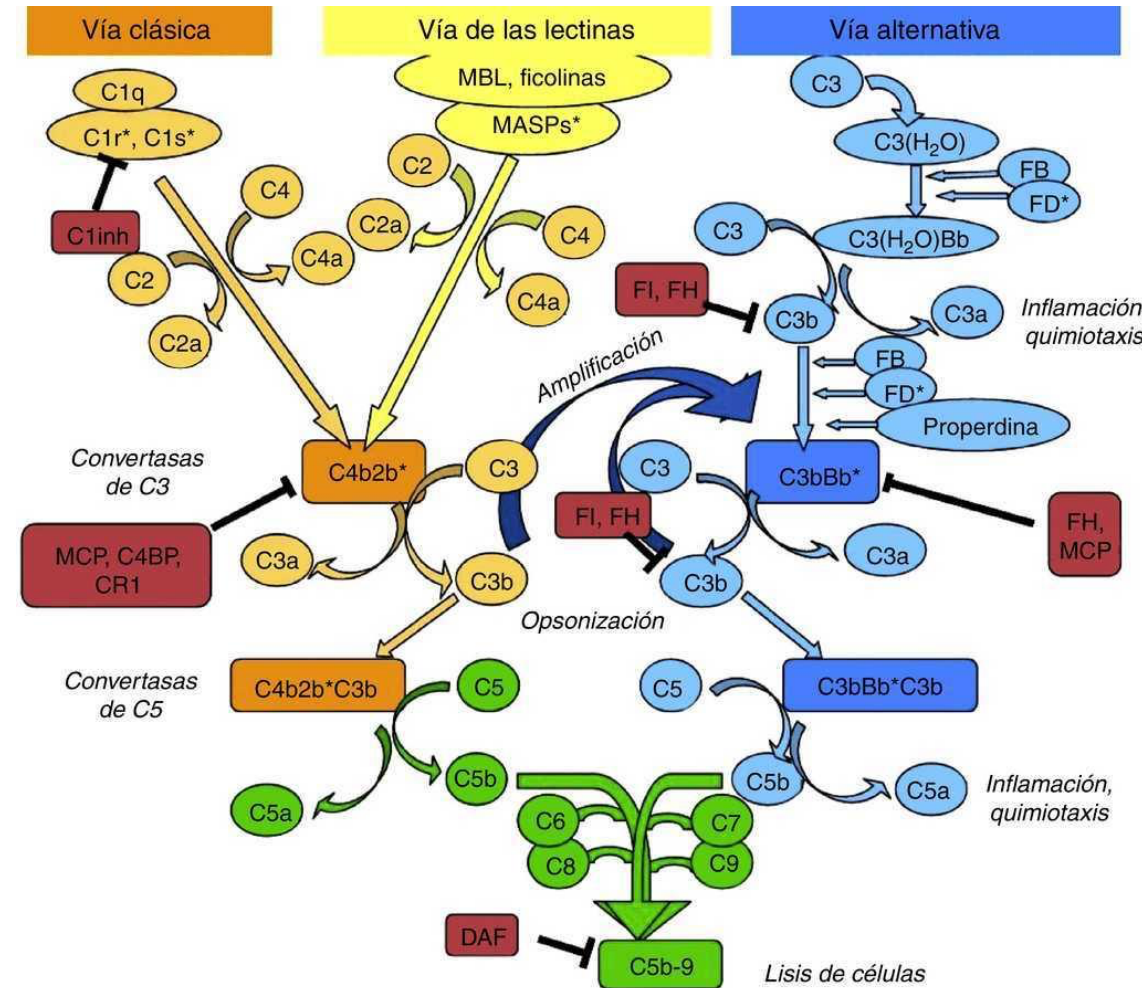
Harmand Ali

Objectives

- To describe what the complement system is?.
- To emphasize the pathways of complement system.
- To point out the benefits and harmfulness of complement system in humans body.

Complement

- A group of heat-labile serum proteins (consisting of over 20 proteins) participate effectively in the processes of body defense at both innate and specific levels. They can be found in serum and all tissue fluids except urine and CSF. These proteins are synthesis in liver – they appear in fetal circulation during 1st 13 Weeks of age.

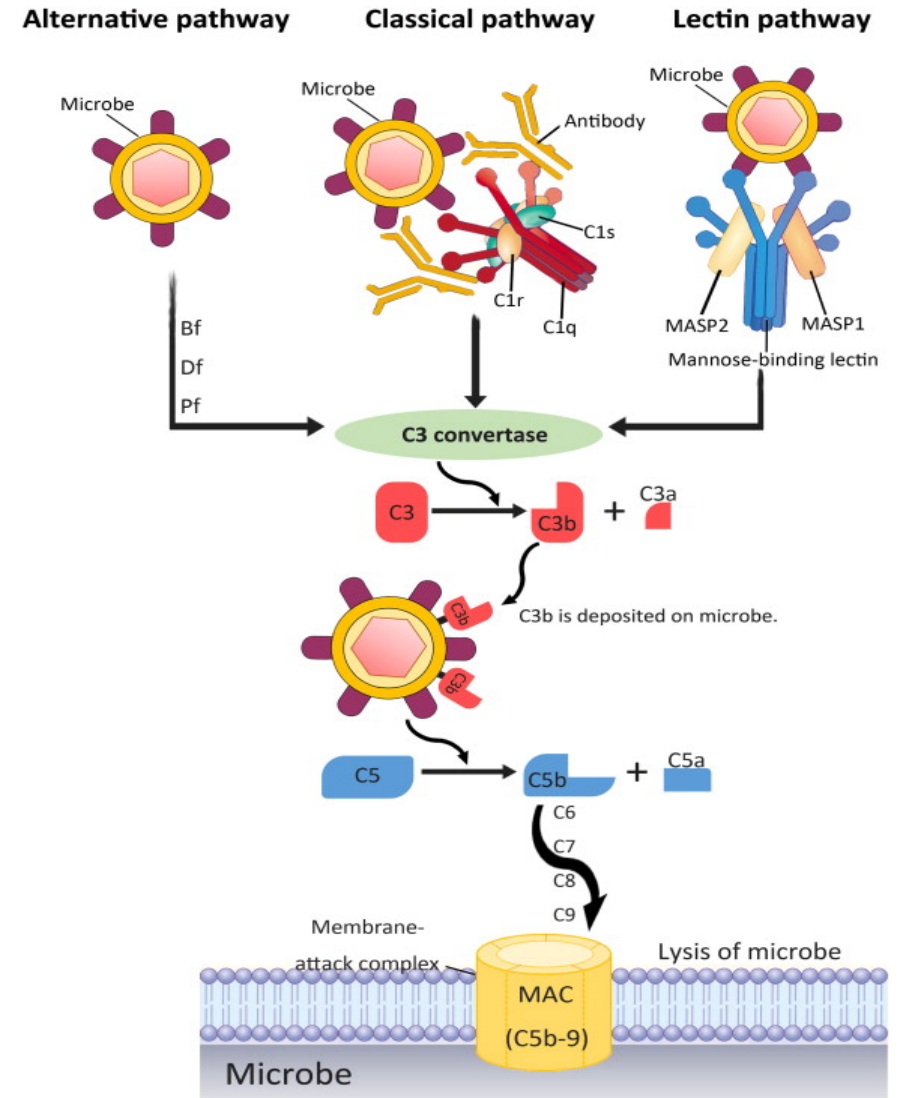


Properties of complement system

- The complement works as a cascade system.
 - **Cascade is when one reaction triggers another reaction** which trigger others and so on. These types of systems can grow exponentially very fast.
- Complement proteins are often designated by an uppercase letter C and are inactive until they are split into products.
- – Example: C1
- When the products are **split** they become active.
- The active products are usually designated with a lower case a or b. – Example: C1a and C1b

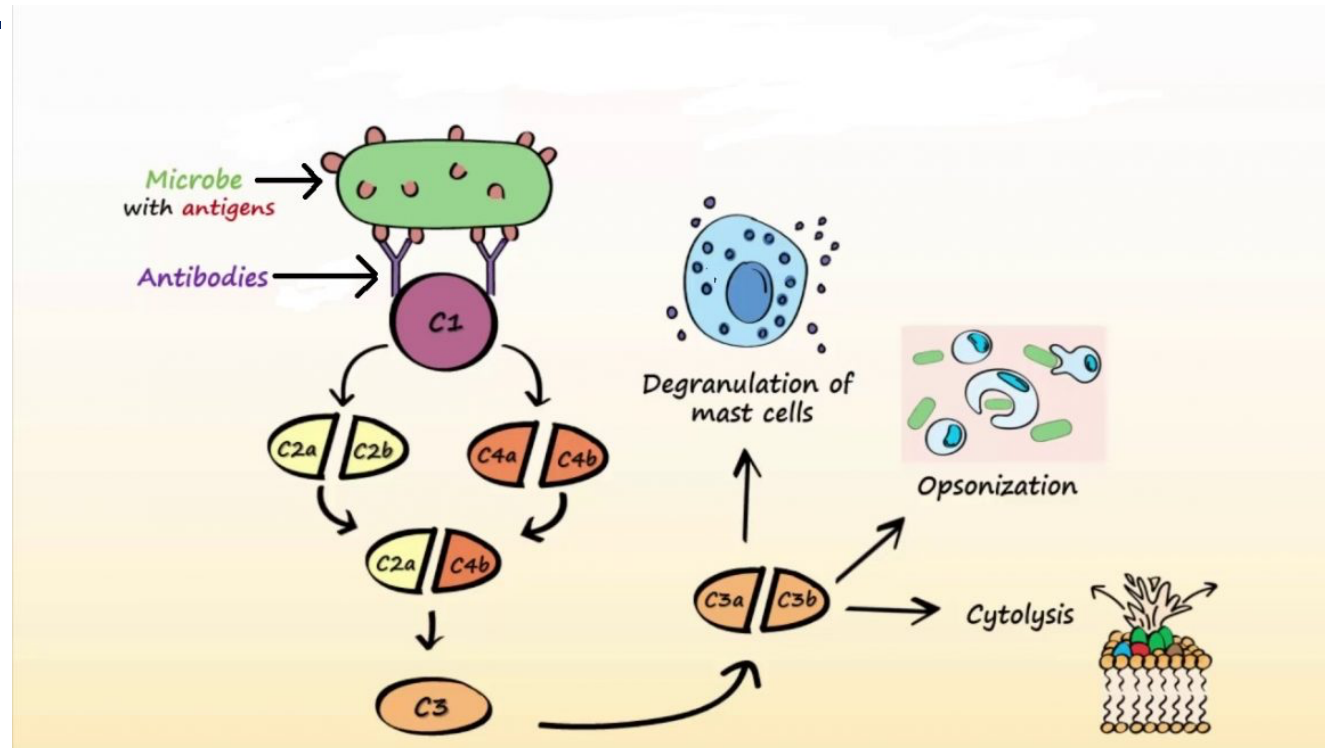
Complement activation pathways

- Generally complement proteins can be activated through different pathways although there are two main pathways. Classical and alternative (moreover lectin pathway also may occur). This lecture will concentrate on the two main mentioned pathways.



A) Classical pathway:

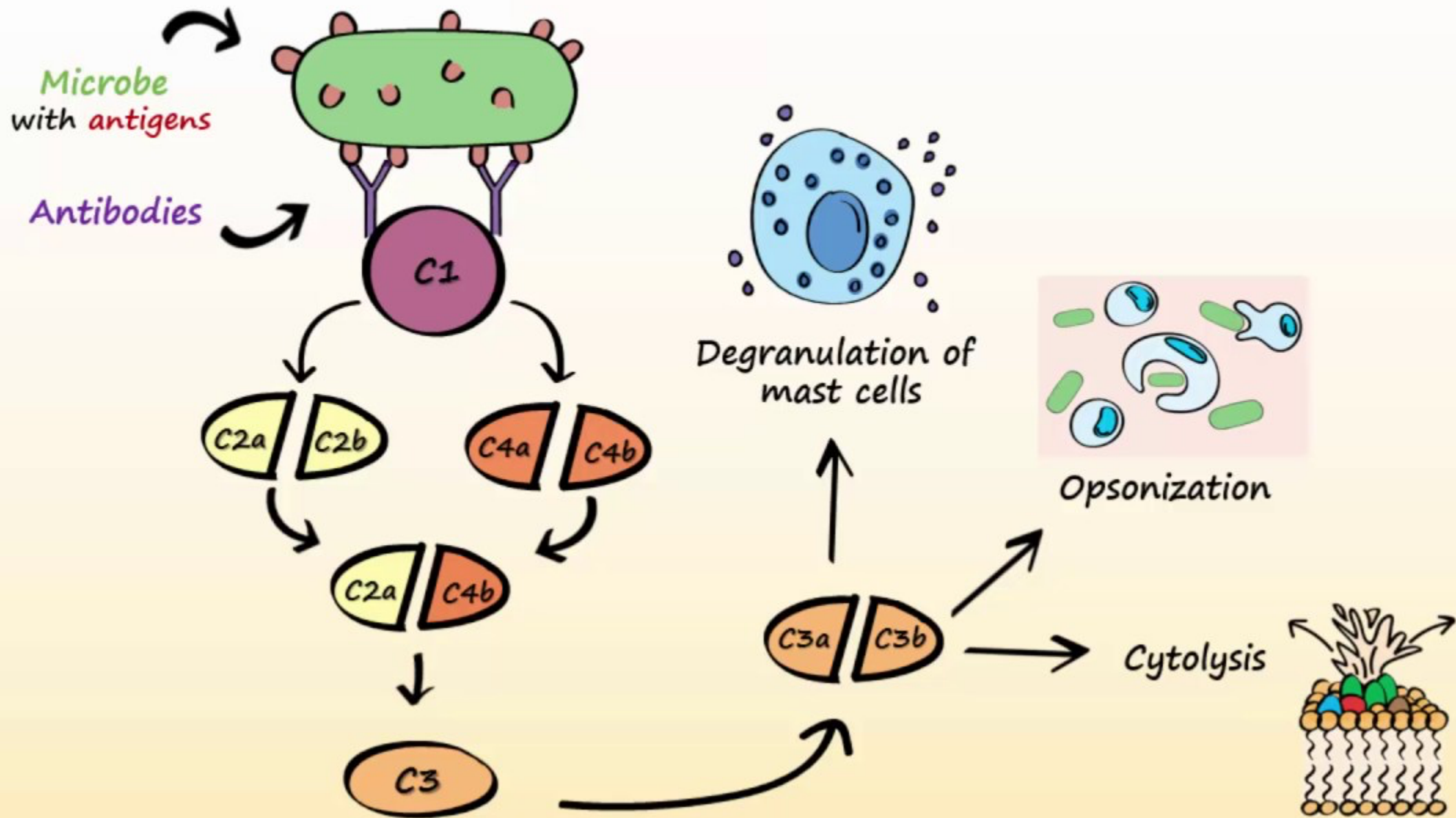
- Complement is activated by antigen –antibody complex (IgM or IgG)
- The classical pathway is considered to be strongly related to the specific immune response because it **relies on antibodies** to initiate it.



C1: The Recognition Unit

- C1 consists of 3 subunits: C1q, C1r, and C1s.
- C1q molecule consists of a collagenous region with six globular
- head groups globe end serves as recognition unit
- When antibody binds to antigen, binding sites for the globular head groups of C1q are exposed on the Fc region of the antibody.
- C1q to initiate the cascade it must attach to at least 2 Fc fragments, requires at least 2 molecules of IgG or one molecule of IgM.
- C1q binding causes C1r to enzymatically activate C1s.

The Classical Pathway

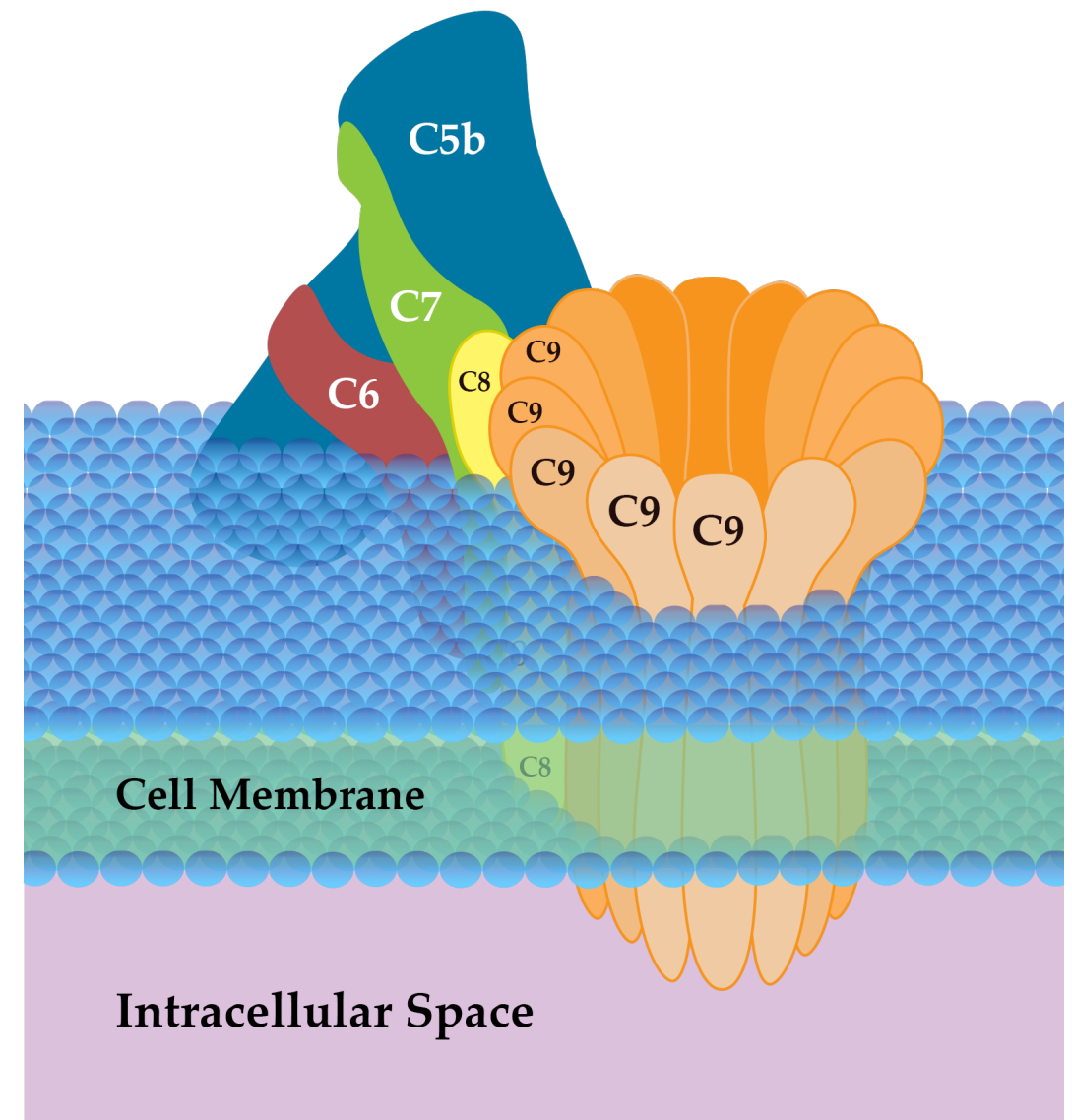


- C1s cleaves C4 into C4a and C4b, and also cleaves C2 into C2a and C2b
- C4b2a or C14b2a (**C3 convertase**) will form which is enzymatically active and can cleave many molecules of C3 into C3a and C3b. Finally the Activation Unit (C4b2a3b) (also called **C5 convertase**) will form that can cleave C5 to a and b fragment .
- In the presence of C5b, molecules of C6, C7, C8 and a variable number of C9 molecules assemble themselves into an aggregates molecular complex which causes a change in membrane permeability **Membrane attack complex (MAC)** and cause cell lysis.

<https://www.youtube.com/watch?v=mfCeCvkQbul>

The Membrane attack complex (MAC) causes Cytolysis.

- The circular membrane attack complex acts as a channel in which cytoplasm lost its permeability and the water moves in and out freely. Causing cell burst and lysis

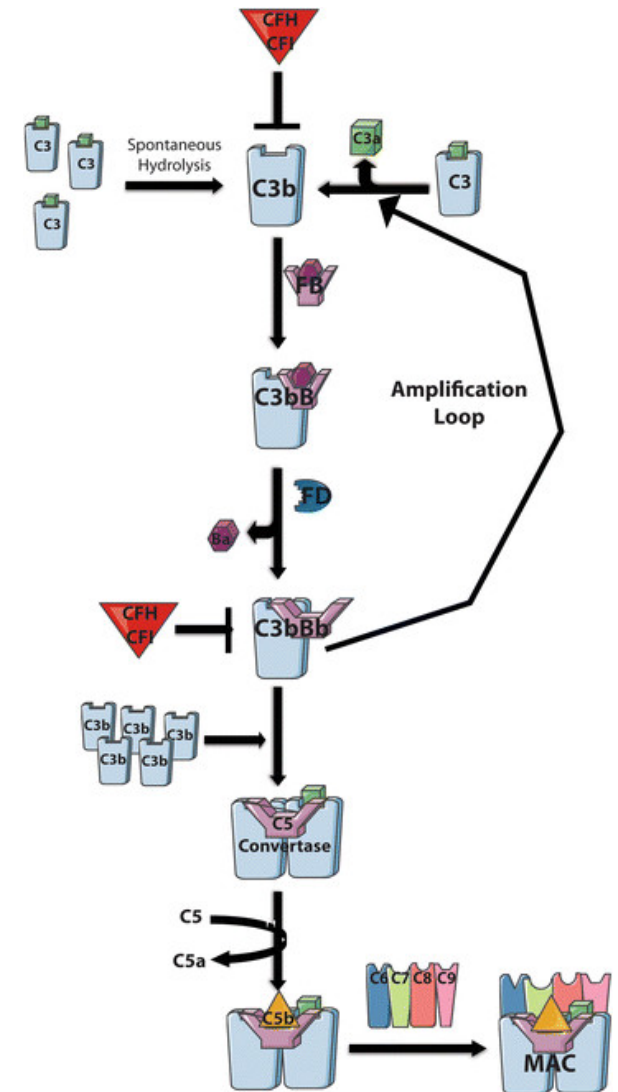


B. Alternative Pathway (Properdin Pathway)

- In this pathway cleavage of C3 and activation of the remainder of the complement cascade **occurs independently of antibody.**
- Triggers for the alternative pathway include
 - **Bacterial cell walls**
 - **Bacterial lipopolysaccharide**
 - **Fungal cell walls**
 - **Some virus infected cells**
 - **Rabbit erythrocytes**
 - **Cobra's venom.**

Alternative Pathway

- In this pathway molecules of C3 undergoes cleavage at continuous low levels in normal plasma (At least four serum proteins functionally participate in this pathway which are (factor B, factor D, properdin (P), and initiating factor -IF-).
- This leads to formation of C3a and C3b (Thus C3 becomes activated without participation of C1, C4 or C2) (also antibodies are not required in this process).





- The alternative pathway is mostly mentioned with non-specific defense because it does **not** need antibodies to initiate the pathway.
- This pathway is slower than the Classical pathway

Classic VS Alternative pathways

Classic Pathway

- * Mostly with specific immunity
- * Initiated by antibody
- * Interaction of all components
- * Properdin system not involved

Alternative pathway

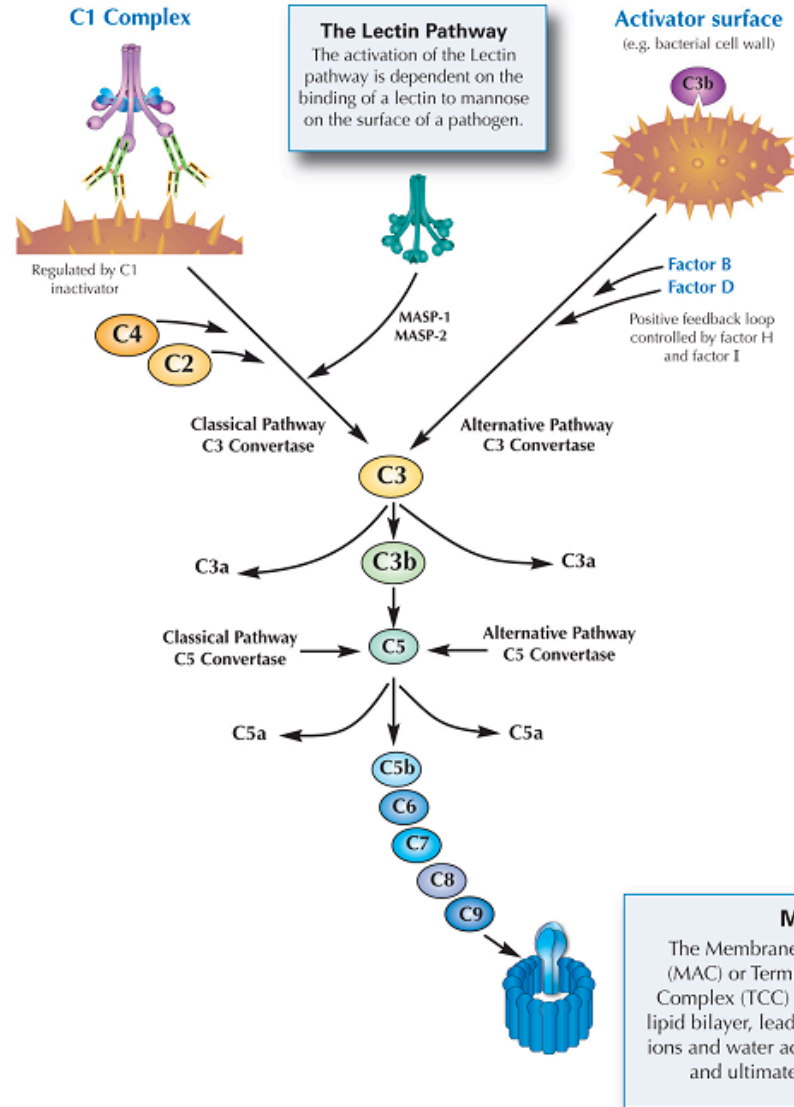
- * mostly with non-specific immunity
- * Bacterial endotoxin, capsule
- * C1, C4, C2 are by-passed
- * Properdin system is involved

Classical Pathway

The Classical Pathway is activated by the Fc portion of an immunoglobulin in an antigen-antibody complex. It can also be activated by enzymes (e.g. trypsin and plasmin) and a variety of substances which include endotoxins, cell membranes and viruses.

Alternative Pathway

The Alternative Pathway does not depend on an antigen-antibody reaction in order to become active. Biological activators of this pathway include bacterial endotoxins, yeast cell walls, aggregated immunoglobulins and snake venom.



Biological Effects of Complement

- Beneficial effects:

1. Cytolysis:

- Activated complement proteins polymerize on cell surfaces of bacteria or erythrocyte to form pores in its membrane (killing by osmotic lysis).

2. Opsonization:

- Binding of complement proteins opsonin (C3b) to surfaces of foreign organisms or particles
- Phagocytic cells express specific receptors for opsonins, so promote phagocytosis

- **3. Inflammatory response :**

- Small fragments released during complement activation have several inflammatory actions:
- C5a is chemotactic and attract neutrophils and macrophages
- C5a activate phagocytes and neutrophils
- C3,C4 and C5 are anaphylatoxins and can cause degranulation of mast cells and release of histamine and other inflammatory mediators

- **4. Immune complex clearance:**

- - C3b facilitate binding of immune complex to several surfaces (erythrocytes) and enhance removal by liver and spleen
- - binds erythrocytes to blood vessels , make them as easy prey for phagocytosis
- - C3 deficiency associated with Immunocomplex disease and susceptibility to recurrent infections

- **5-Enhancement of antibody production:**

- - Binding of C3b to its receptors on activated B cells (CR2) greatly enhances antibody production
- - Patient who are deficient in C3b produce much less antibody than normal individuals and more susceptible to pyogenic infection

- **Harmful effects:**

- These proteins may be harm the body after **activation if:**
 - • Complement activate systematically on a large scale.
 - • Activated by an autoimmune response to host cells
- **Notes: Deficiency in these proteins can cause different complications from the immune responses and immunological processes.**