COMPLEMENT SYSTEM

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Introduction

- Complement was discovered by "Jules Bordet" as a heat-labile component of normal plasma that causes the opsonization and killing of bacteria.

- Consists of serum and cell surface proteins involved in defense against pathogens and tissue damage mediated by antibodies.

- The complement system is the major effector of humoral branch of immune system

A Cascade 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.

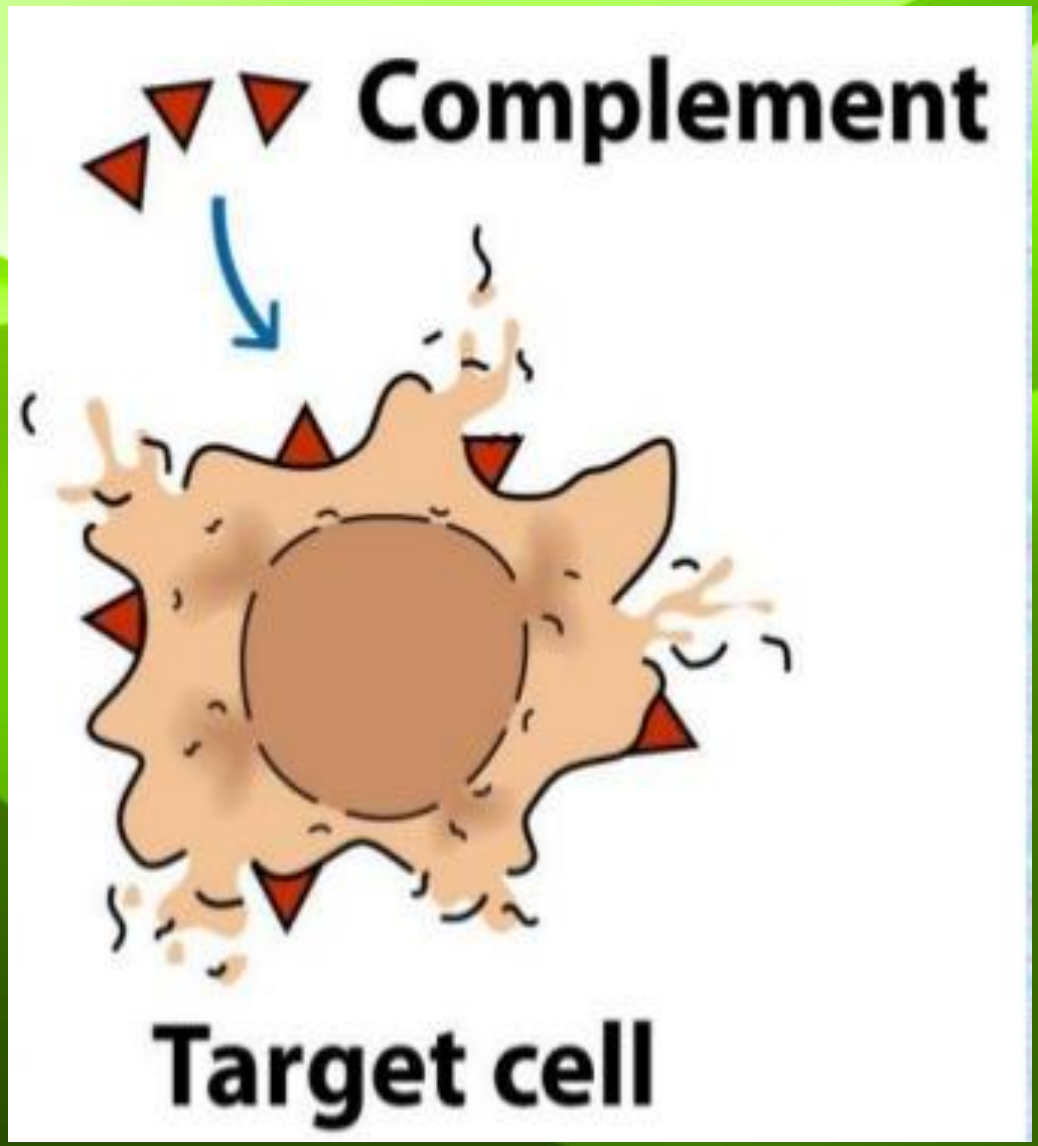
Cascade activation

- 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

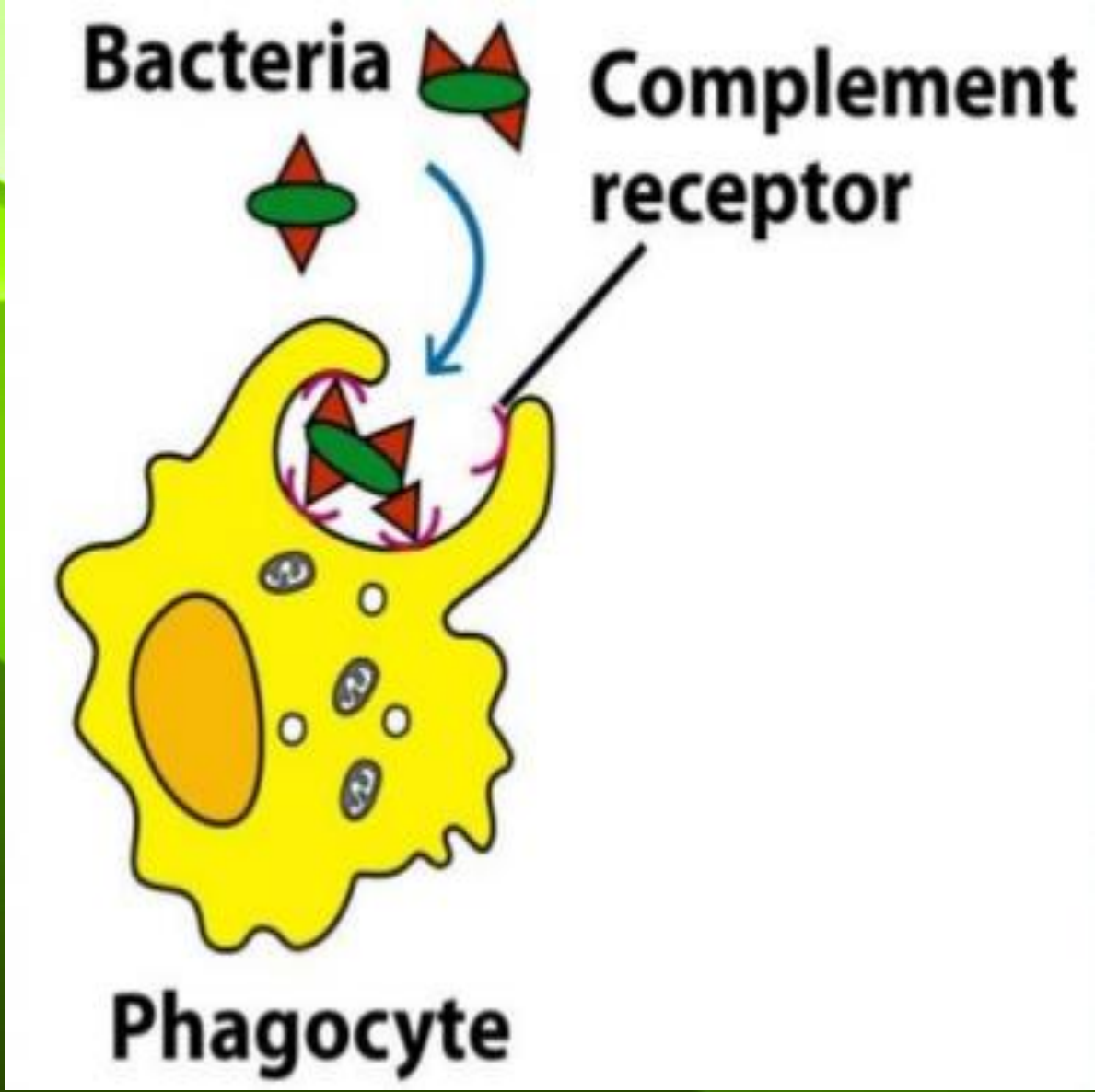
❖ FOUR IMPORTANT FUNCTION:

- Lysis
- Opsonization
- Activation of inflammatory response
- clearance of immune complexes

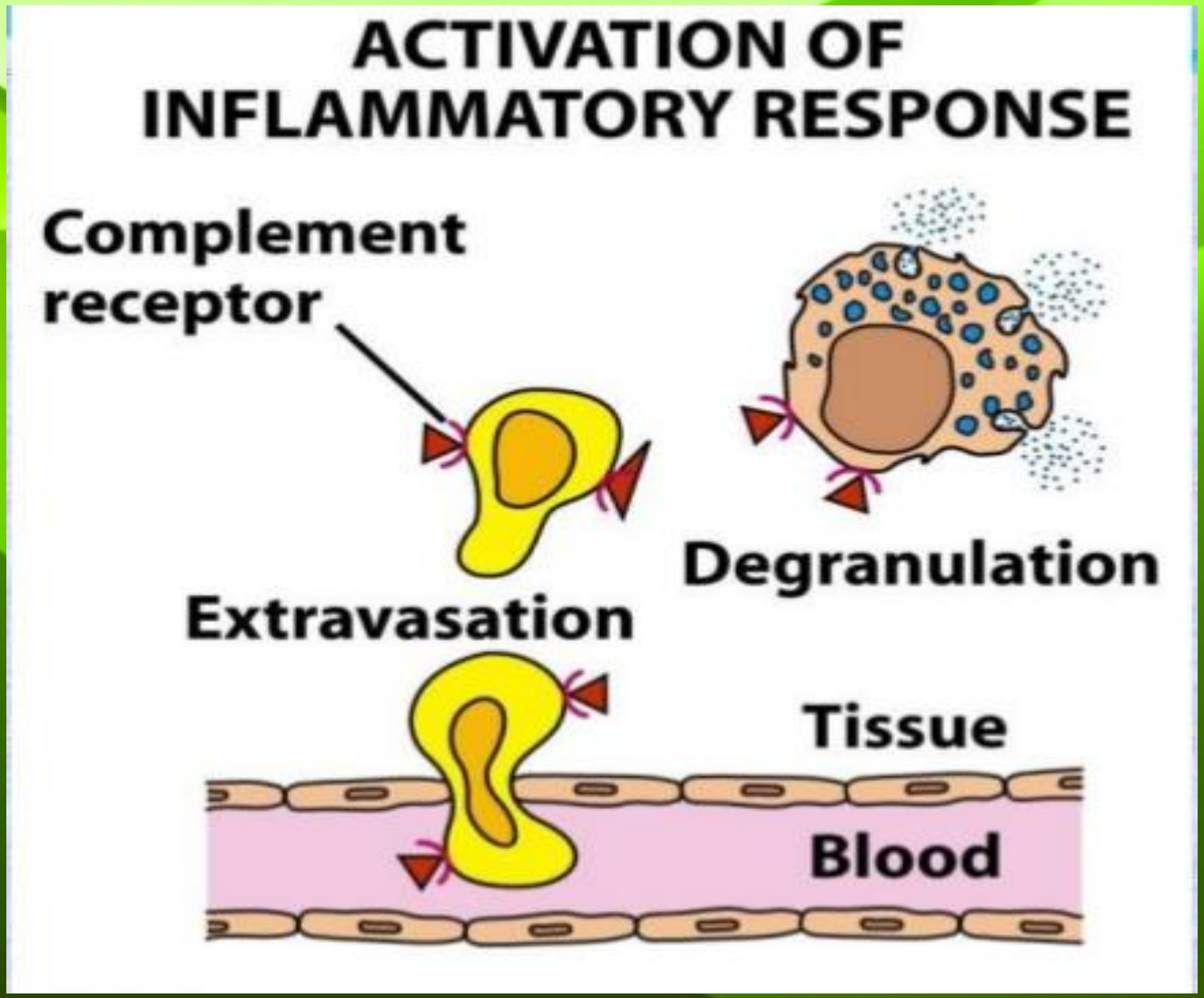
Lysis



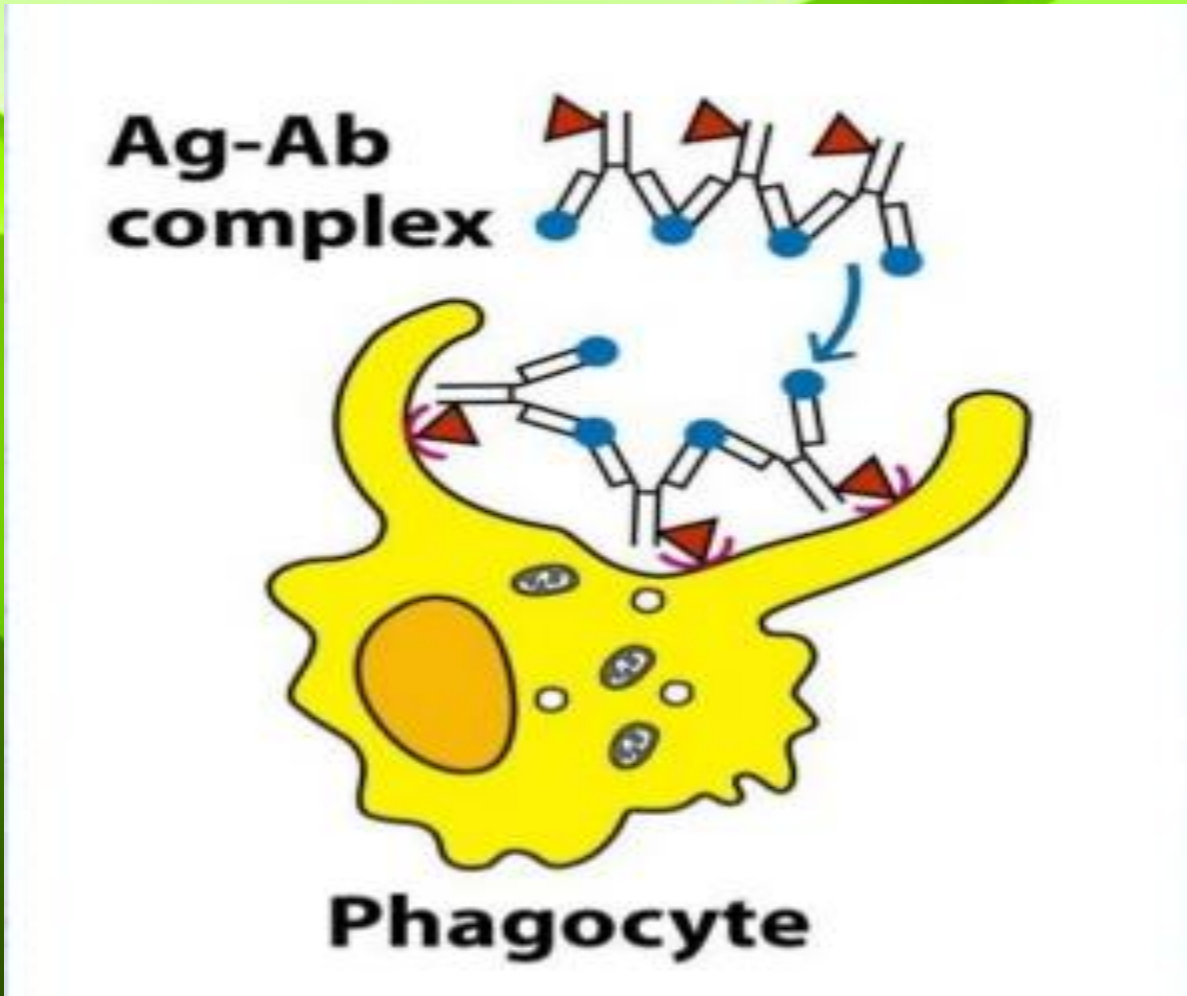
opsonization



Activation of inflammatory response



Clearance of immune complexes



Three Pathways

- The complement pathway can be activated by either of three different pathways.

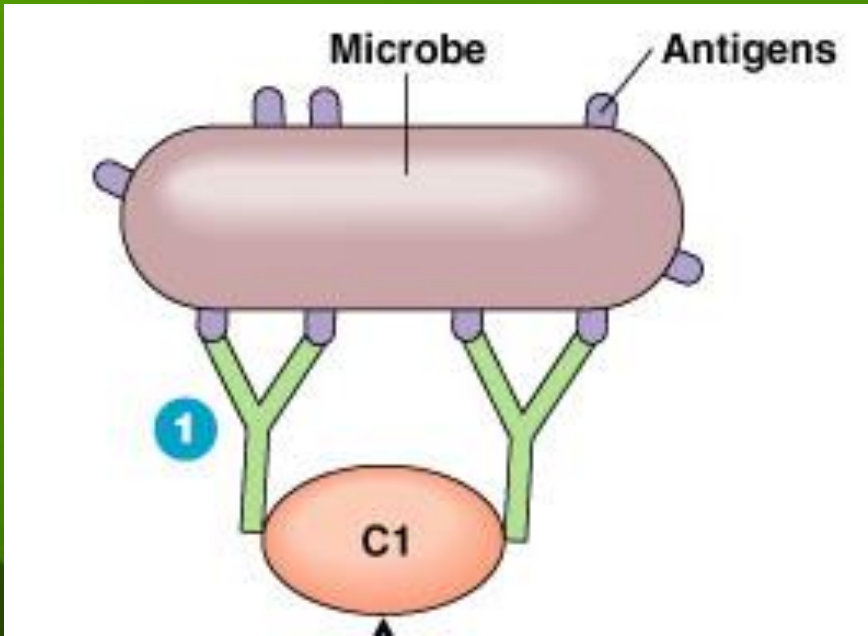
  * **Classical pathway (specific immune system)**

  * **Alternative (non-specific immune system)**

  * **Mannose binding lectin pathway**

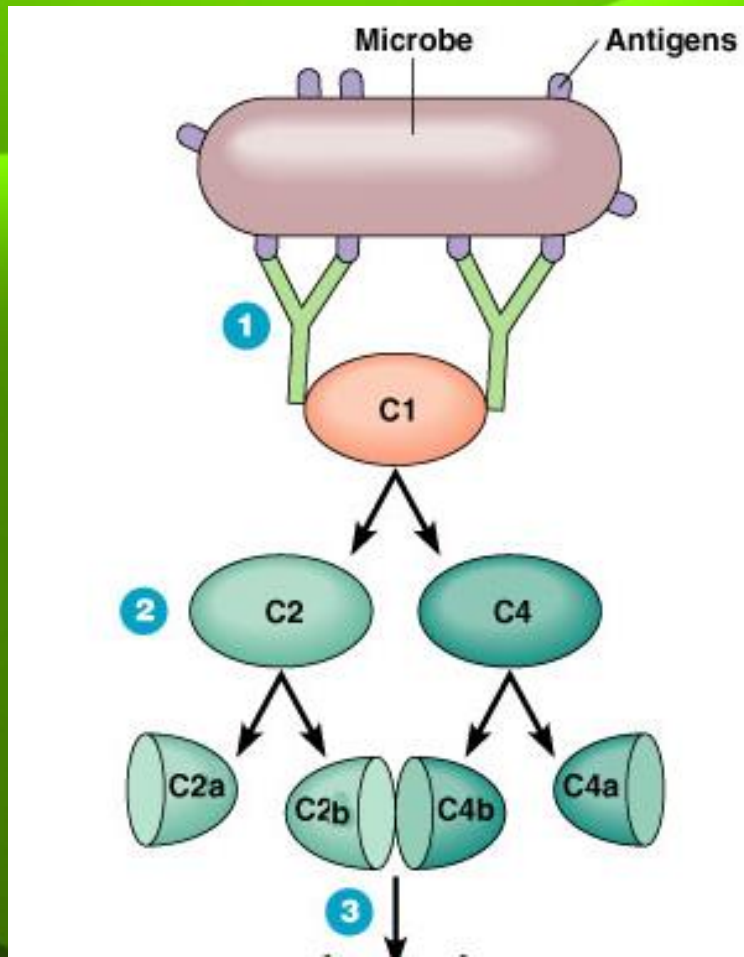
The Classical Pathway

- The classical pathway is considered to be part of the specific immune response because it relies on antibodies to initiate it.
- C1 becomes activated when it binds to the ends of antibodies



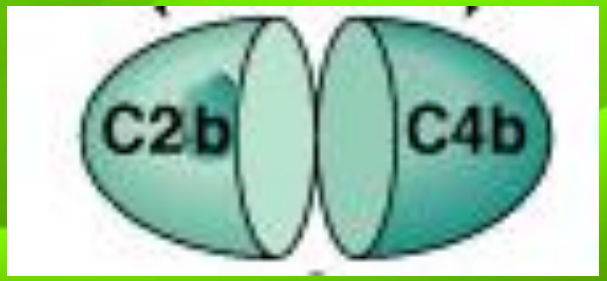
The building of a C3 activation complex

- 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

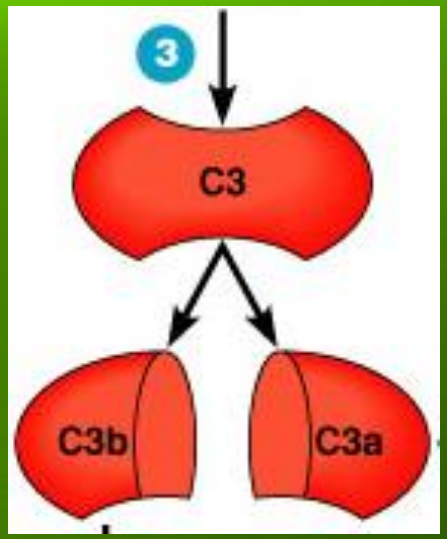


C3 Activation complex

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

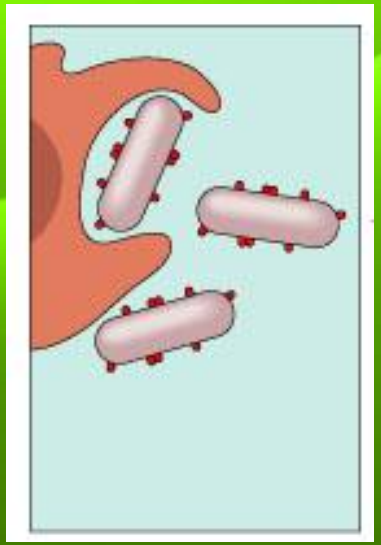


- The function of the C3 activation complex is to activate C3 proteins.
  - This is done by cleaving C3 into C3a and C3b

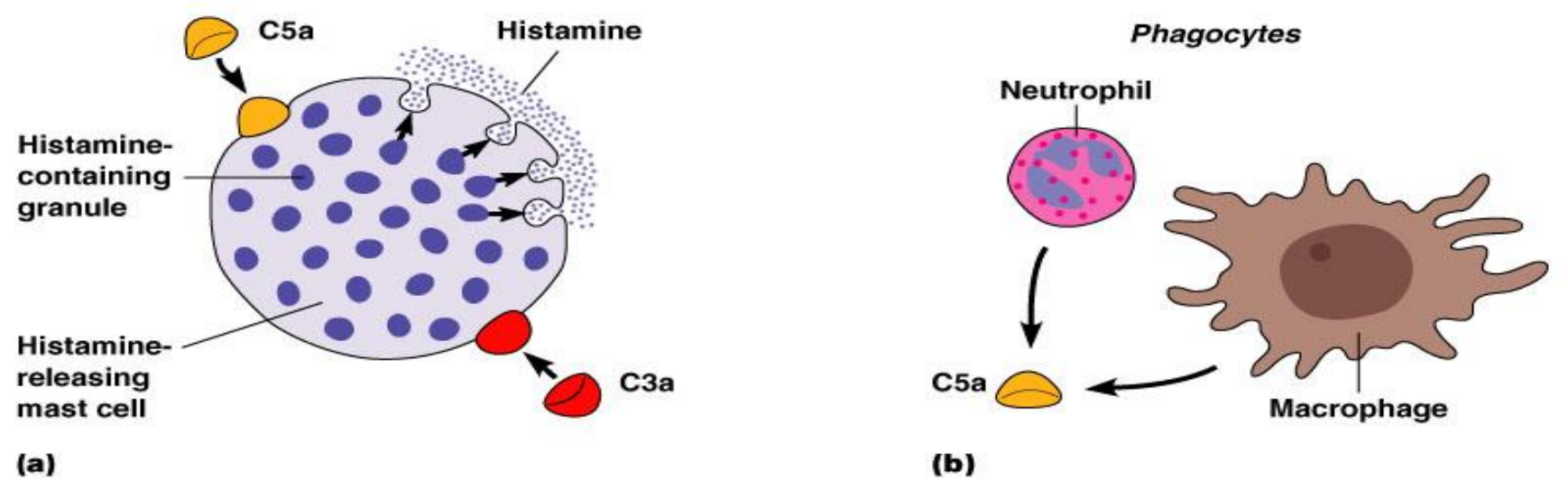


C3b

- Many C3b molecules are produced by the C3 activation complex.
- 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.



C3a



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

Building the C5 activation complex

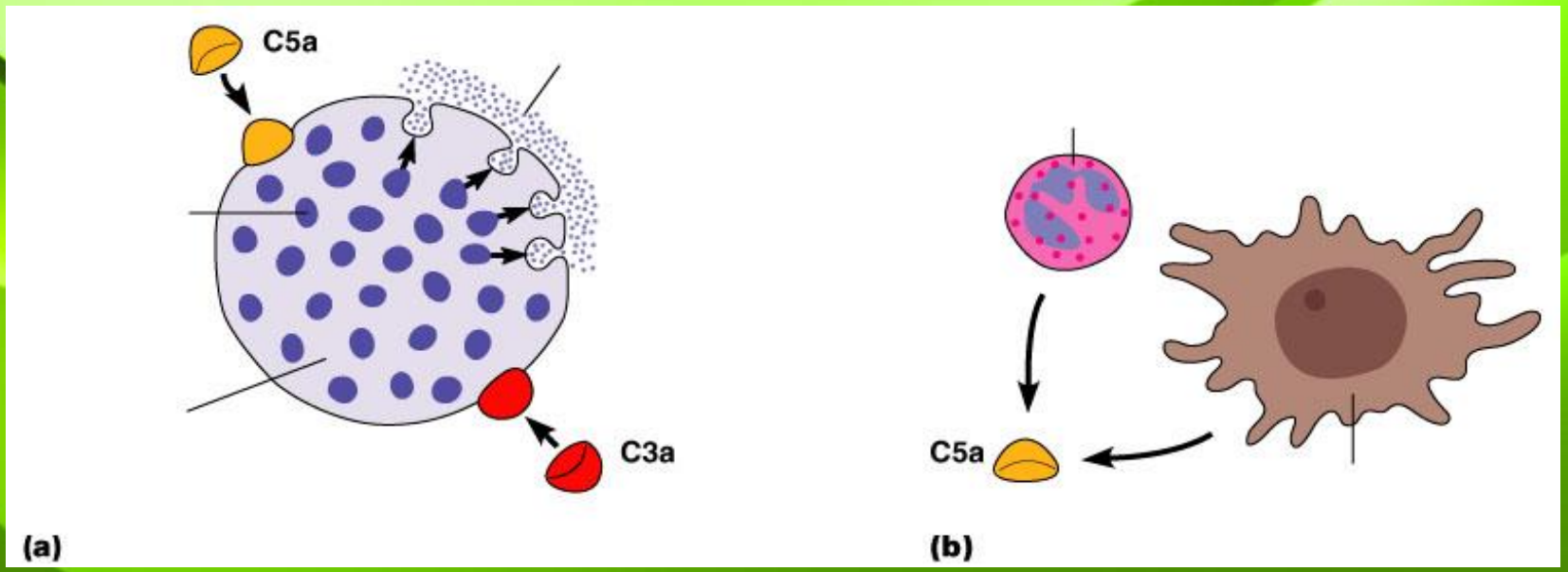
- Eventually enough C3b is cleaved that the surface of the bacteria begins to become saturated with it.
- C2b and C4b which make up the C3 activation complex has a slight affinity for C3b and C3b binds to them
- When C3b binds to C2b and C4b it forms a new complex referred to as the C5 activation complex

The C5 activation complex

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

- Many C5b proteins are produced by the C5activation complex. These C5b begin to coat the surface of the bacteria.

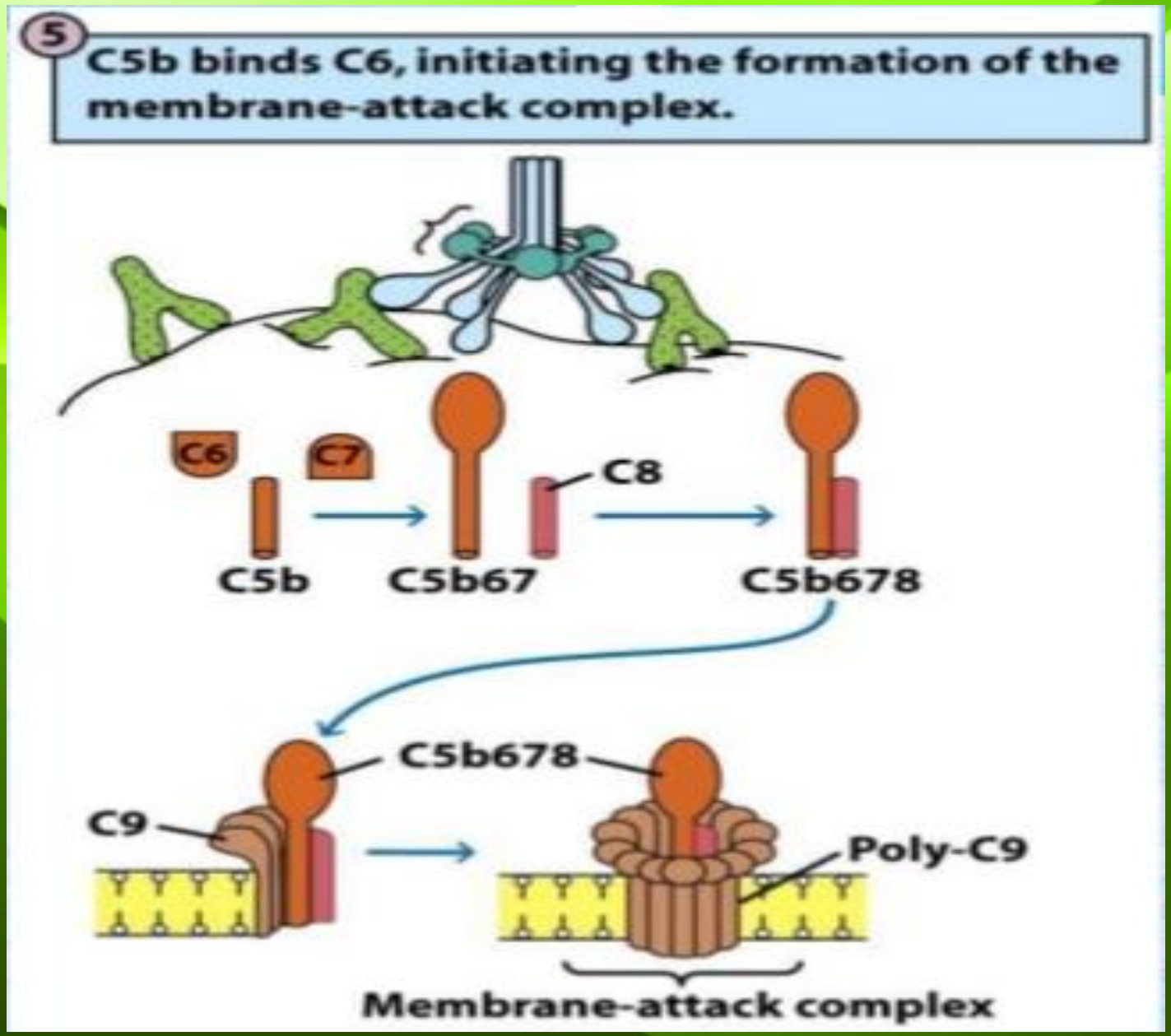
The function of C5a



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

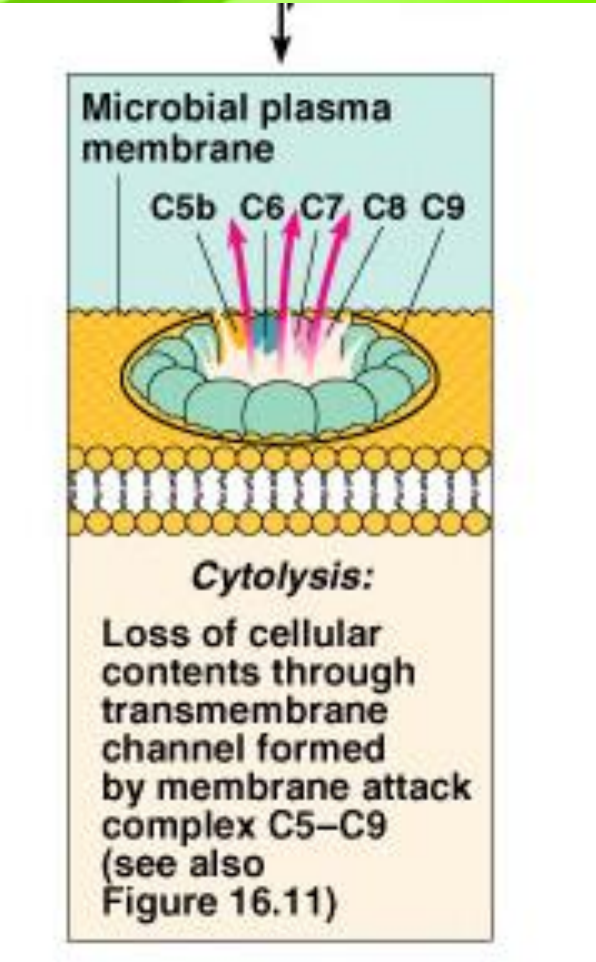
Building the Membrane Attack complex

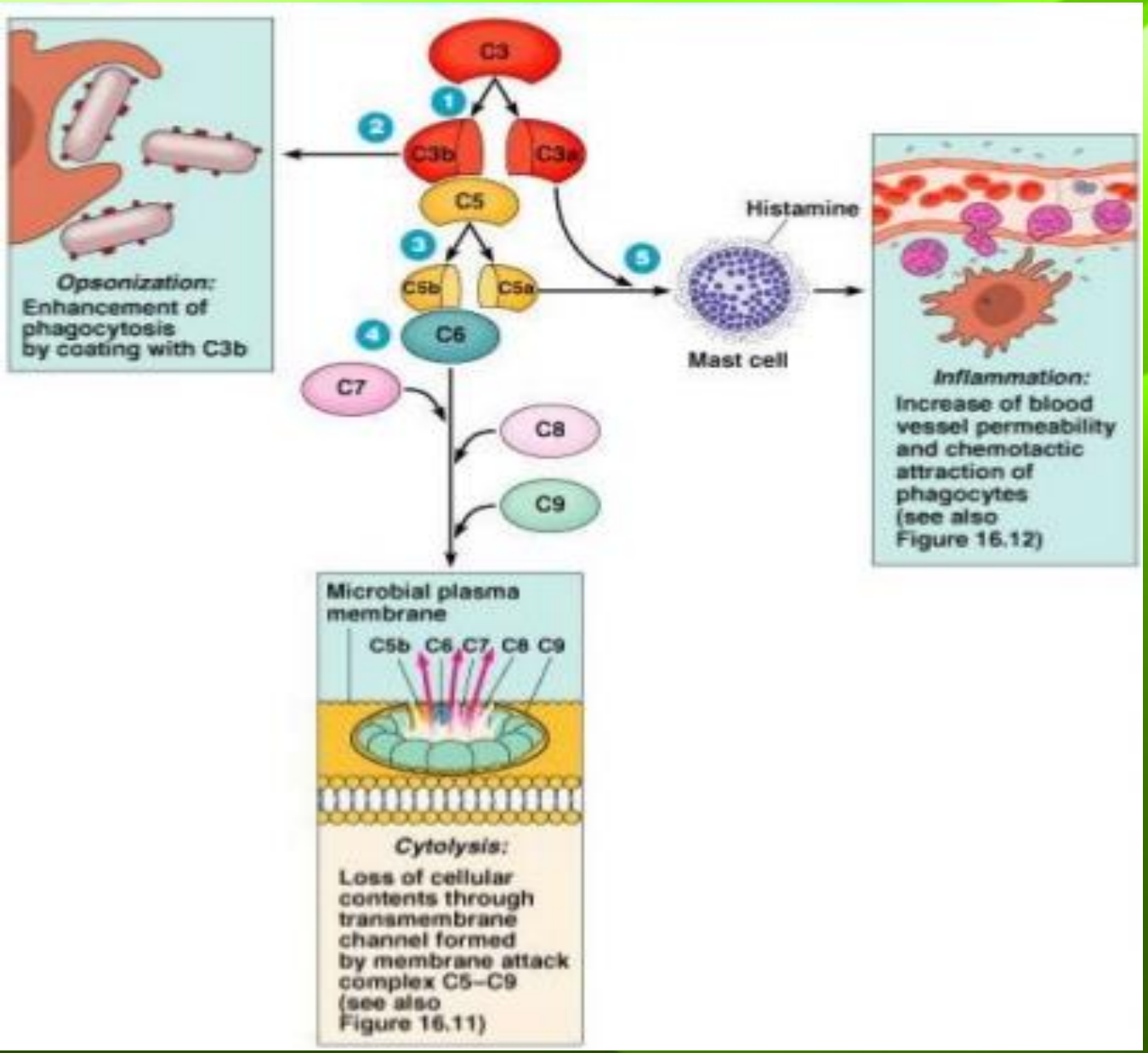
- C5b on the surface of bacteria binds to C6
- The binding of C6 to C5b activates C6 so that it can bind to C7
- C7 binds to C8 which in turn binds to many C9's
- Together these proteins form a circular complex called the Membrane attack complex (MAC)


5
C5b binds C6, initiating the formation of the membrane-attack complex.
C6
C7
C8
C5b
C5b67
C5b678
C5b678
C9
Poly-C9
Membrane-attack complex

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 cells inner integrity is compromised and it dies**




C3
1
2
C3b
C3a
C5
3
C5b
C5a
4
C6
C7
C8
C9
5
Histamine
Mast cell
Opsonization:
Enhancement of phagocytosis by coating with C3b
Inflammation:
Increase of blood vessel permeability and chemotactic attraction of phagocytes (see also Figure 16.12)
Microbial plasma membrane
C5b C6 C7 C8 C9
Cytolysis:
Loss of cellular contents through transmembrane channel formed by membrane attack complex C5–C9 (see also Figure 16.11)

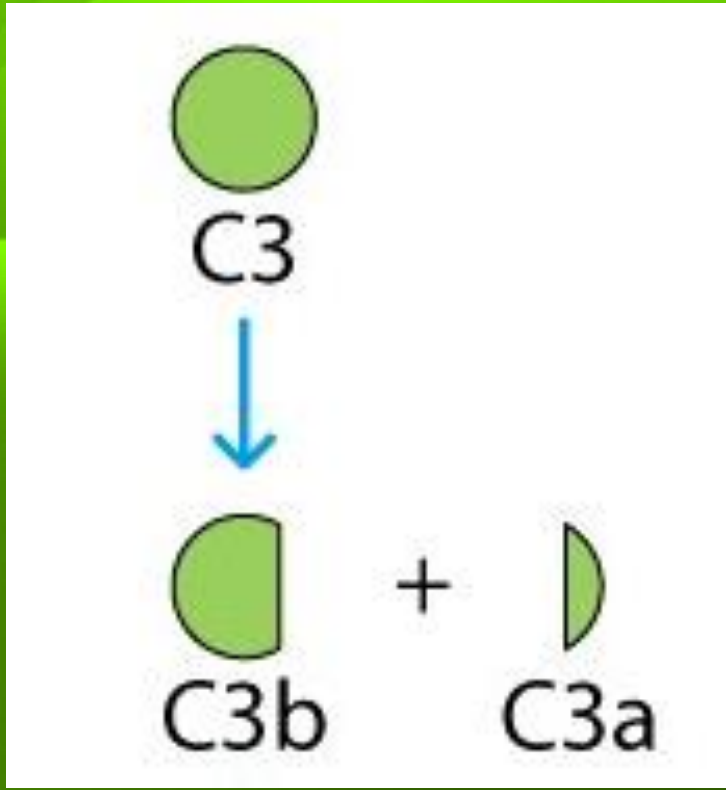
The alternative pathway

- The alternative pathway is part of the non-specific defense because it does not need antibodies to initiate the pathway.

- The alternative pathway is slower than the Classical pathway

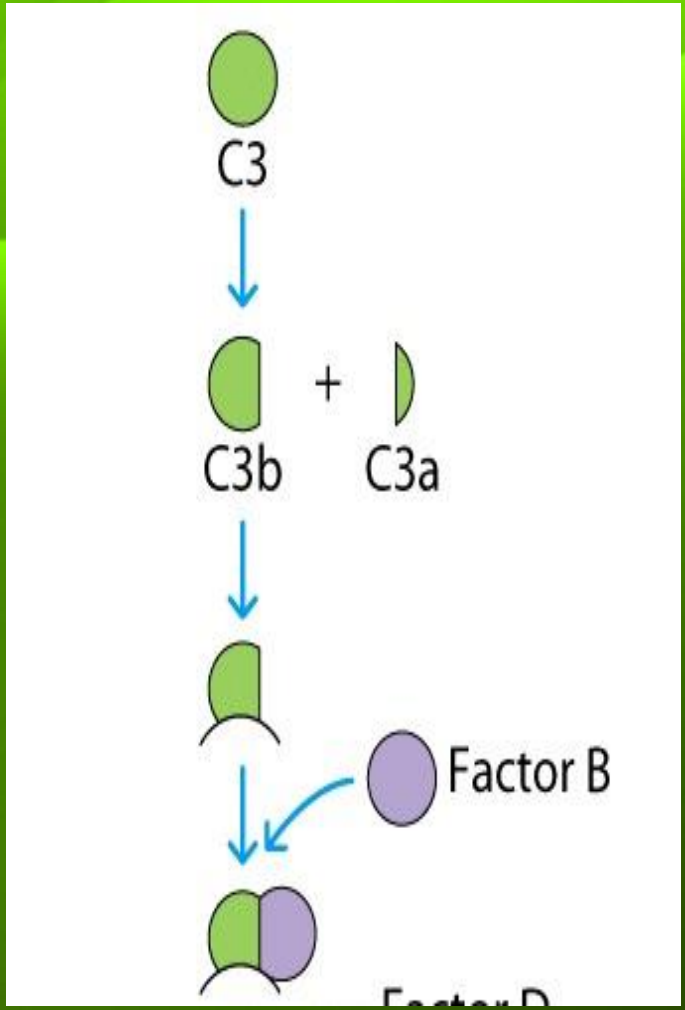
Initiation of The Alternative pathway

- C3 contains a unstable bond.
- This unstable bond makesC3 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



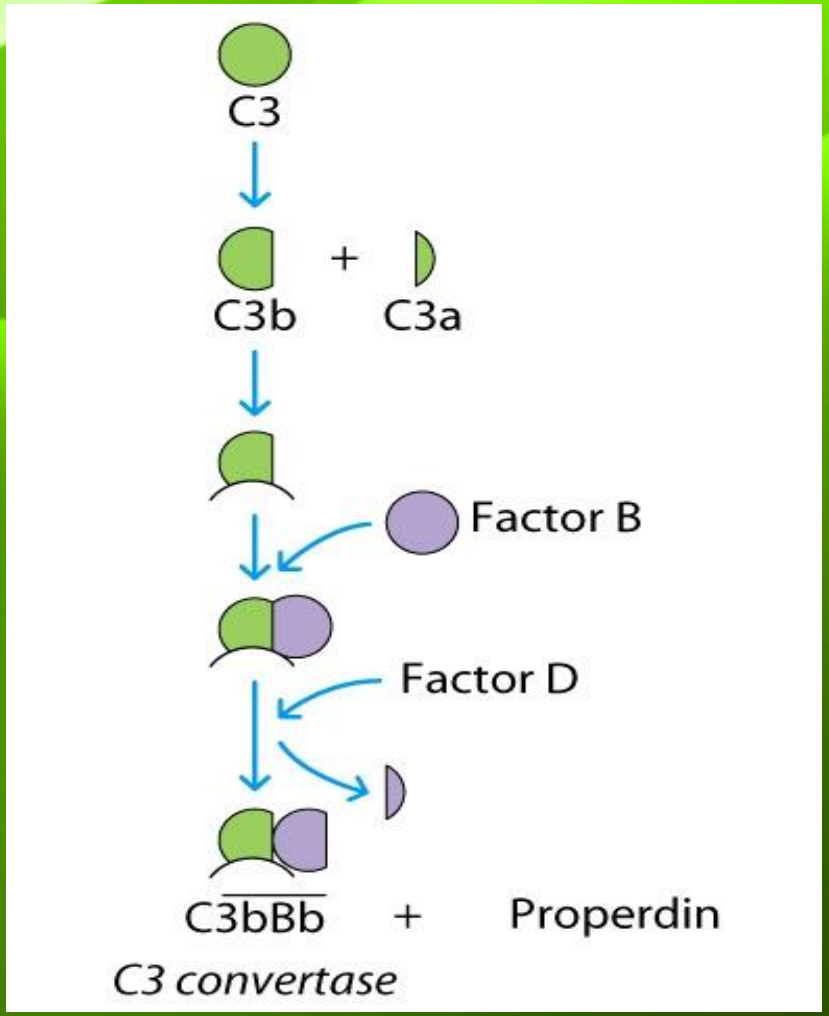
Factor B

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

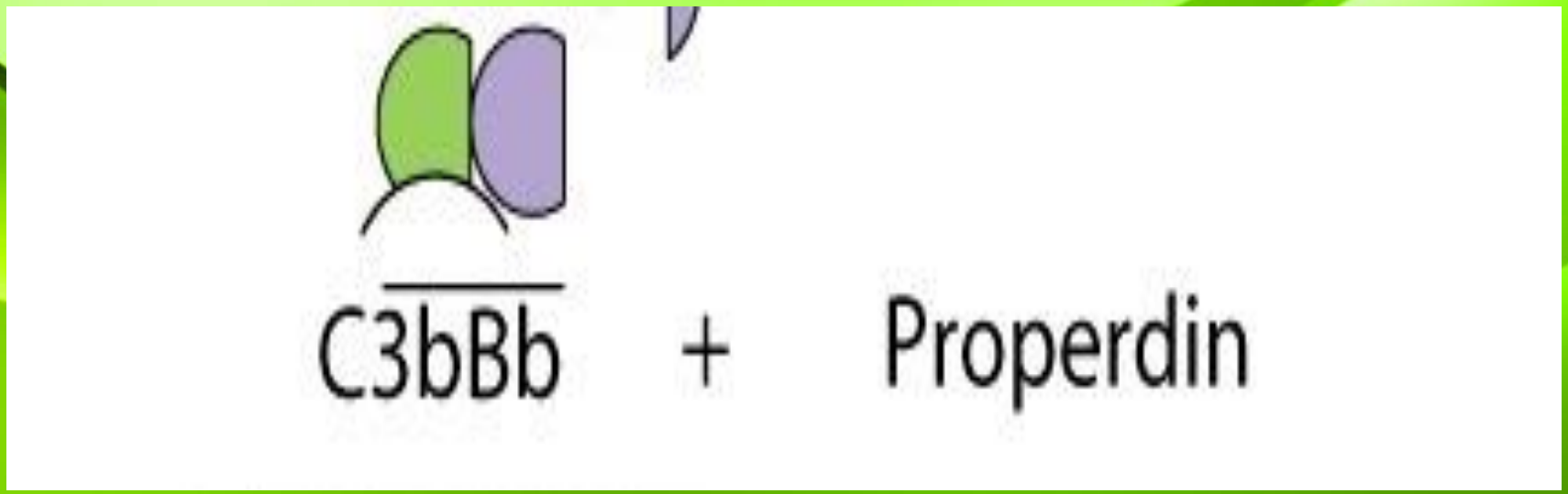


Factor D

- 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.



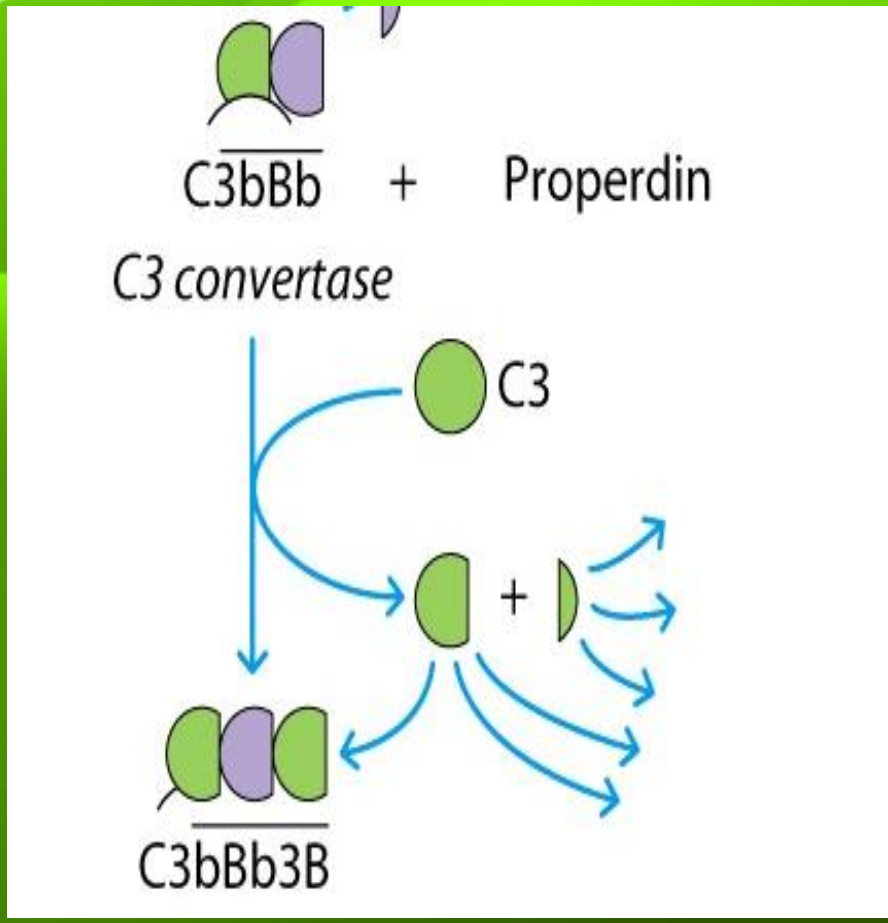
The C3 activation complex



- Properdin, also called factor P, binds to the C3bBb complex to stabilize it.
- C3bBbP make up the C3 activation complex for the alternative pathway

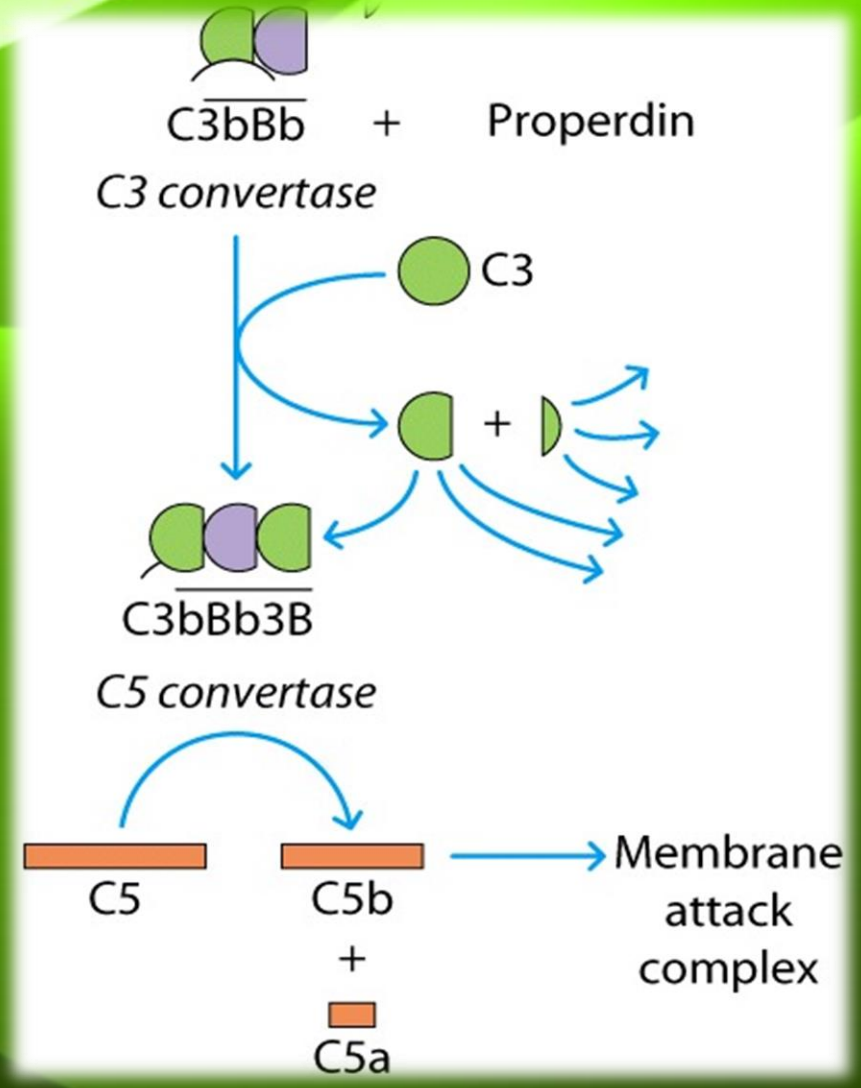
The C3 activation Complex

- **The C3 activation complex causes the production of more C3b.**
- **This allows the initial steps of this pathway to be repeated and amplified.**

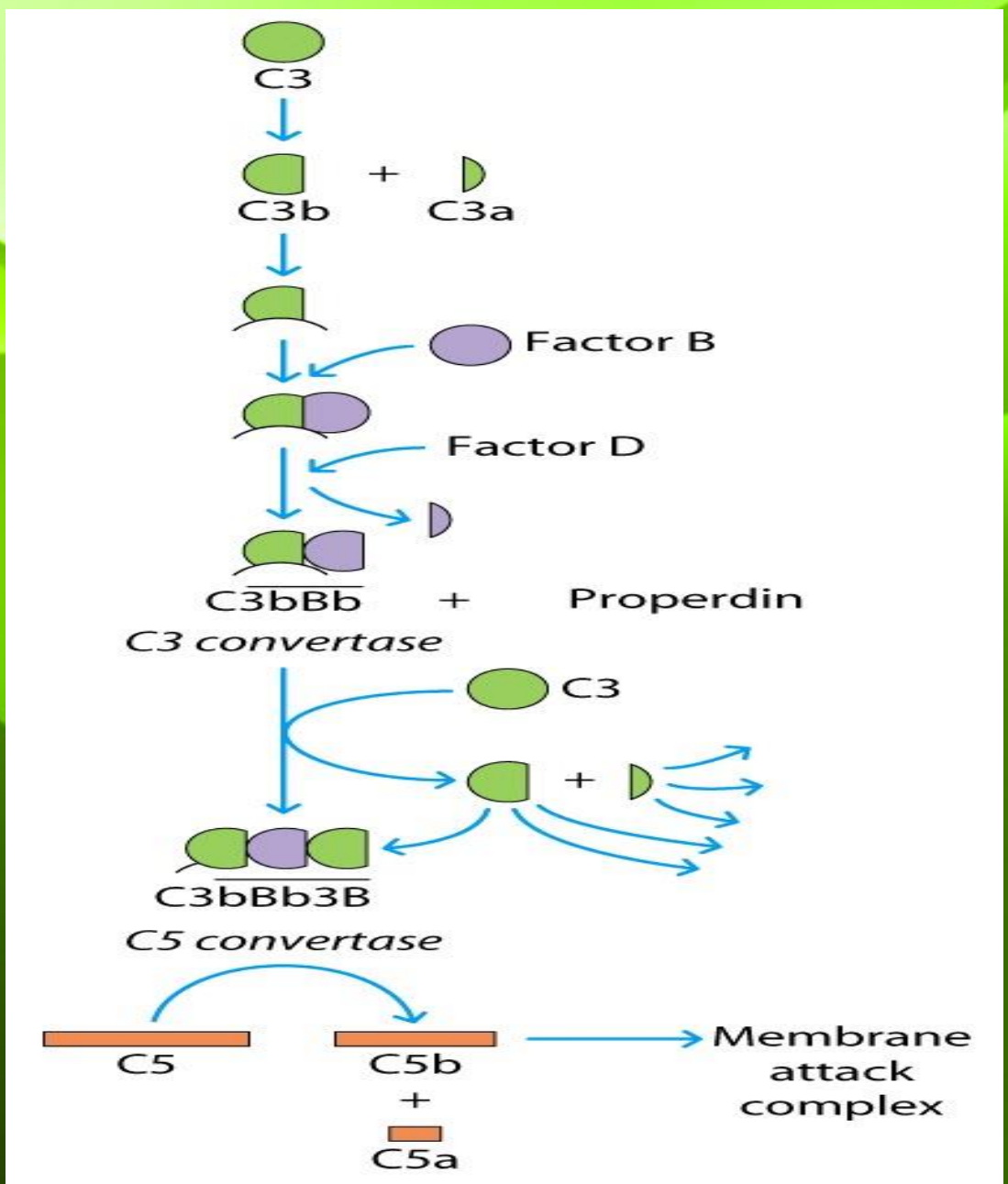


C5 activation complex

- 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**



Mannose binding lectin pathway

- Independent of antibodies
- Lectins are proteins that bind to specific cb targets.
- Activated by mannose binding lectin (MBL) – lectin that binds to mannose residues on the microbes.
- MBL is similar to c1q in structure and function.

Lectin pathway