The Complement System

By
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- The **complement system** refers to a group of nonimmunoglobulin plasma/serum proteins (more than 30 proteins) circulating in the blood and bathing the fluids surrounding tissues usually inactive form. They are sequentially activated. Majority of the plasma complement components are made in hepatic parenchymal cells, except for C1 (a calcium-dependent complex of the three glycoproteins C1q, C1r, and C1s), which is primarily synthesized in the epithelium of the gastrointestinal and urogenital tracts.

❖ **Some of them are specialized to recognize :-**

- 1- Antigen-antibody complexes
- 2- Microbial cell surface molecules
- 3- Soluble pattern-recognition receptors such as MBL

They are causing irreversible damage to membranes of target cells.

❖ **While others control complement activation.**

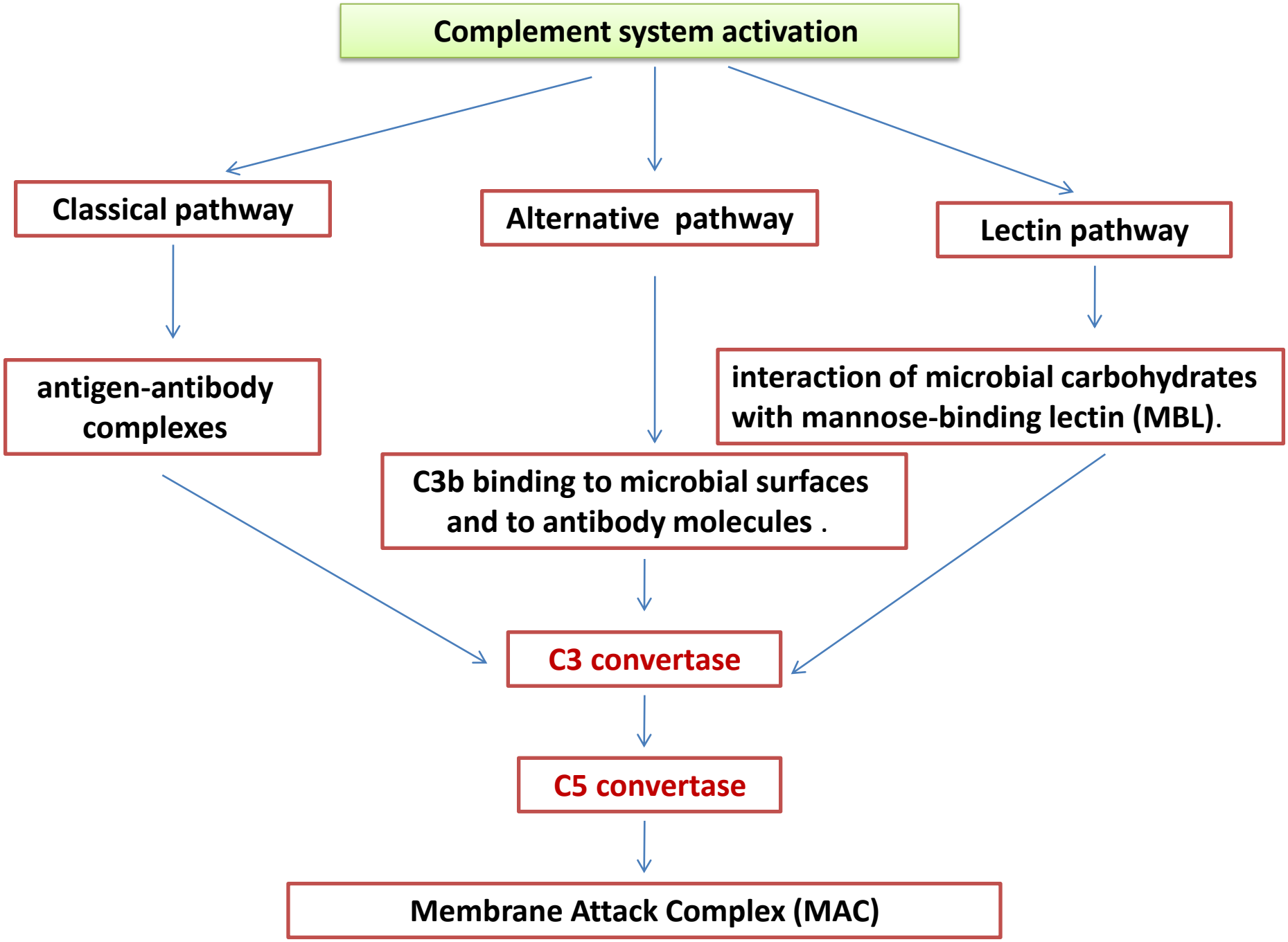

Complement system activation
Classical pathway
Alternative pathway
Lectin pathway
antigen-antibody complexes
interaction of microbial carbohydrates with mannose-binding lectin (MBL).
C3b binding to microbial surfaces and to antibody molecules .
C3 convertase
C5 convertase
Membrane Attack Complex (MAC)

Table 5-2 Initiators of Three Complement Activation Pathways

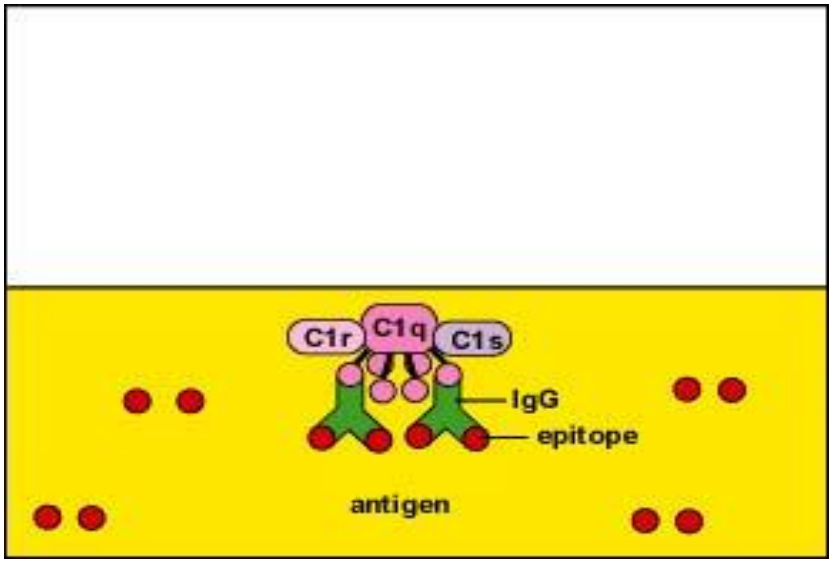
Pathway	Initiators
Classic	Immune complexes Apoptotic cells Certain viruses and gram-negative bacteria C-reactive protein bound to ligand
Alternate	Various bacteria, fungi, viruses, or tumor cells
Mannose-binding lectin	Microbes with terminal mannose groups

Adapted from Walport MJ: Complement, N Engl J Med 344:1058–1065, 2001.

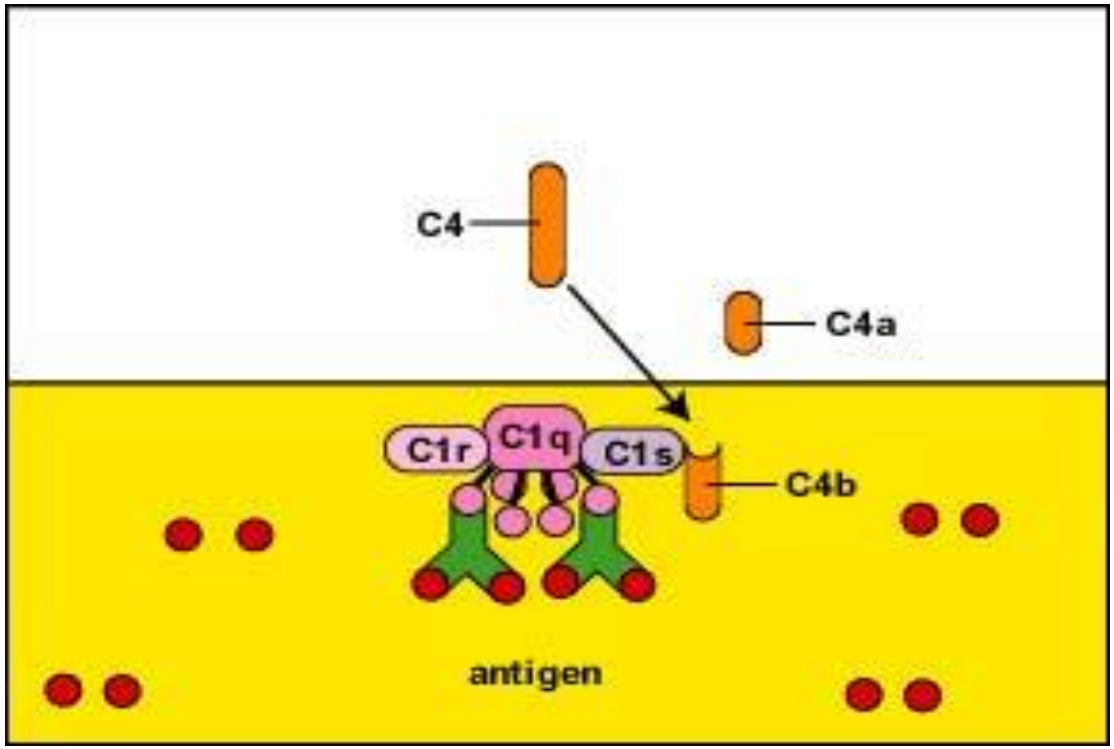
1. The Classical Complement Pathway

- The classic complement pathway is one of the major effector mechanisms of antibody-mediated immunity. The principal components of the classic pathway are C1 through C9. The sequence of component activation—C1, 4, 2, 3, 5, 6, 7, 8, and 9— does not follow the expected numeric order.

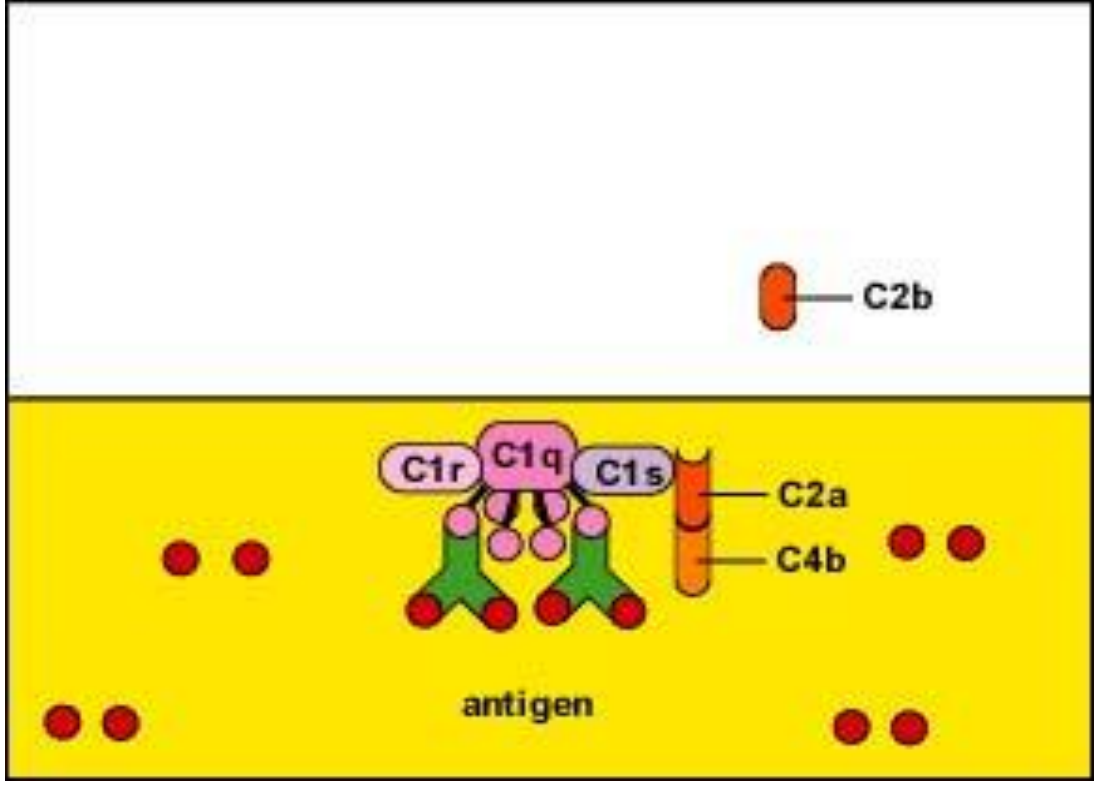
- The complement pathway typically requiring IgG or IgM reacting with an antigen for activation and it is involve**11 major serum protein components**.
- The reactions occur as follows:



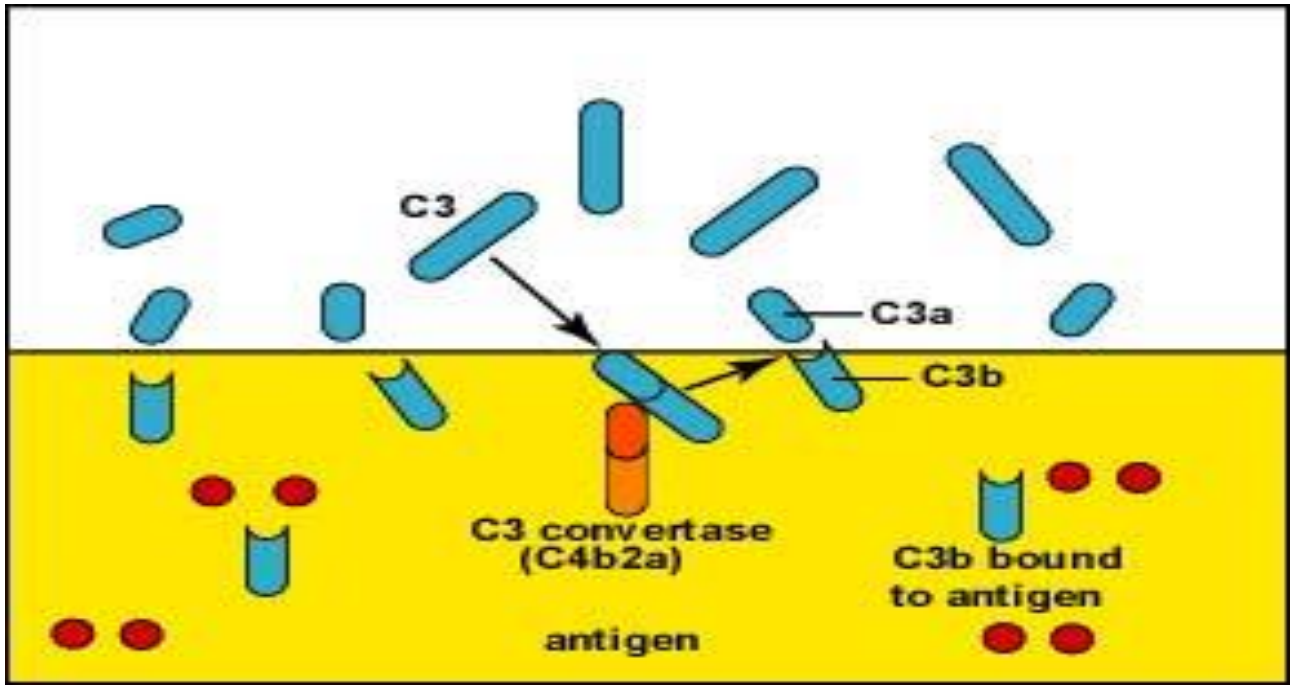
a. A**ctivating** the classical complement pathway occurs when **C1q** bind to immune complex (Ag+Ab) (Ab=**IgG or IgM)**. The Fab of Ab molecules bind to epitopes on an antigen. C1q, C1r, and C1s then assembles on the Fc portion of the antibodies to form **C1**, the first enzyme of the classical complement pathway.



b. The activated C1 now enzymatically cleaves C4 into C4a and C4b. The C4b then binds to adjacent proteins and carbohydrates on the surface of the antigen and then binds C2. The activated C1 cleaves C2 into C2a and C2b forming **C4b2a,** the enzyme activity of this complex is called **C3 convertase**



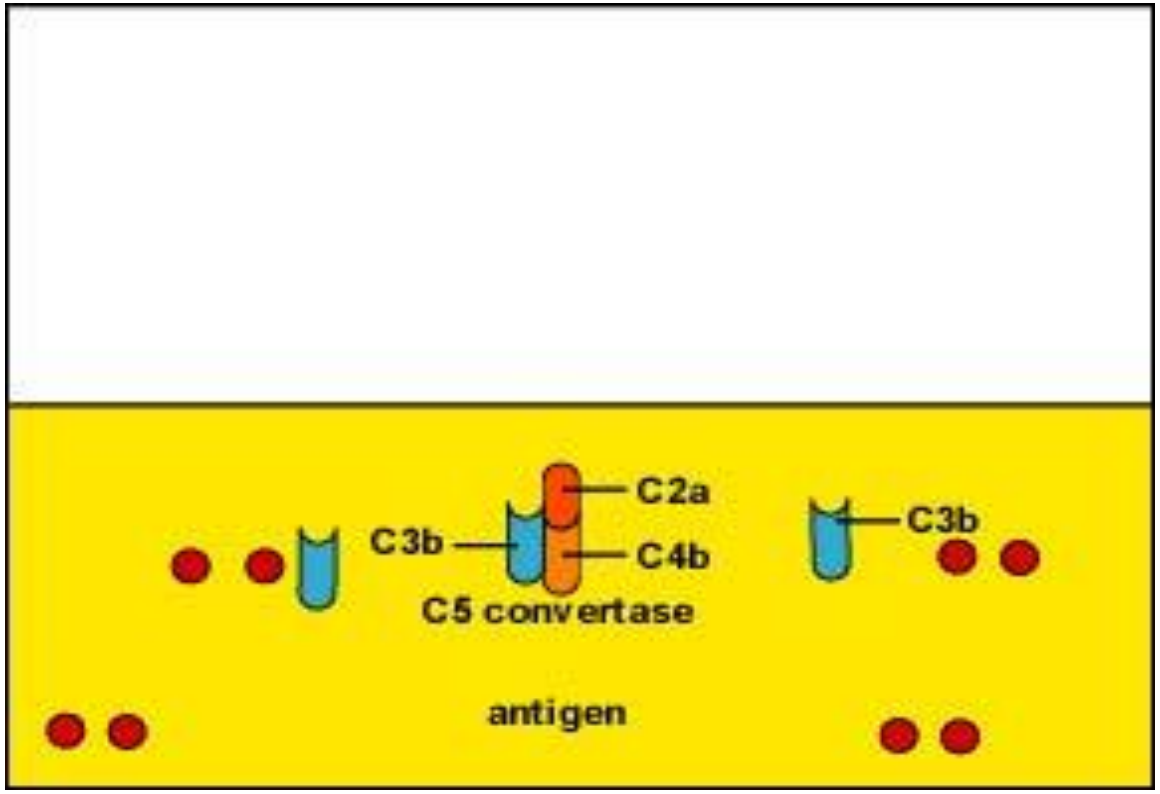
Cleavage of C2 and Formation of C3 Convertase during the Classical Complement Pathway

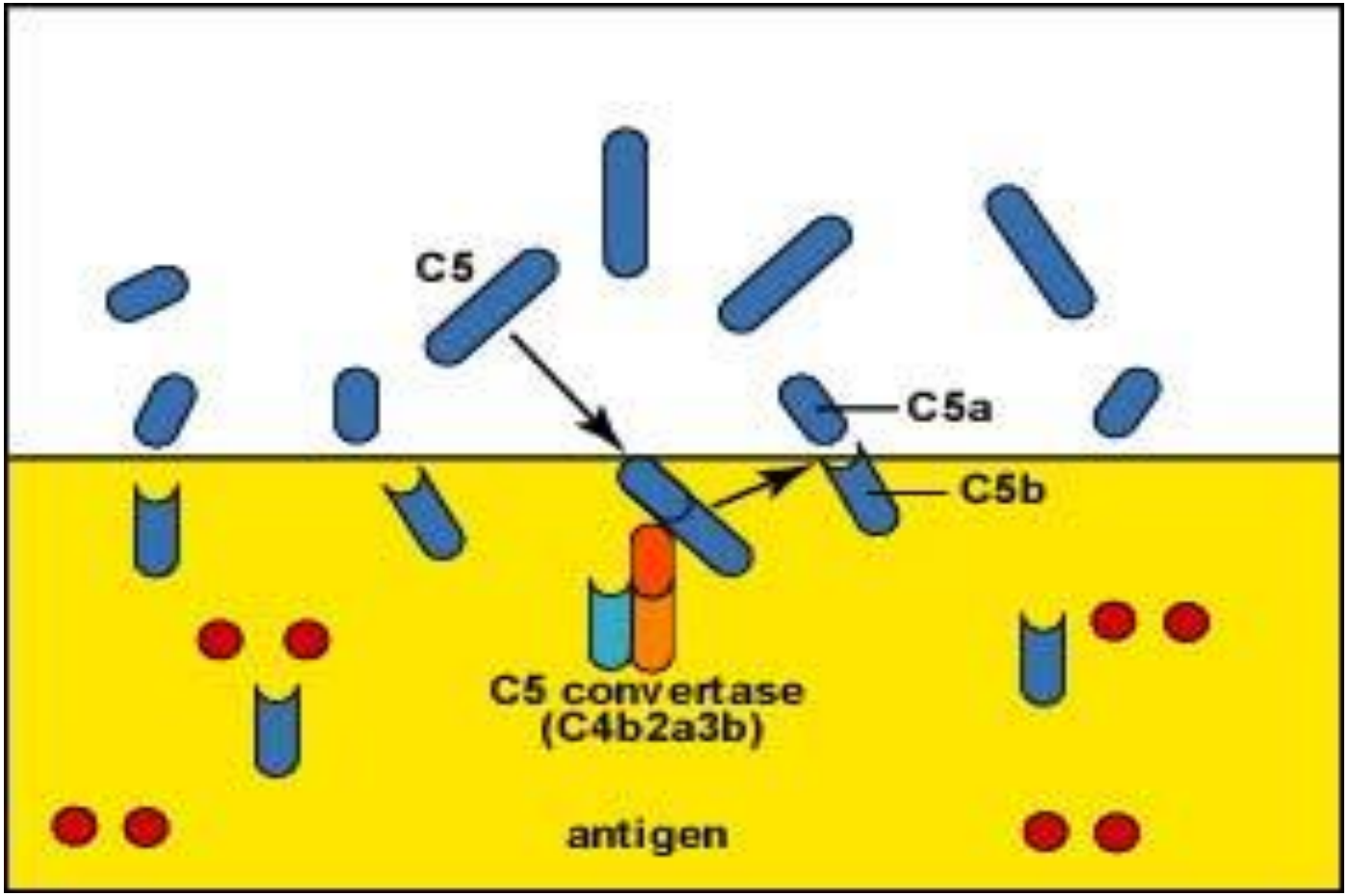


The C4b2a functions (as a C3 convertase) can enzymatically cleave hundreds of molecules of C3 into C3a and C3b. C3b, and to a lesser extent C4b, attaches antigens to phagocytes for opsonization (enhanced attachment). One portion of the **C3b** binds to proteins and polysaccharides on microbial surfaces; another portion binds to complement receptor (CR1) receptors on phagocytes, B-lymphocytes, and dendritic cells. This results improved phagocytosis.

C3a can promote inflammatory responses that enable body defense cells and defense chemicals to leave the blood and enter the tissues.

c. Some molecules of C3b bind to C4b2a, to form **C4b2a3b**,which is called **a C5 convertase** that cleaves C5 into C5a and C5b.




C5
C5a
C5b
C5 convertase
(C4b2a3b)
antigen

C4b2a3b functions as a C5 convertase that cleaves C5 into C5a and C5b.

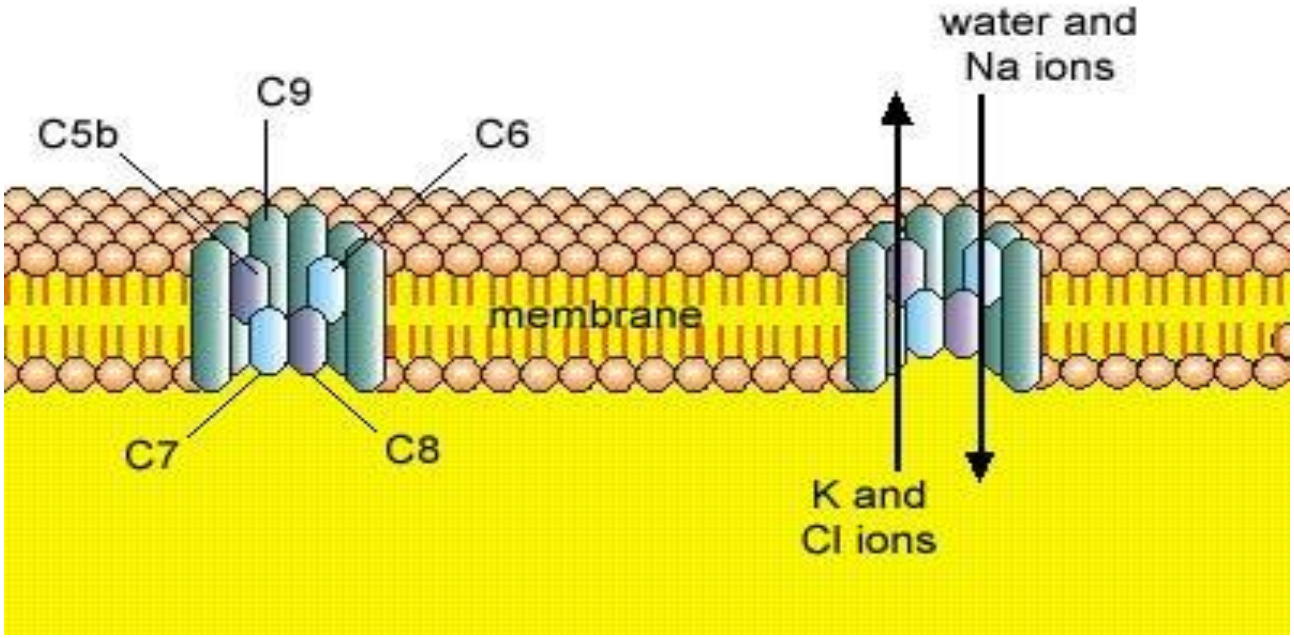
C5a is the most potent complement protein triggering ***inflammation***.
It causes :-
1- mast cells to release vasodilators such as histamine so that blood vessels become more permeable.

2- it increases the expression of adhesion molecules on leukocytes and the vascular endothelium so that leukocytes can squeeze out of the blood vessels and enter the tissue (diapedesis).

3- it causes neutrophils to release toxic oxygen radicals for extracellular killing.
4- it induces fever.

C5a also functions as a ***chemoattractant*** for phagocytes.
Leukocytes will move towards increasing concentrations of C5a.

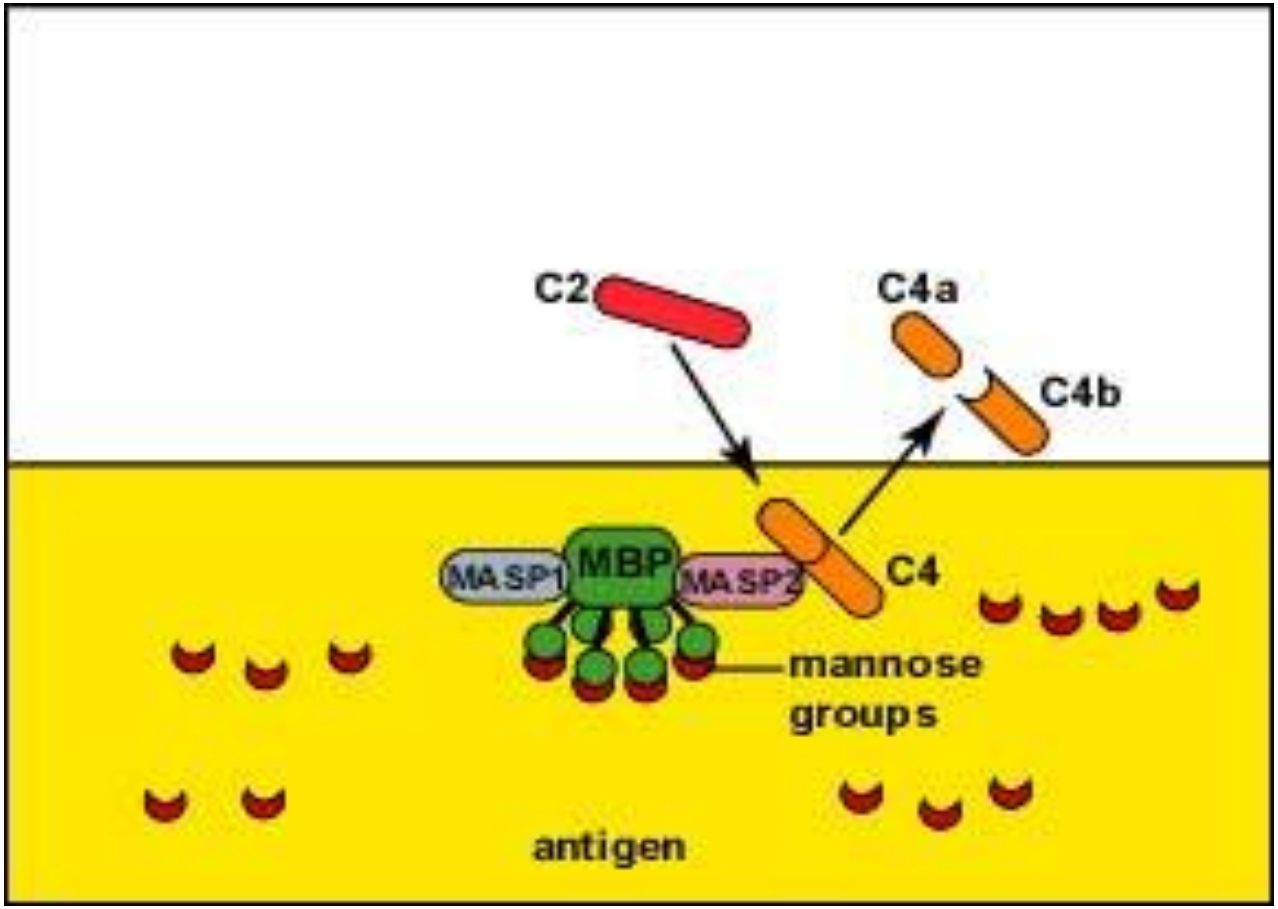
C5b becomes part of the **Membrane Attack Complex (MAC).**



d. C5b binds to the surface of the target cell and subsequently binds C6, C7, C8, and a number of monomers of C9 to form **C5b6789n, the Membrane Attack Complex (MAC)**

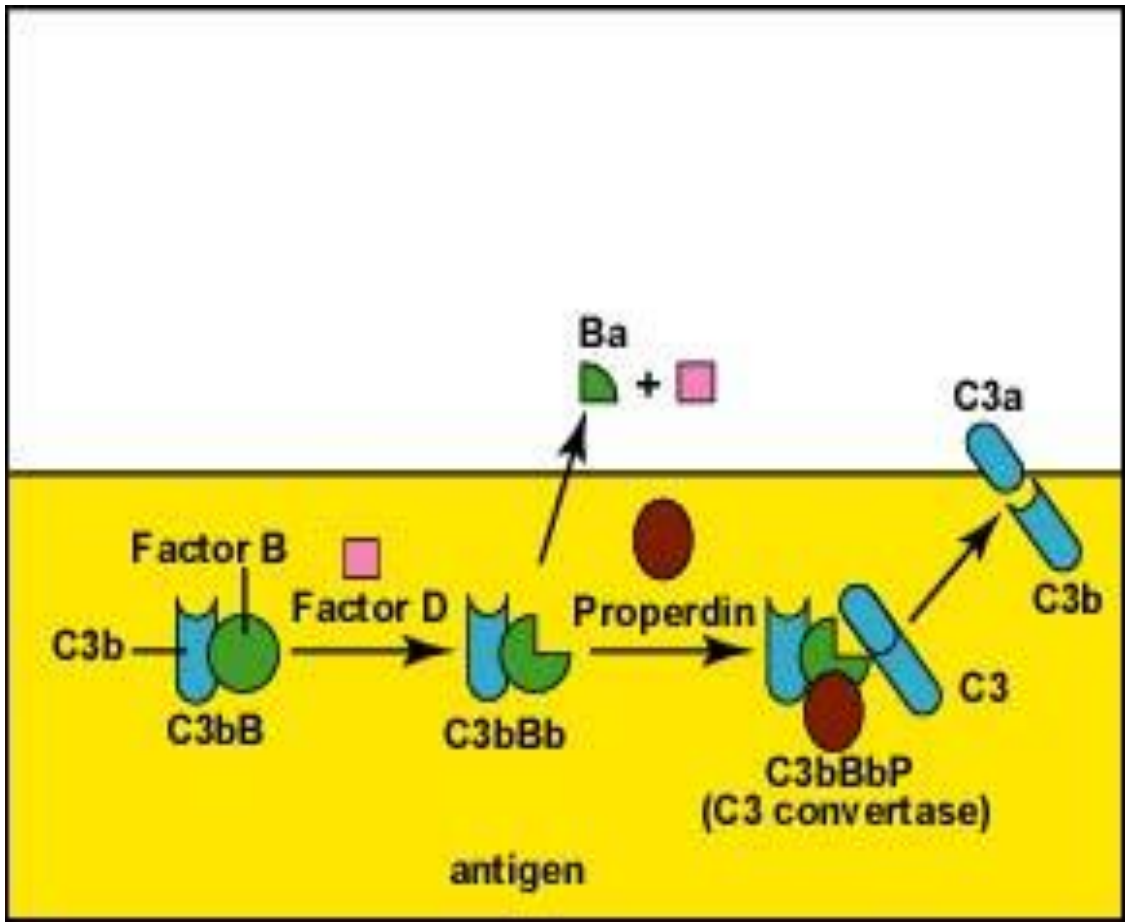
2. The Lectin Pathway

- The lectin pathway is mediated by circulating proteins called **mannose-binding lectin (MBL) - also known as mannan-binding protein (MBP)**. MBL is a type of soluble pattern-recognition receptor that binds to **mannose-rich glycans** which are common in microbial glycoproteins and glycolipids but rare in those of humans. MBL is synthesized by the liver and released into the bloodstream as part of the acute phase response . The MBL is equivalent to C1q in the classical complement pathway.
- Activation of the lectin pathway begins when **mannose-binding lectin (MBL) binds to the mannose groups of microbial carbohydrates**. Two proteins of the lectin pathway called (**M**annose **A**ssociated **S**erine **P**roteases) **MASP1 and MASP2** (equivalent to C1r and C1s of the classical pathway) now bind to the microbial surface .This forms an enzyme similar to C1 of the classical complement pathway that is able to cleave C4 and C2 to form **C4bC2a, the C3 convertase** capable of enzymatically splitting hundreds of molecules of C3 into C3a and C3b.


C2
C4a
C4b
MASP1
MBP
MASP2
C4
mannose
groups
antigen

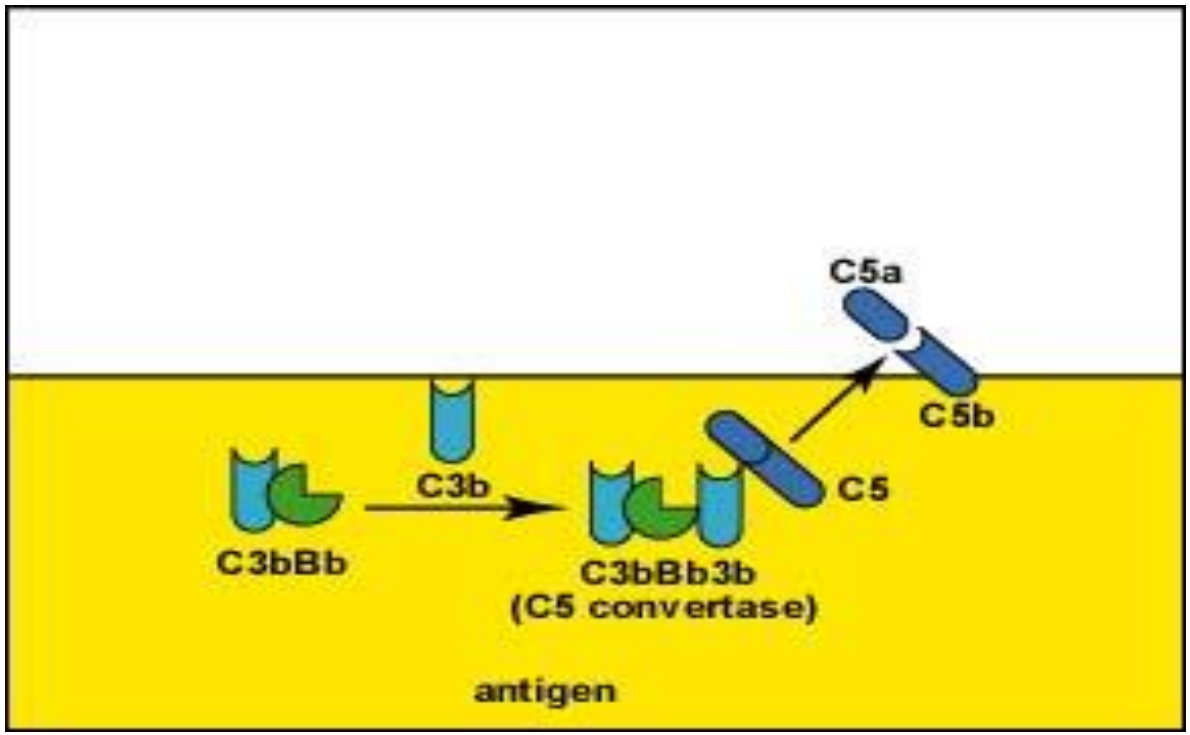
3. The Alternative Complement Pathway

- The alternative complement pathway is **mediated by C3b**, produced either by the classical or lectin pathways or from C3 hydrolysis by water. (Water can hydrolize C3 and form C3i, a molecule that functions in a manner similar to C3b.)



Activation of the alternative complement pathway begins when C3b (or C3i) binds to the cell wall and other surface components of microbes. In the alternative pathway there is protein Factor B which combines with the cell-bound C3b to form C3bB. Then Factor D splits the bound Factor B into Bb and Ba, forming C3bBb. Then a serum protein called properdin binds to the Bb to form C3bBbP. C3bBbP functions as a C3 convertase that can enzymatically split hundreds of molecules of C3 into C3a and C3b.

Some of the C3b subsequently binds to some of the C3bBb to form **C3bBb3b, a C5 convertase** capable of splitting molecules of C5 into C5a and C5b.



The most important function of the complement protein products are:

1. ***Physiologic consequences*** include blood vessel dilation , increased vascular permeability and this help to trigger inflammation:- C5a>C3a>c4a.

2. ***The cellular consequences include the following:***

- Cell activation, such as production of inflammatory mediators.
- Cytolysis or hemolysis, if the cells are erythrocytes.
- Cause lysis of gram-negative bacteria and human cells displaying foreign epitopes(MAC)
- Remove harmful immune complexes from the body by fragmented it to small ,soluble particles
- chemotactically attract phagocytes to the infection site C5a
- promote the attachment of antigens to phagocytes (enhanced attachment) or opsonization (C3b>C4b).

Decreased Complement Levels

Low levels of complement suggest one of the following biological effects:-

- Complement has been excessively activated due to recent infection.
- A single complement component is absent because of a genetic defect.

Elevated Complement Levels

Increased complement levels are often associated with inflammatory conditions, trauma, or acute illness such as myocardial infarction because separate complement components (e.g., C3) as acute-phase proteins.

Complement activation is also associated with intravascular thrombosis, which leads to ischemic injury to tissues. Complement levels may be abnormal in certain disease states (e.g., rheumatoid arthritis, systemic lupus erythematosus [SLE]) and in some genetic disorders.