IMMUNOLOGY

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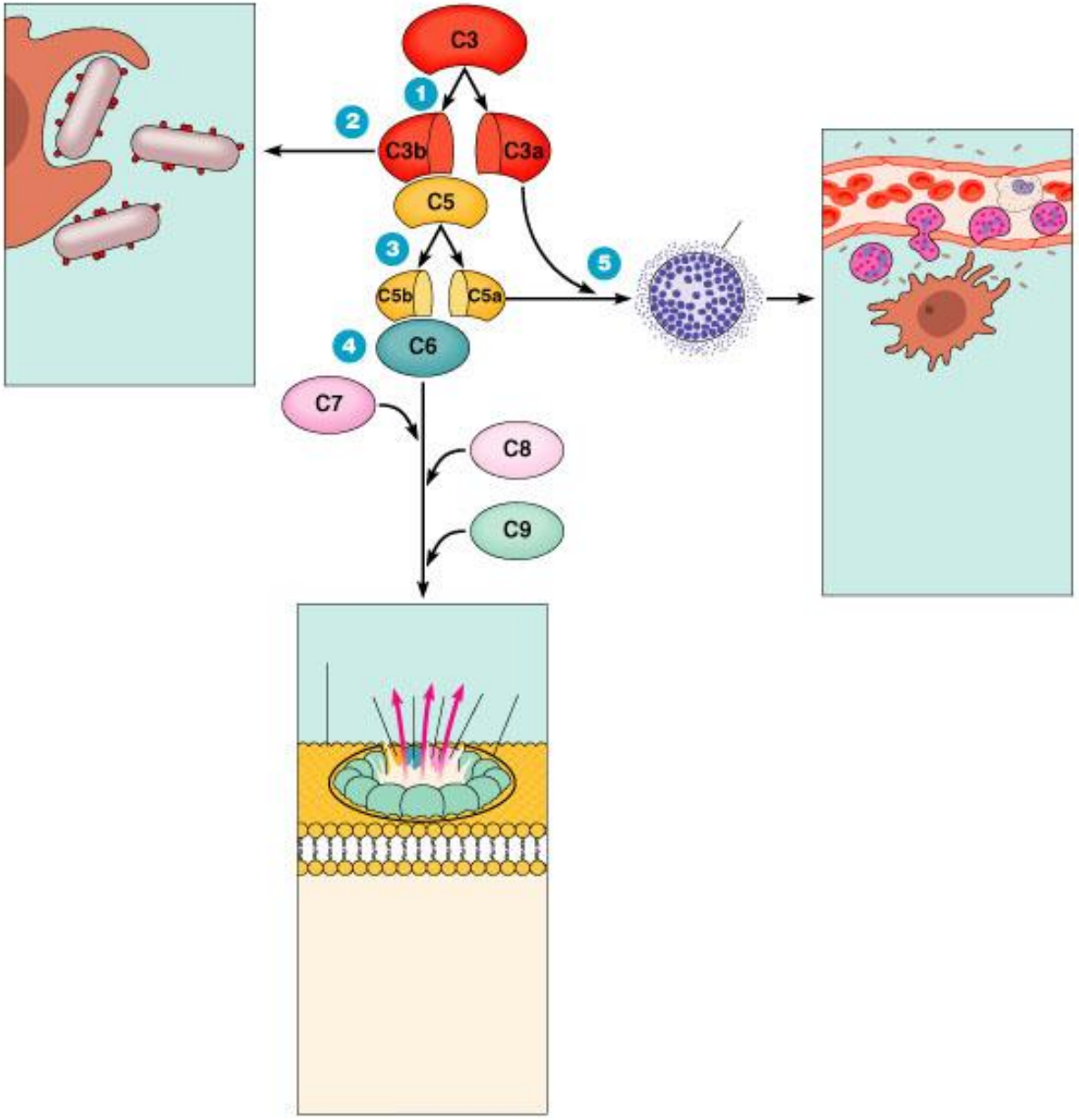
The complemen system



- The **complement system** or “complements” helps the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is a part of innate and adaptive immune system

The complement system

- Over 20 proteins produced by the liver hepatocytes and other cells such as tissue macrophages, blood monocytes, and epithelial cells of the genitourinal tract and gastrointestinal tract and found in circulating blood serum in inactive form.

- The end-result of this activation cascade is massive amplification of the response and activation of the cell-killing membrane attack complex (MAC).

- Once activated, 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.

- Part of the innate and adaptive immune system

- The **complement system** is a part of the immune system that enhances (complements) the ability of Abs andphagocytic cells to clear microbes and damaged cells from an organism, promotes inflammation, and attacks the pathogen's plasma membrane. It is part of the innate immune system , which is not adaptable and does not change over the course of an individual's lifetime. It can be recruited and brought into action by the adaptive immune system

Complement system nomenclature

- Complement proteins are often designated by an **upper case 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: C2a and C2b

Pathways

- Three biochemical pathways activate the complement system: the classical complement pathway, the alternative complement pathway, and the lectin pathway
- The classical complement pathway typically requires antigen-antibody complexes for activation (specific immune response), whereas the alternative and mannose-binding lectin pathways can be activated by C3 hydrolysis or antigens without the presence of antibodies (non-specific immune response).

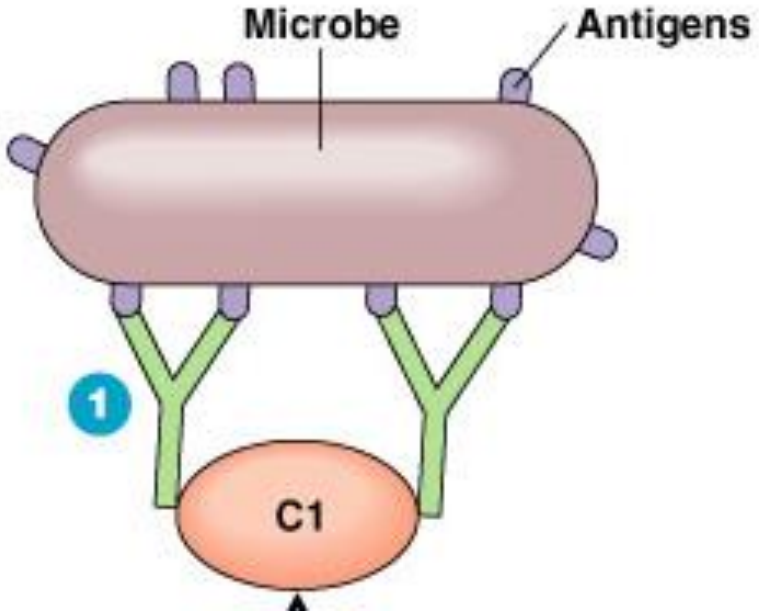
- The following are the basic functions of complement:
- 1- **Opsonization** - enhancing phagocytosis of antigens.
- **2-Chemotaxis** - attracting macrophages and neutrophils.
- 3- **Clearance of immune complexes.**
- **4-Clumping of antigen-bearing agents.**
- **5- Cell Lysis** - rupturing membranes of foreign cells.

The Classical Pathway

- Part of the specific immune response because it relies on antibodies to initiate it.

- First step C1 becomes activated when it binds to the ends of antibodies. It must attach to at least 2 Fc fragments, requires at least 2 molecules of IgG or one molecule of IgM.

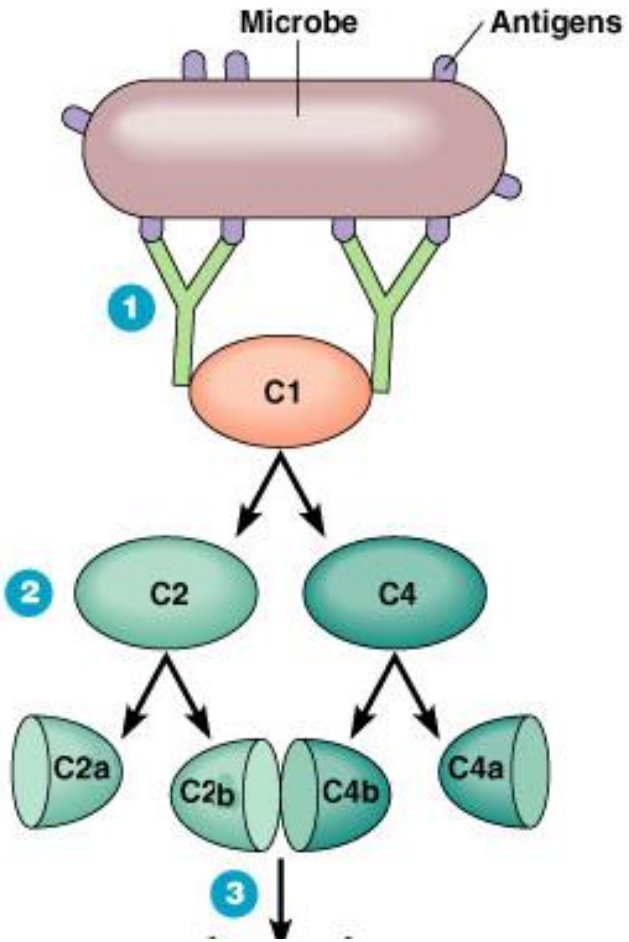
- C1 is called recognition unit



The building of a C3 activation complex

- Once C1 is activated, it activates 2 other complement proteins, C2 and C4 by cutting them in half
- C2 is cleaved into C2a and C2b
- C4 is cleaved into C4a and C4b
- Both C2b and C4b bind together on the surface of the bacteria

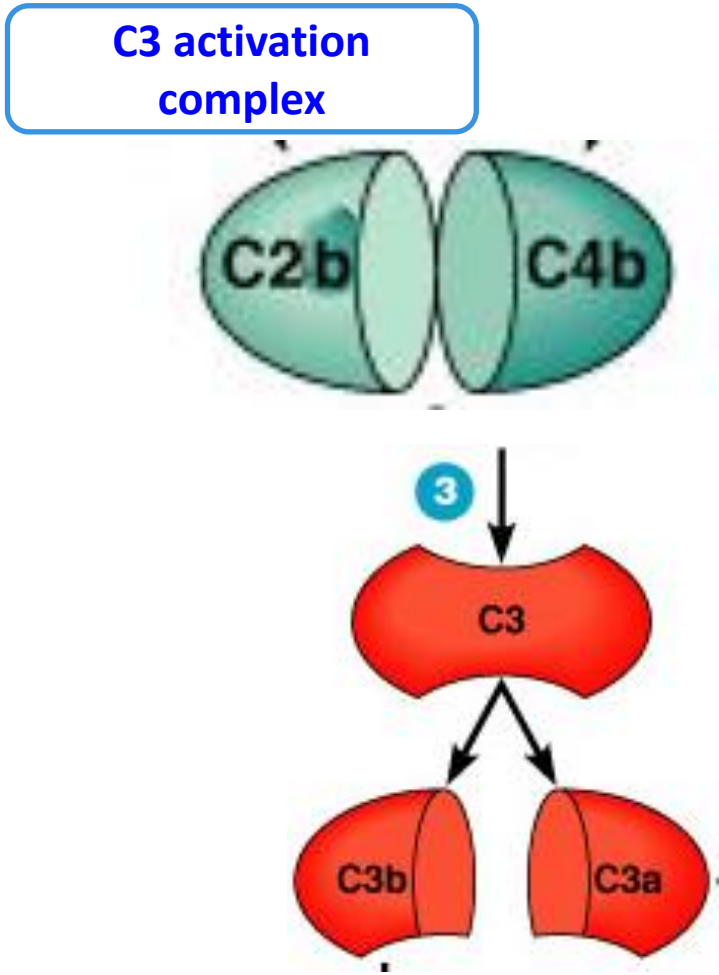
C2a and C4a diffuse away



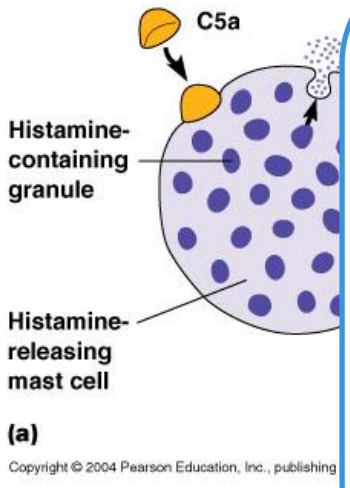
C3 Activation complex

- C2b and C4b bind together on the surface of bacteria to form a **C3 activation complex**

- The function of the C3 activation complex is to activate C3 proteins.
  - This is done by cleaving C3 into C3a and C3b



C3a

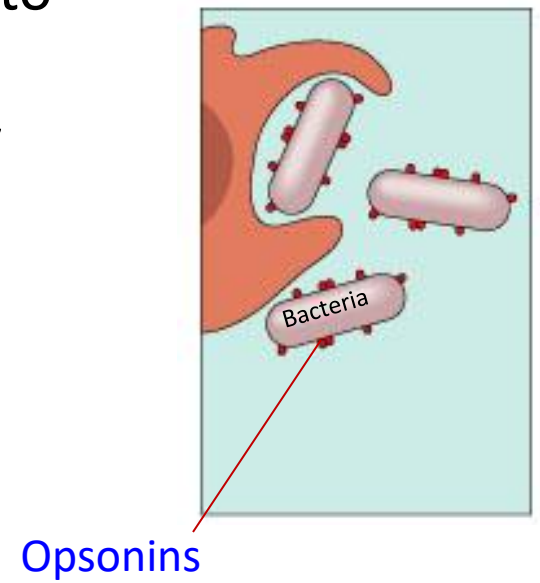


C3a increases the inflammatory response by binding to mast cells and causing them to release histamine

C3b

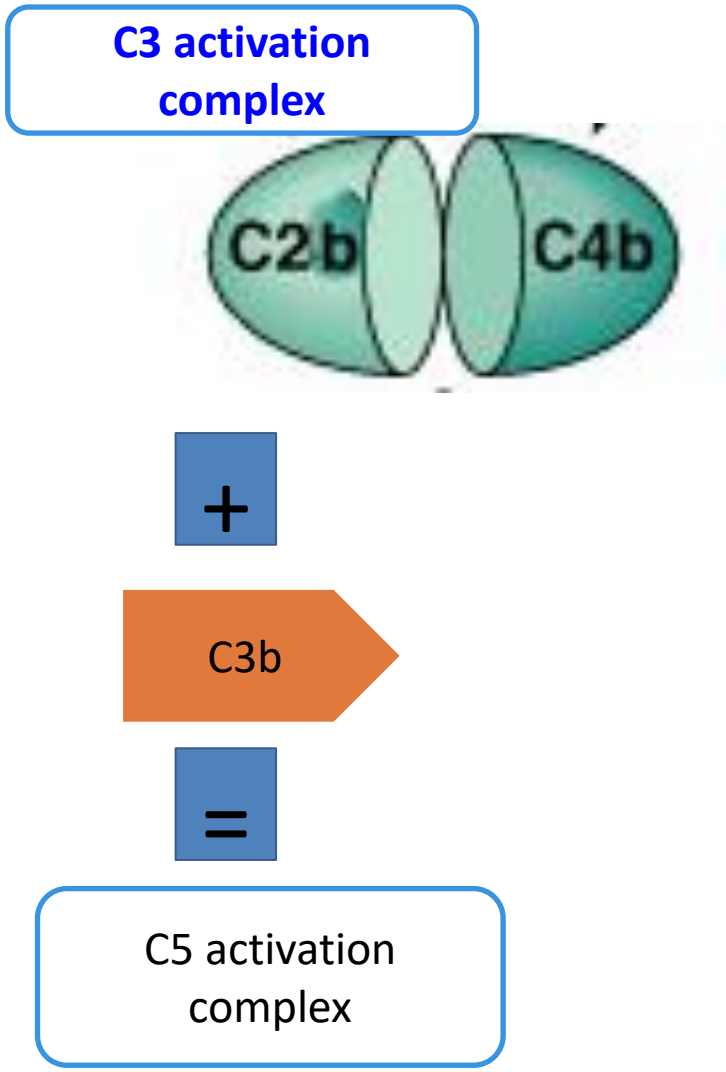
- The C3b bind to and coat the surface of the bacteria.

- C3b is an opsonin
  - Opsonins are molecules that bind both to bacteria and phagocytes
  - Opsonization increases phagocytosis by 1,000 fold.



Building the C5 activation complex

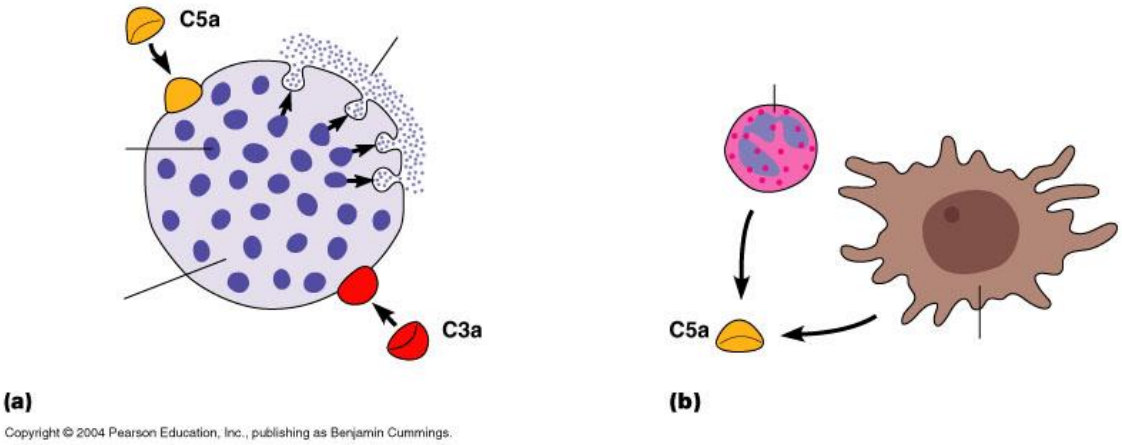
- Eventially enough C3b is cleaved that the surface of the bacteria begins to become saturated with it.
- C2b and C4b which make up the C3 activation complex has a slight affinity for C3b and C3b binds to them
- When C3b binds to C2b and C4b it forms a new complex referred to as the **C5 activation complex**



The C5 activation complex

- The C5 activation complex (C2b, C4b, C3b) activates C5 proteins by cleaving them into C5a and C5b

The function of C5a



- C5a disperses away from the bacteria.
  - Binds to mast cells and increases inflammation.
  - Most powerful chemotactic factor known for leukocytes

- **Both C3a and C5a have anaphylatoxin activity**, directly triggering degranulation of mast cells as well as increasing vascular permeability and smooth muscle contraction

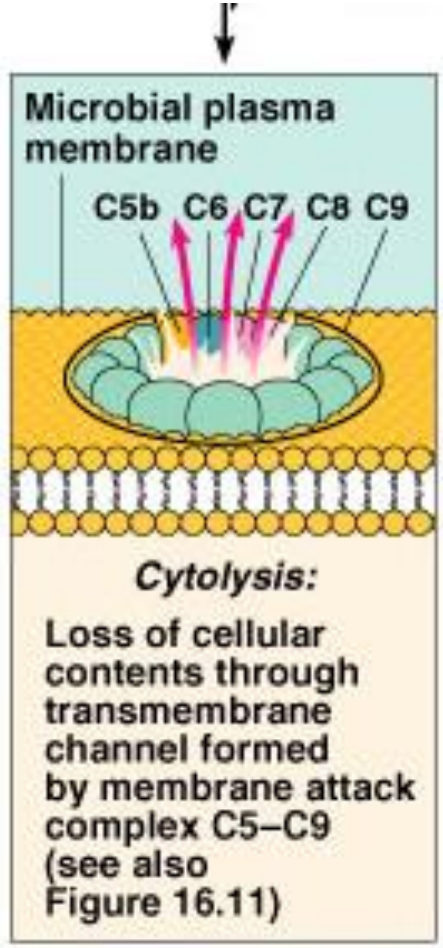
Building the Membrane Attack Complex

- Many C5b proteins are produced by the C5 activation complex. These C5b begin to coat the surface of the bacteria
- C5b on the surface of bacteria binds to C6
- The binding of C6 to C5b activates C6 so that it can bind to C7
- C7 binds to C8 which in turn binds to C9's
- Together these proteins form a circular complex called the Membrane Attack Complex (MAC)

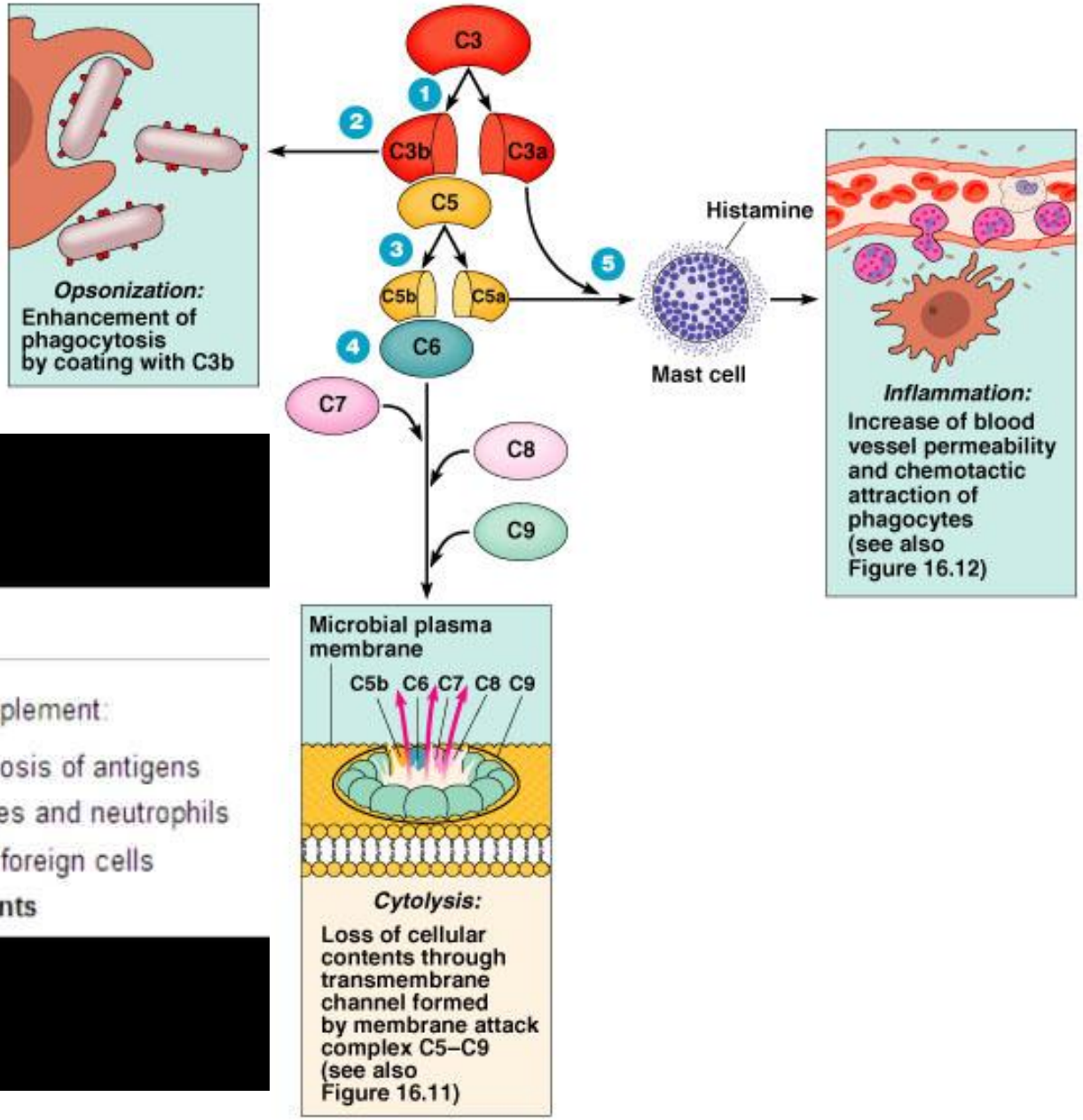
Membrane Attack complex

- The MAC causes Cytolysis.
  - The circular membrane attack complex acts as a channel in which cytoplasm can rush out of and water rushes in.

- The cell's inner integrity is compromised and it dies



Overview



Functions of complement

The following are the basic functions of complement:

1. **Opsonization** - enhancing phagocytosis of antigens
2. **Chemotaxis** - attracting macrophages and neutrophils
3. **Cell Lysis** - rupturing membranes of foreign cells
4. **Clumping of antigen-bearing agents**

Classical pathway has three units to work:

- 1- Recognition unit includes: C1
- 2- Activation or amplification unit includes: C4, C2 and C3.
- 3- Membrane Attack Complex (MAC): consists of C5b-C9.

The alternative pathway

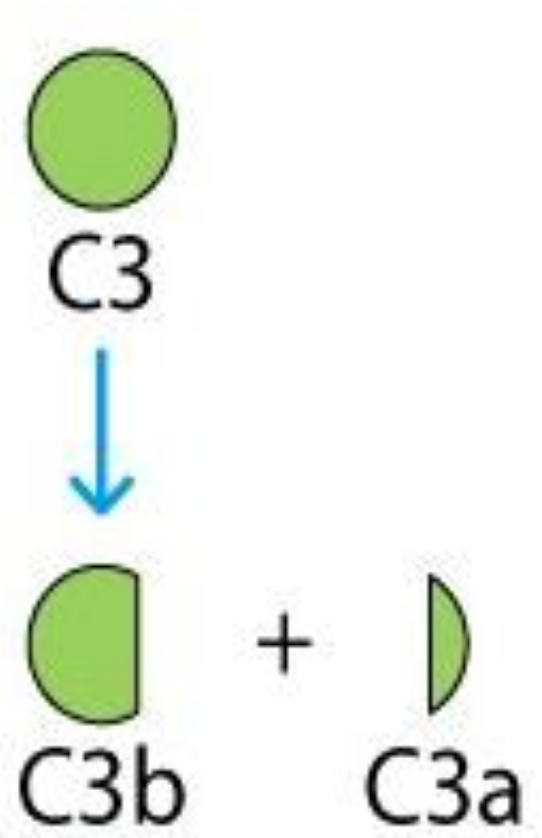
- The alternative pathway is part of the non-specific defense because it does not need antibodies to initiate the pathway.
- **The alternative complement pathway is one element of innate immunity**

- The alternative pathway is slower than the classical pathway

- Triggering by cell wall components of bacteria, fungi, viruses and some parasites, like: lipopolysaccharides (LPS) in gram –ve bacteria and teichoic acid in gram +ve bacteria.

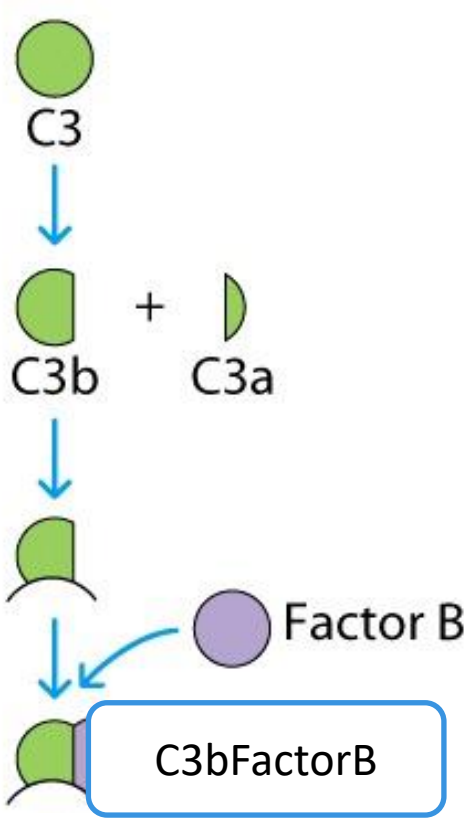
Initiation of The Alternative pathway

- C3 contains unstable thioester bond.
- This unstable bond makes C3 subject to slow spontaneous hydrolysis to C3b and C3a
- The C3b is able to bind to foreign surface antigens.
- Mammalian cells contain sialic acid which inactivates C3b



Factor B

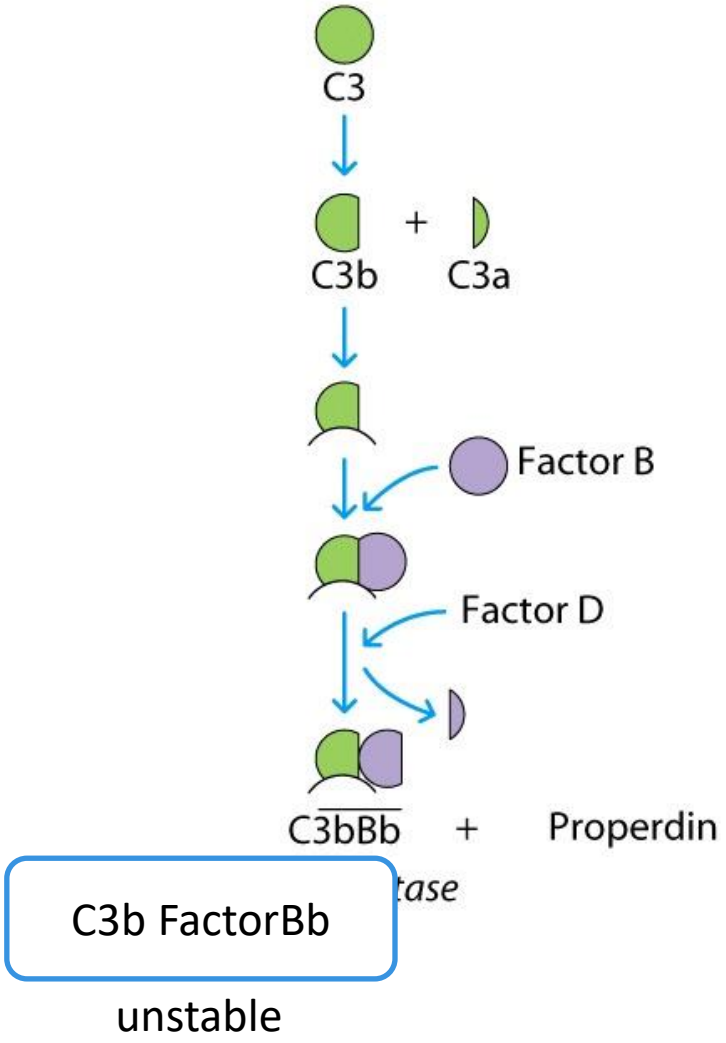
- C3b on the surface of a foreign cells binds to another plasma protein called factor B



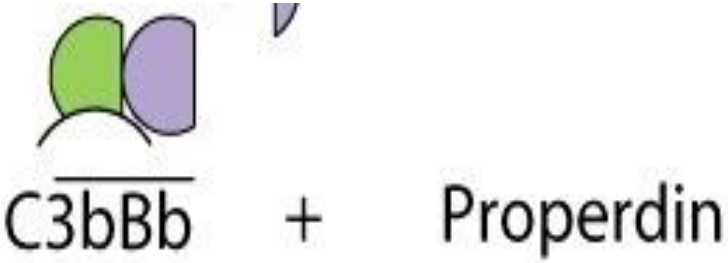
Factor D

- The binding of C3b to factor B allows a protein enzyme called Factor D to cleave Factor B to Ba and Bb.

- Factor Bb remains bound to C3b while Ba and Factor D disperse away.



The C3 activation complex

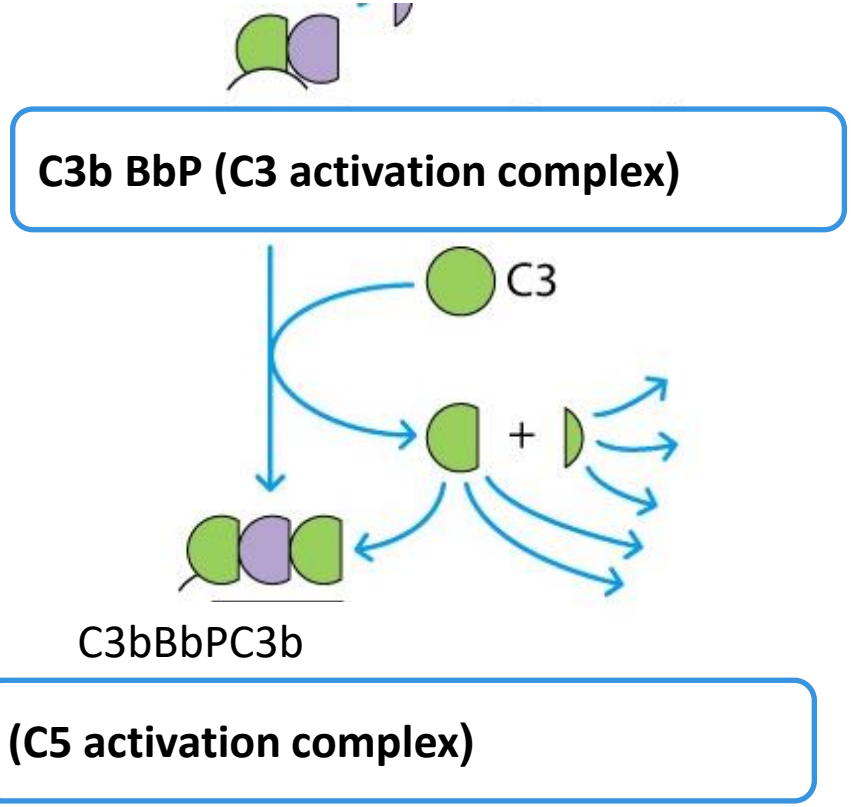


- Properdin, also called factor P, binds to the C3bBb complex to stabilize it.

- C3bBbP make up the C3 activation complex for the alternative pathway

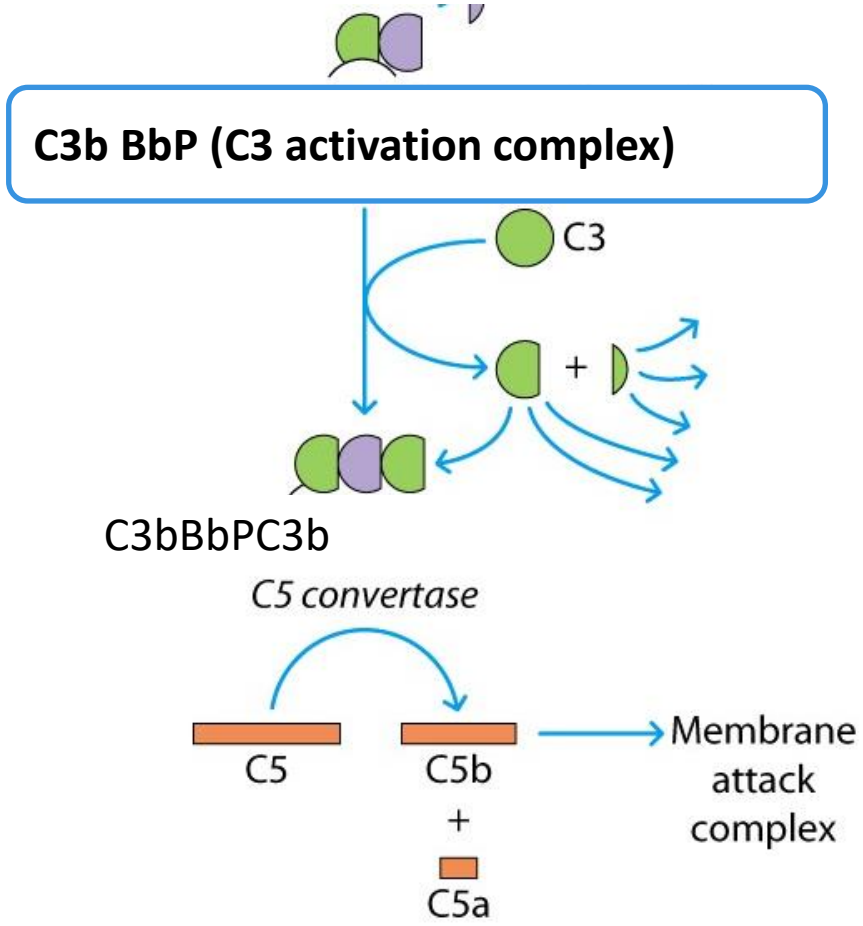
The C3 activation Complex

- The C3 activation complex causes the production of more C3b.
- This allows the initial steps of this pathway to be repeated and amplified
- $2X10^6$ molecules can be generated in 5 minutes

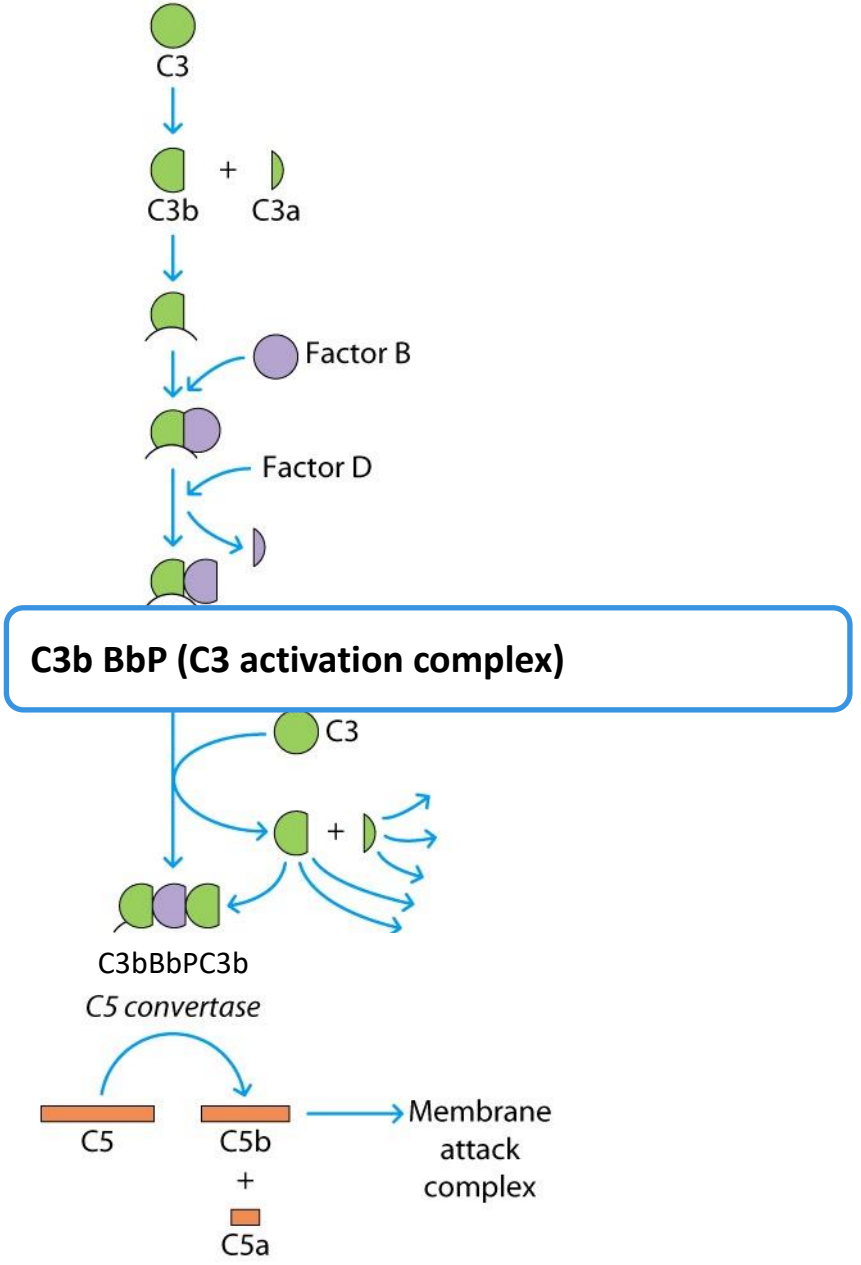


C5 activation complex

- When an additional C3b binds to the C3 activation complex it converts it into a C5 activation complex.
- The C5 activation complex cleaves C5 into C5a and C5b.
- C5b begins the production of the MAC.



The Alternative complement pathway



Thank You