The Complement system

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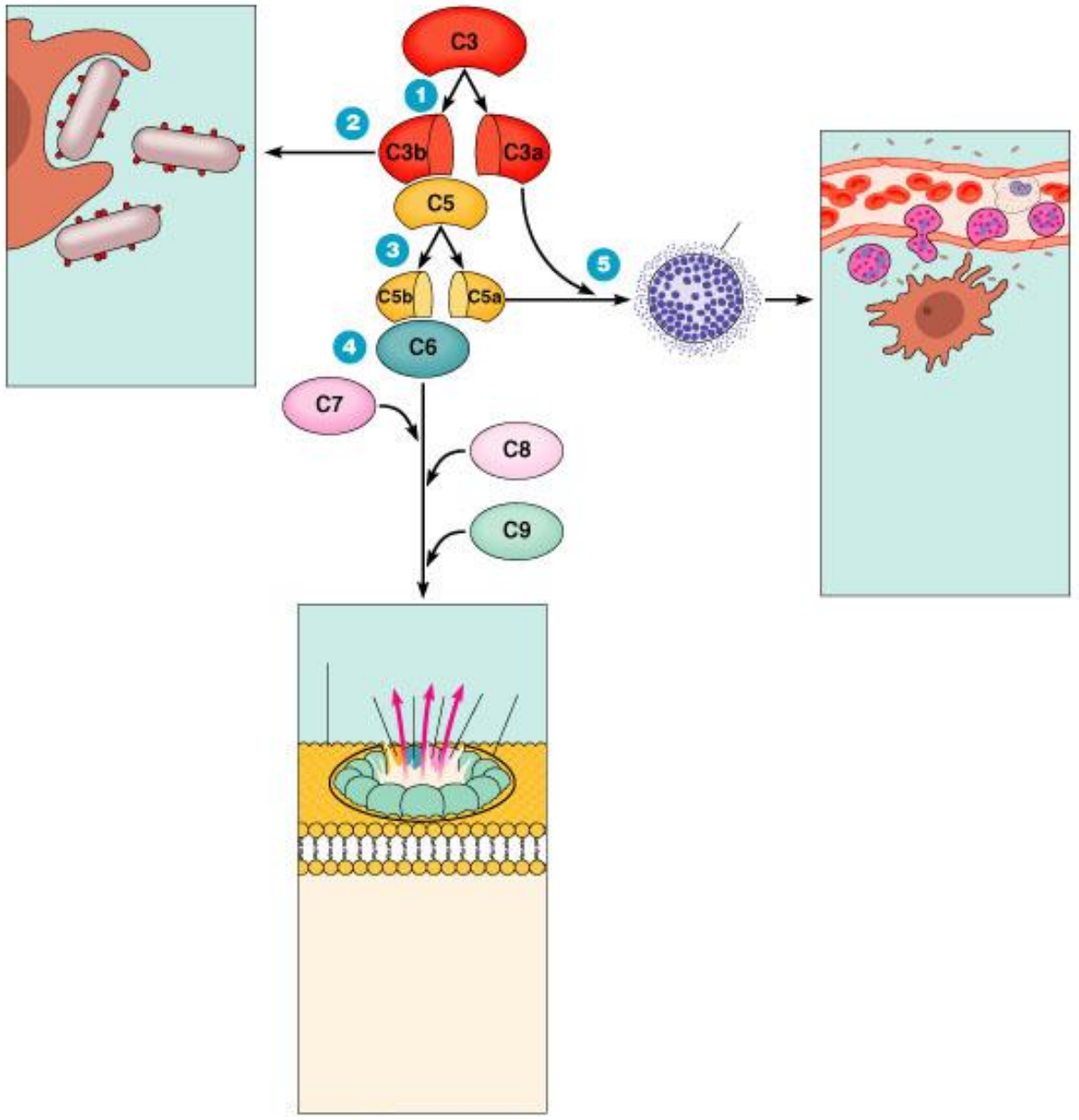


The complement system

- A defensive system consisting of over 30 proteins produced by the liver and found in circulating blood serum.
- Complement kills microbes in three different ways
  - 1. opsonization
  - 2. inflammation
  - 3. Cytolysis

A Cascade system

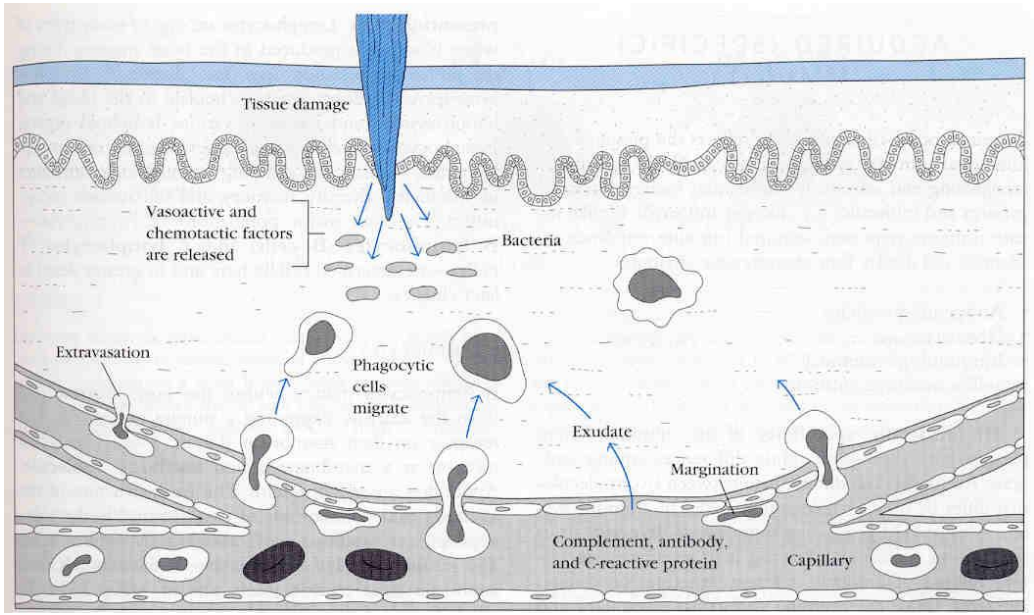
- The complement works as a cascade system.
  - Cascade is when one reaction triggers another reaction which trigger others and so on. These types of systems can grow exponentially very fast.

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

Two Pathways

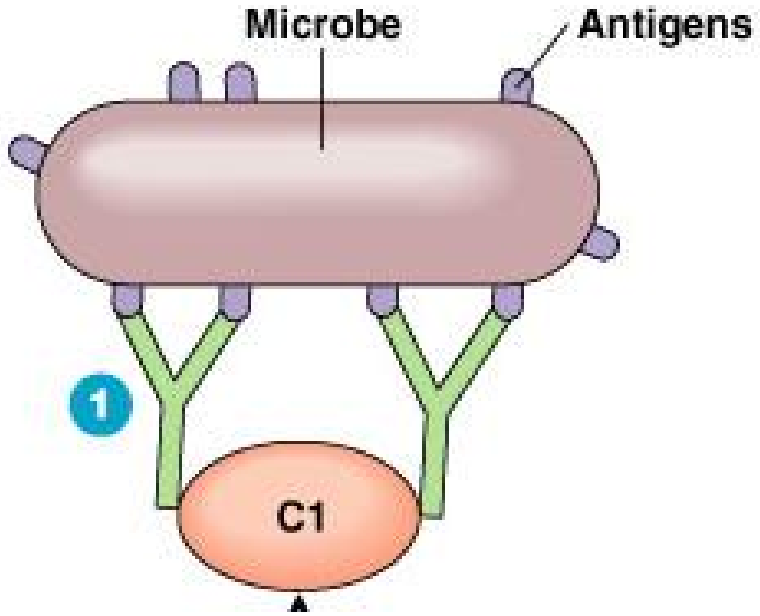
- The complement pathway can be activated by either of two different pathways.
  - Classical pathway (specific immune system)
  - alternative (non-specific immune system)



The Classical Pathway

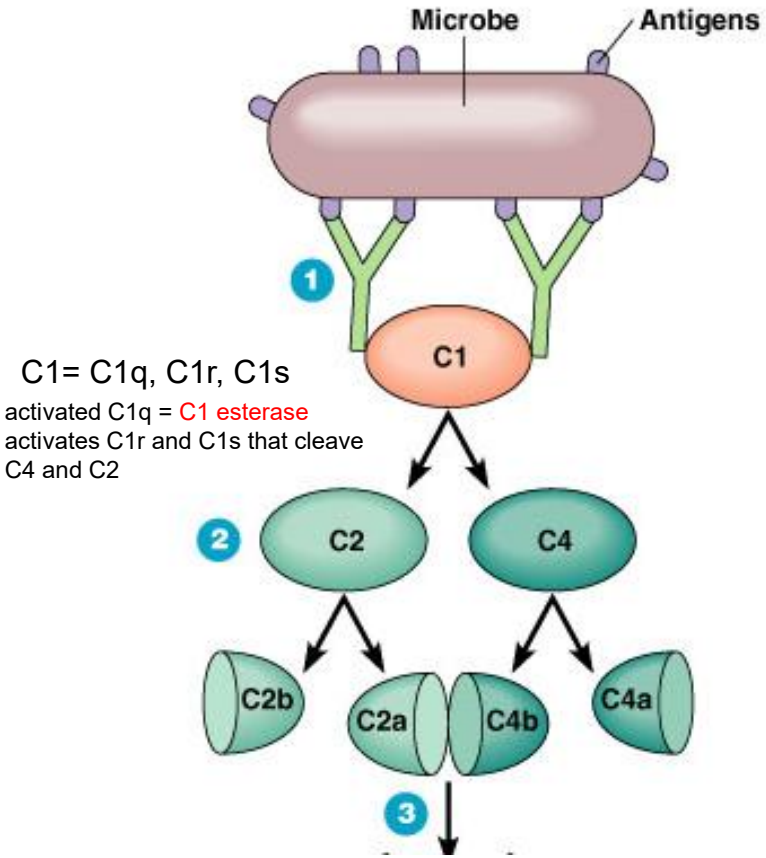
- The classical pathway is considered to be part of the specific immune response because it relies on antibodies to initiate it.

- C1 becomes activated when it binds to the ends of antibodies



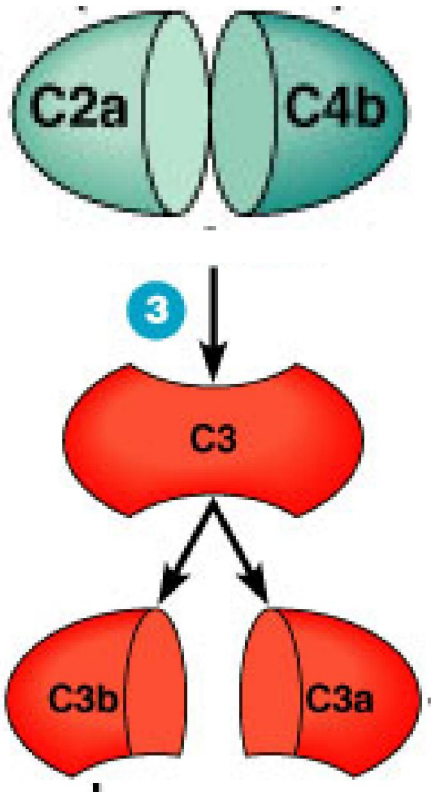
The building of a C3 activation complex

- 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 C2a and C4b bind together on the surface of the bacteria C3 convertase
- C2b and C4a diffuse away



C3 Activation complex

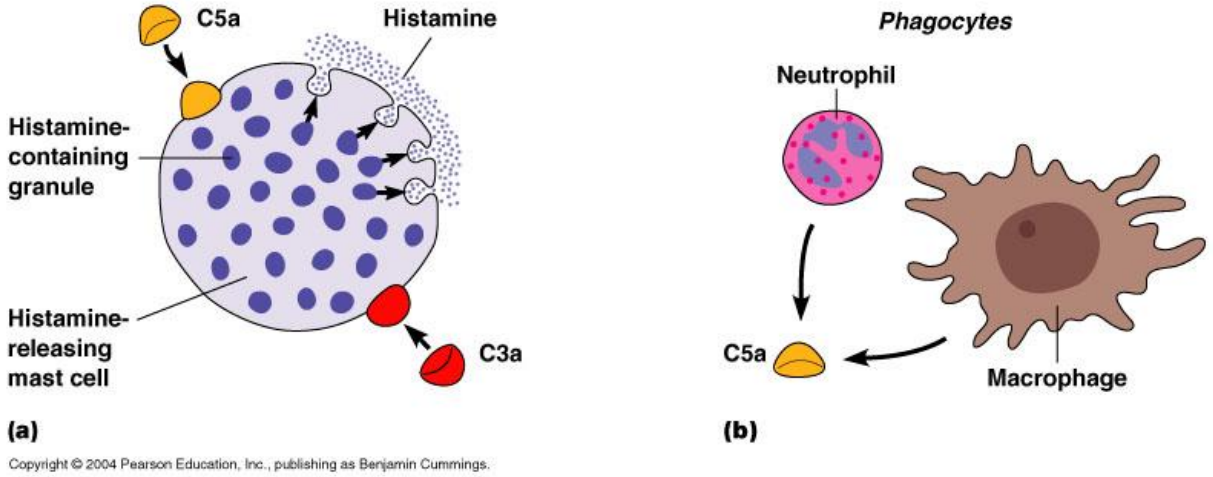
- C2a and C4b bind together on the surface to form a C3 activation complex C3 convertase
- The function of the C3 activation complex is to activate C3 proteins.
  - This is done by cleaving C3 into C3a and C3b



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

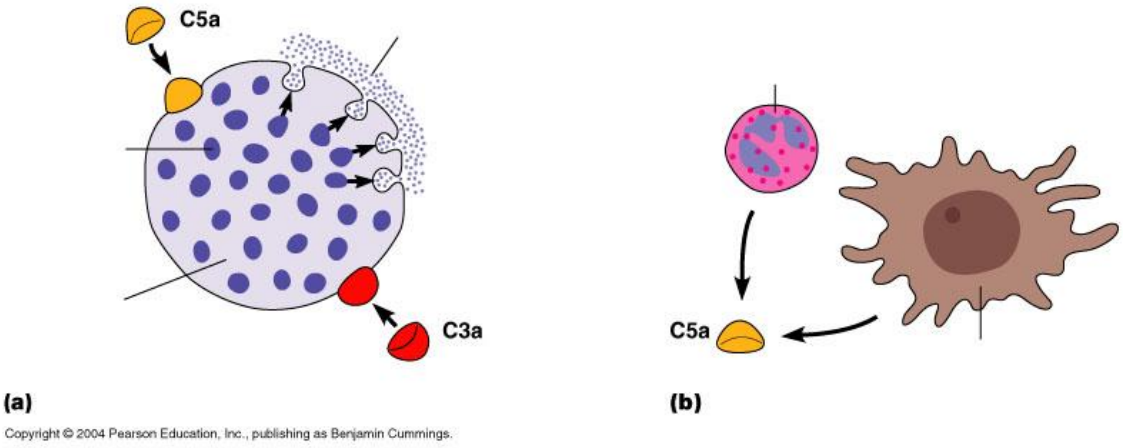
- Eventially enough C3b is cleaved that the surface of the bacteria begins to become saturated with it.
- C2a and C4b which make up the C3 activation complex has a slight affinity for C3b and C3b binds to them
- When C3b binds to C2a and C4b it forms a new complex referred to as the C5 activation complex C5 convertase

The C5 activation complex

- The C5 activation complex (C2a, 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



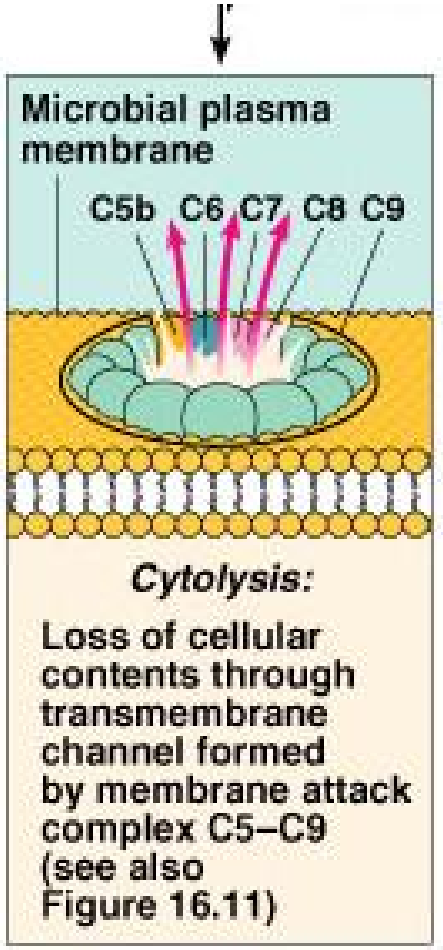
- C5a disperses away from the bacteria.
  - Binds to mast cells and increases inflammation.
  - Most powerful chemotactic factor known for leukocytes

Building the Membrane Attack complex

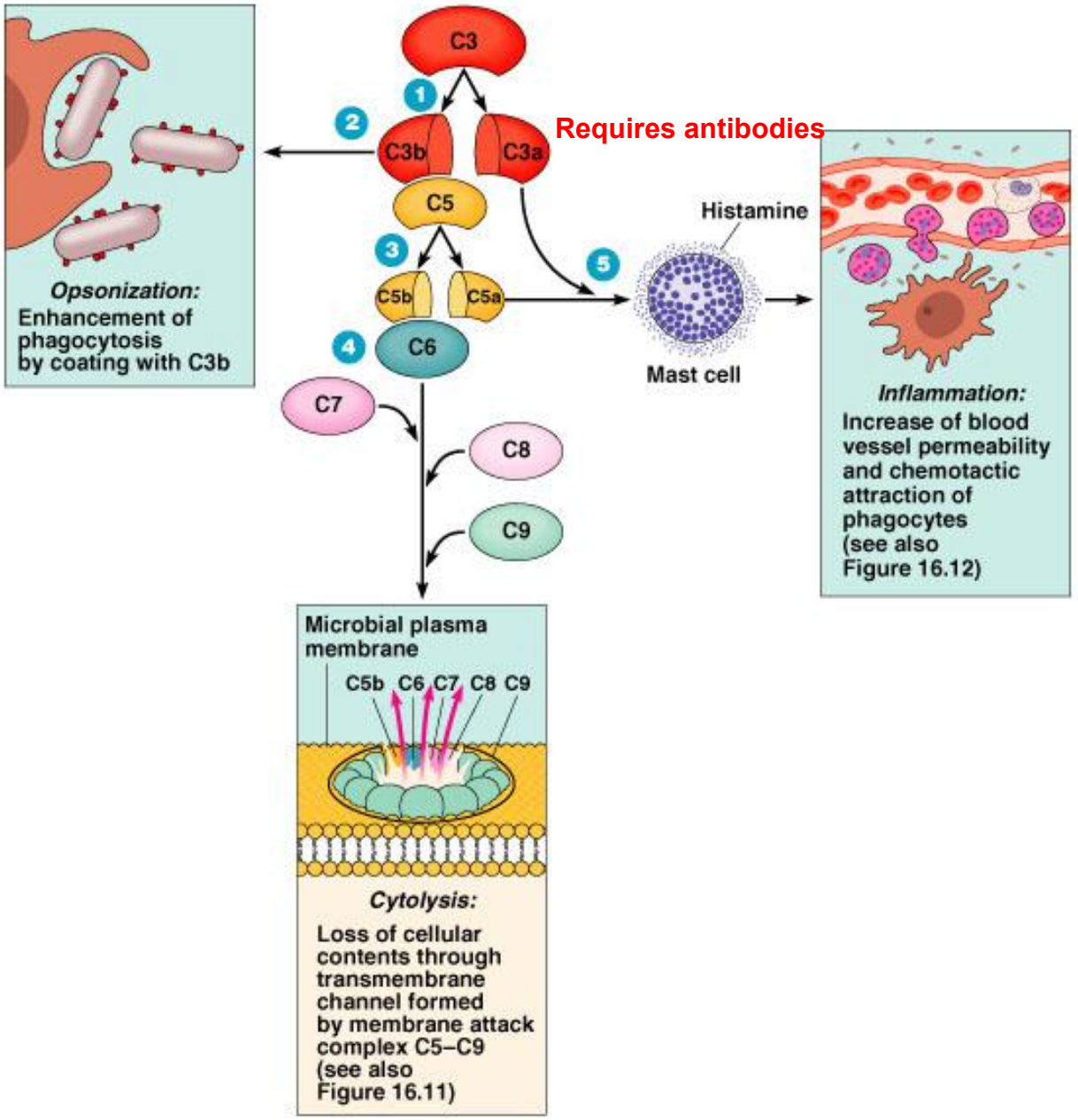
- C5b on the surface of bacteria binds to C6
- The binding of C6 to C5b activates C6 so that it can bind to C7
- C7 binds to C8 which in turn binds to many C9’s
- Together these proteins form a circular complex called the Membrane attack complex (MAC)

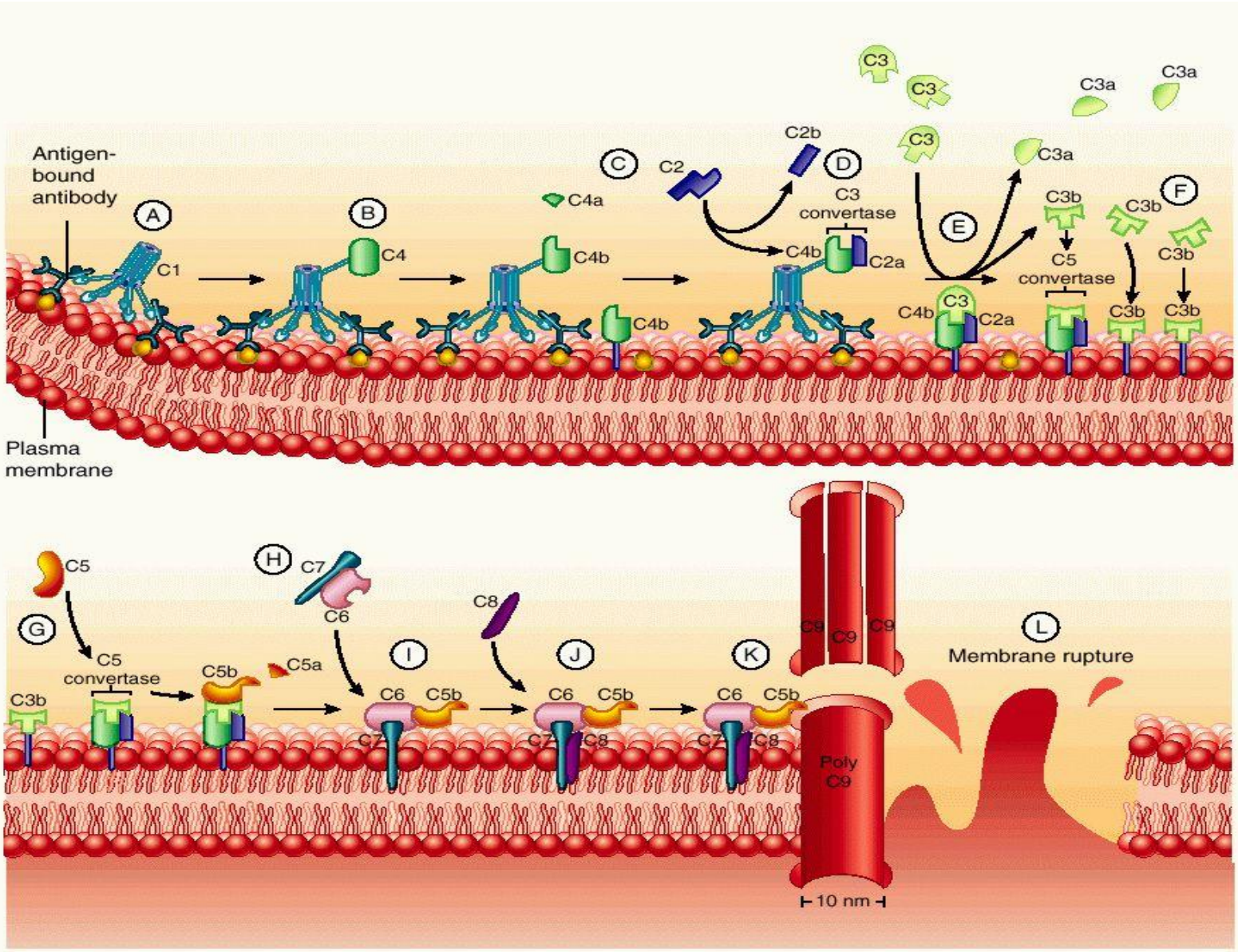
Membrane Attack complex

- 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 bacterium's inner integrity is compromised and it dies



Overview



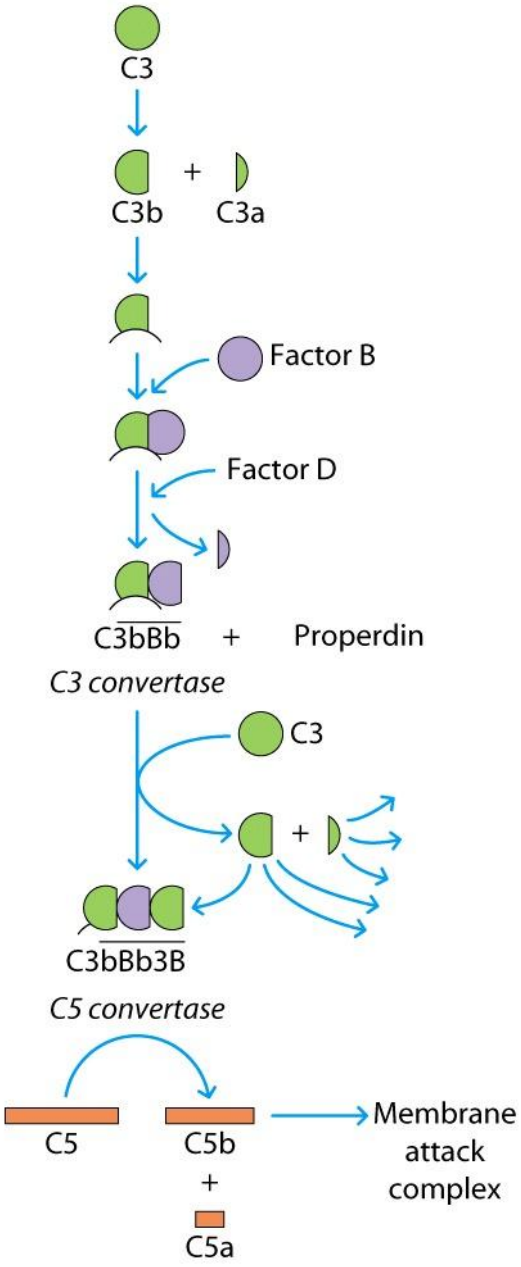

Antigen-bound antibody
A
C1
B
C4
C4a
C4b
C4b
C
C2
C2b
D
C3 convertase
C4b
C2a
C3
C3
C3
C3a
C3a
E
C3b
C5 convertase
C4b
C3
C2a
C3b
C3b
F
C3b
C3b
Plasma membrane
C5
G
C5 convertase
C3b
C5b
C5a
H
C7
C6
C8
I
C6
C5b
CZ
J
C6
C5b
CZ
C8
K
C6
C5b
CZ
C8
C9
C9
C9
Poly C9
10 nm
L
Membrane rupture

The alternative pathway

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

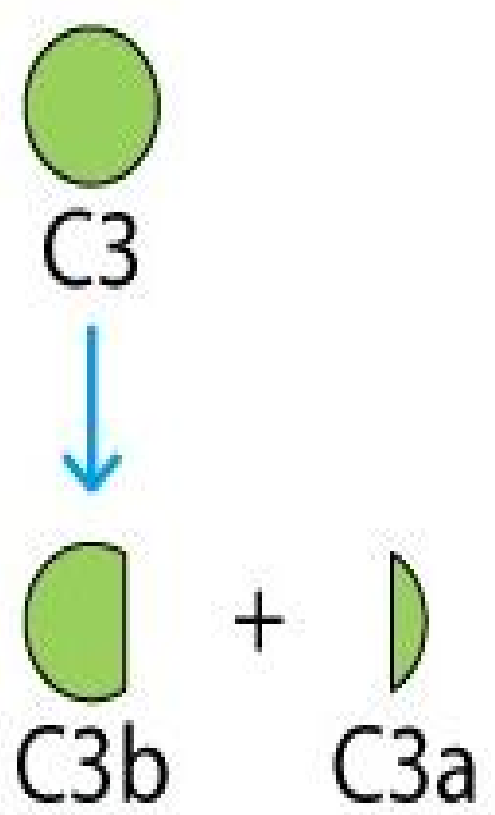
- The alternative pathway is slower than the Classical pathway

The Alternative complement pathway



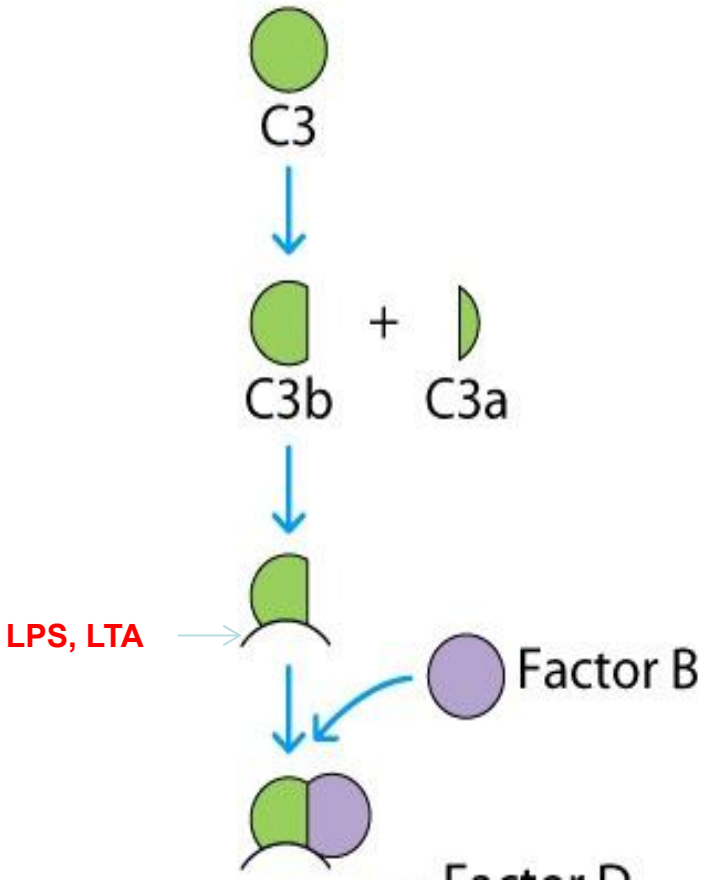
Initiation of The Alternative pathway

- 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
- Normal state: C3 → C3a + C3b
- C3b degradation ← C3bH + I ←



Factor B

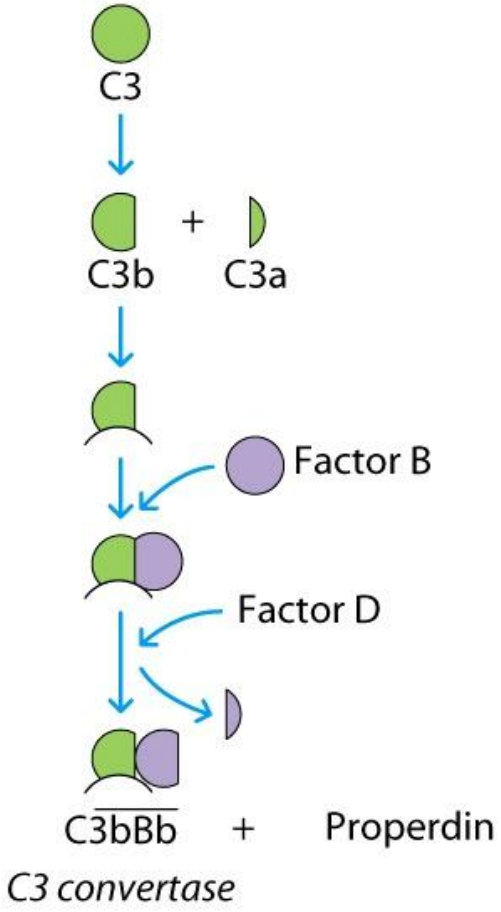
- C3b on the surface of a bacterium (ex. LPS) binds to another plasma protein called factor B



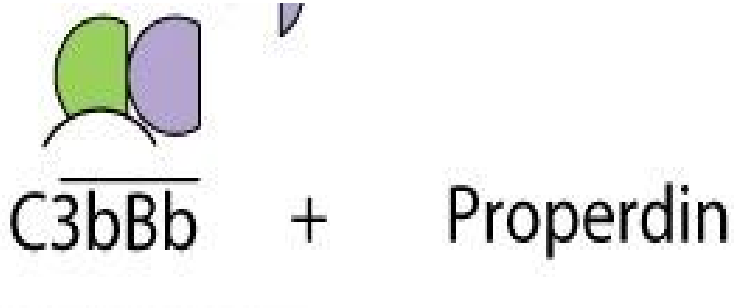
Factor D

- 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

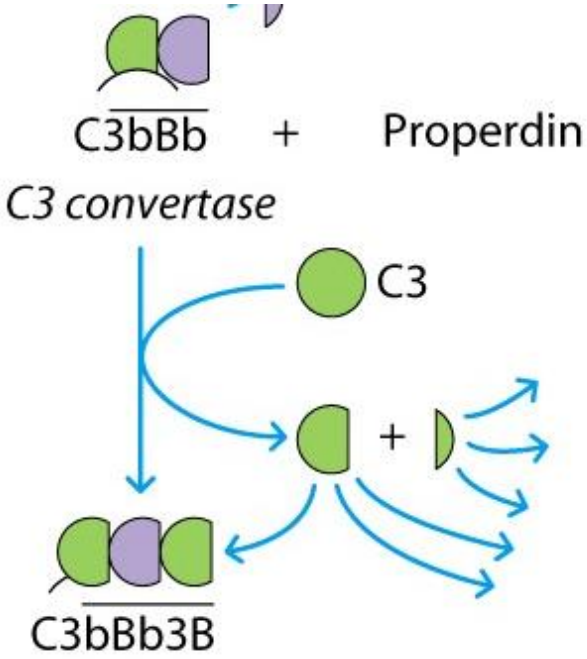


- Properdin, also called factor P, binds to the C3bBb complex to stabilize it.

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

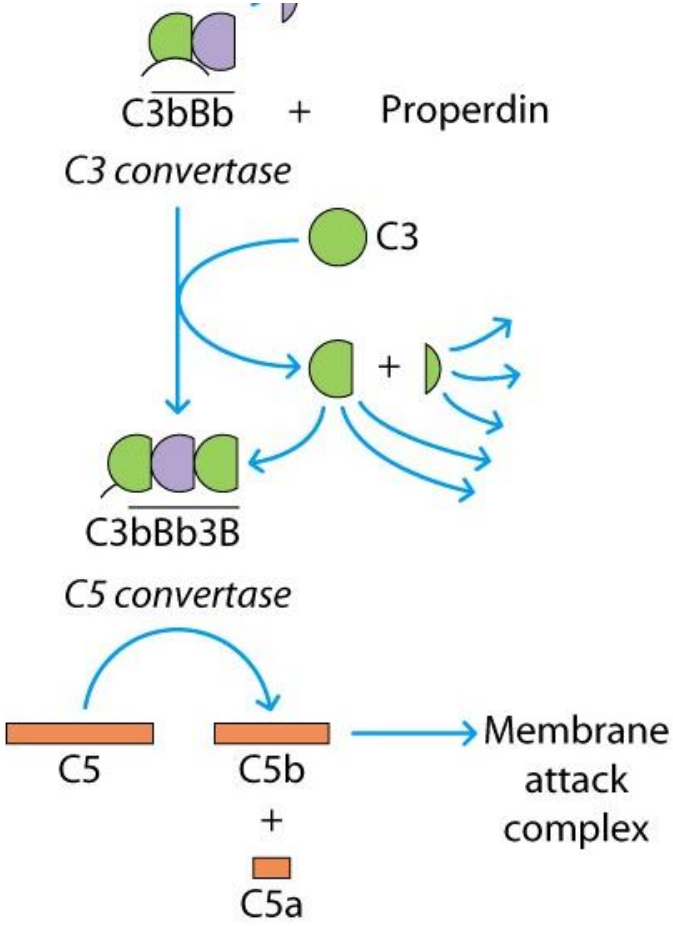
The C3 activation Complex

- 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

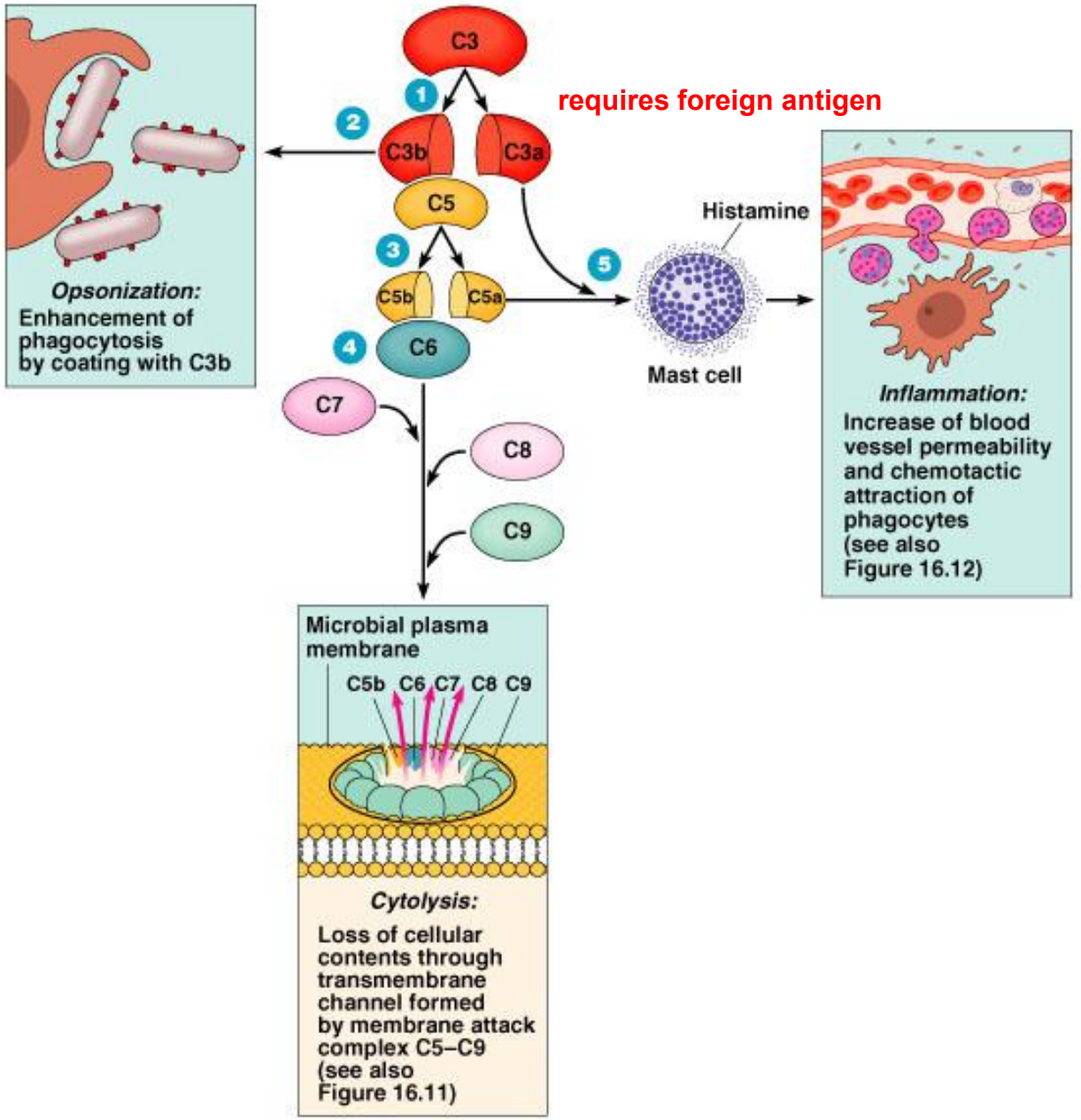


C5 activation complex

- 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.



Overview



requires foreign antigen