

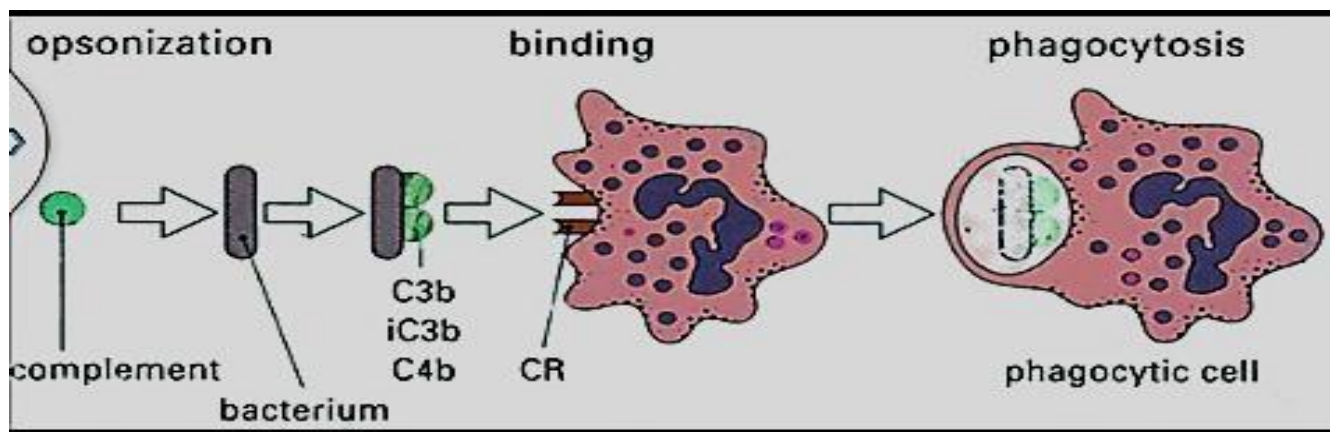
## Complement System

It is the major effectors of humoral branch of immune system. It includes serum and membrane bound proteins that function in both adaptive and innate host defense system, these proteins are highly regulated and interact via a series of proteolytic cascades. The term "Complement" refers to the ability of these proteins to complement (augment) the effects of other components of the immune system.

### **The basic functions of Complement system :**

After initial activation, the various complement components interact in a highly regulated cascade to carry out a number of basic functions including:

1. **Cell lysis:** rupturing membranes of foreign cells.
2. **Opsonization:** enhancing phagocytosis of antigens.
3. **Chemotaxis:** attracting macrophages and neutrophils.
4. **Agglutination:** clustering and binding of pathogens together (sticking).



"Complement system enhancing phagocytosis"

### **The components of Complement**

The soluble proteins and glycoproteins of complement system synthesize in the liver, hepatocytes, monocytes, macrophage and epithelial cells of gastrointestinal tract. They form about 5% of serum globulins and circulate in blood functionally inactivated as proenzyme.

The complement components are designated by numerals (C1.....C9), by letter symbols (Factor D, B, H and I) or by trivial names (homologous restriction factor). In most cases the smaller fragment resulting from cleavage of component is designated "a" and the largest fragment "b" (e.g. C3a, C3b) exception in C2 cleavage C2a is the largest fragment designated.

The complement fragments interact with one another to form functional complexes which have enzymatic activity and designated by a bar over the number or symbol (e.g. C4b2a).

### **system Biochemical pathway; activate the complement:**

Sequential activation of complement components occurs via three main pathways:

- Classical complement pathway
- Alternative complement pathway
- Manose lectin pathway (MLP).

The early steps in the complement activation is the formation of C5b which can be occur by one of the mentioned ways, the final step leading to the formation of the membrane – attack complex or MAC which are identical in all three pathways. Several complement component are proenzyme which must be cleaved to form active enzymes. Activation of the complement system can be initiated either by antigen – antibody complexes or by a variety of non immunological molecules

### **"Classical complement pathway"**

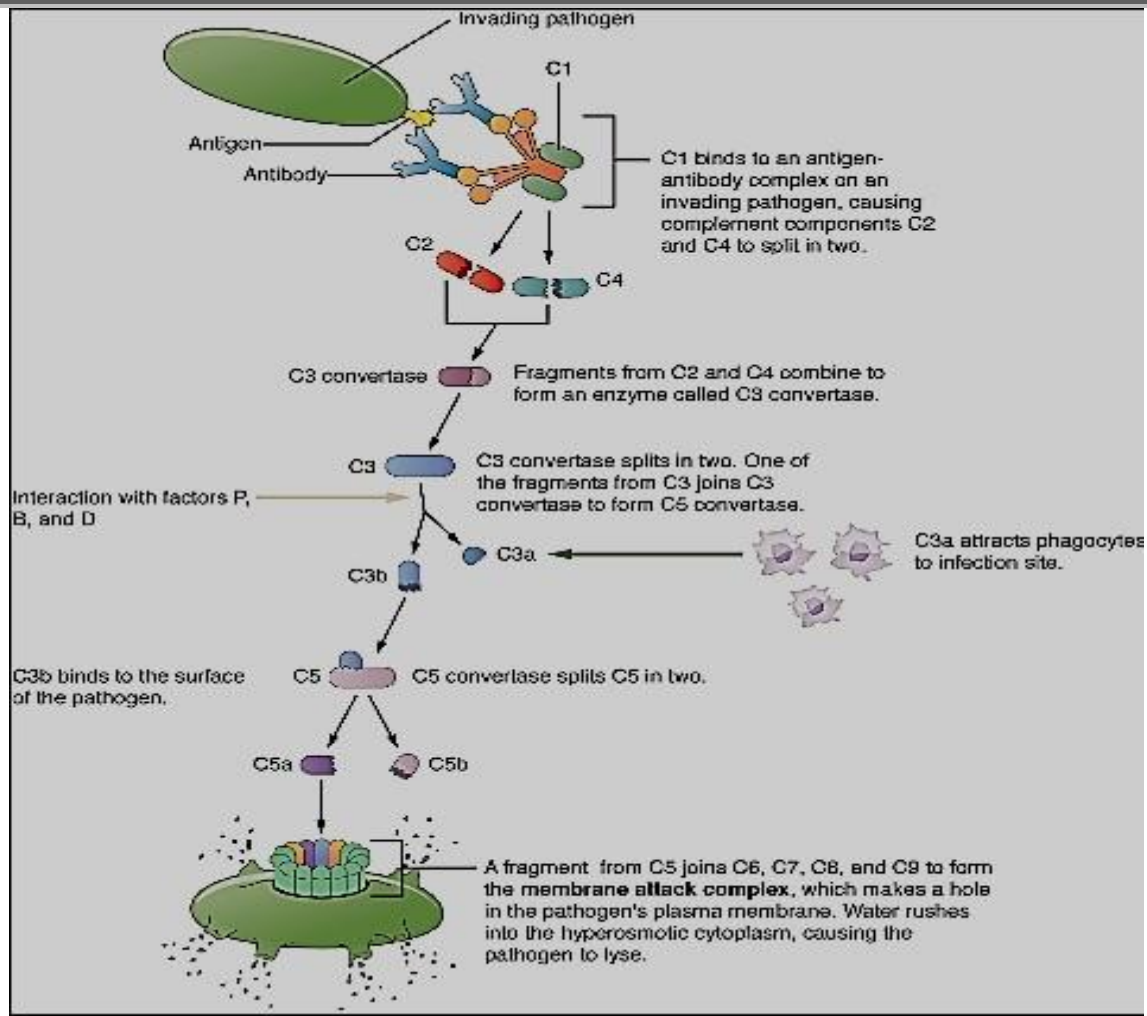
It is activated by the formation of soluble antigen – antibody complex. IgM and certain subclasses of IgG (IgG1, IgG2 and IgG3 but not IgG4) can activate this pathway. Single molecule of IgM can bind to RBCs can activated complement but at least two IgG molecules should be closed enough to each other on the surface of the cell to initiate activation.

#### **:Steps of Classical pathway**

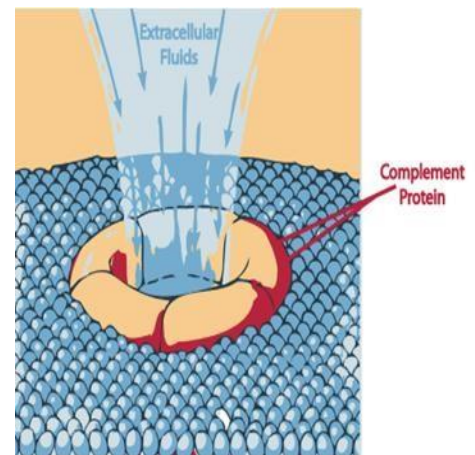
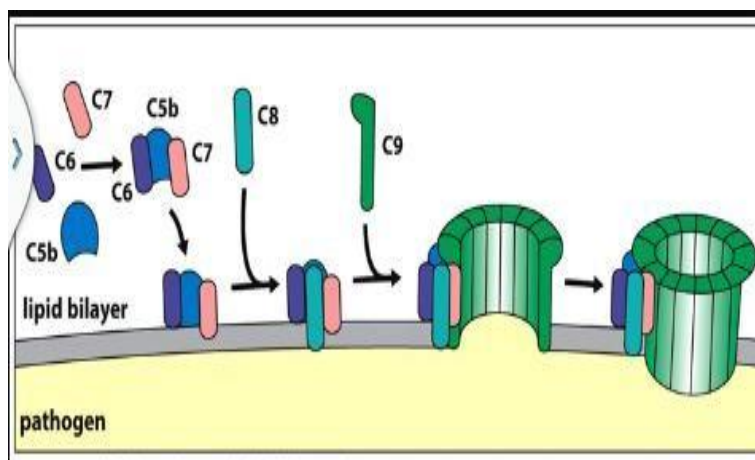
- Ag – Ab complex induce conformational changes in IgM that expose a binding site for the C1 component of the complement system. C1 in serum is a macromolecular complex consist of C1q and two molecules of C1r and C1s held together to form complex (**C1qr2S2**) which stabilized by Ca<sup>+2</sup> ions.
- C1qr2S2 cleave C4 into C4a and C4b, and cleave C2 into C2a and C2b then form (**C4b2a**) complex which is called C3 convertase.
- C3 convertase cleave C3 into C3a and C3b leading to the formation of (**C4b2a3b**) complex which is called C5 convertase.
- C5 will cleave into C5a and **C5b**.
- C5b will bind to C6 to form C5b6789 and initiate the formation of MAC (membrane attack complex) which form a large pore in the membrane of microbial cell.

#### **Membrane attack complex:**

It is the cytolytic end product of the complement cascade, this complex forms a large channel through the membrane of the target cell, enabling ions and small molecules to diffuse freely across the membrane, consisting of C5b, C6, C7, C8 and polymeric C9.



**" Classical Complement Pathway "**



**"Membrane attack complex "**

## **"Alternative complement pathway"**

The alternative pathway is continuously activated at low level, analogous to car engine at idle. It is not rely on pathogen- binding antibodies like classical pathway for initiation, so it's a component of innate immune system. It is activation involves four serum proteins (C3, factor B, factor D and properdin). Some initiators required for this pathway activation may be pathogens like (gram positive, gram negative, Fungal, parasites, viruses and some tumors cells) or non pathogens like (Cobra venom factor, dextran sulfate, agarose and heterologous erythrocyte of mouse and rabbit).

### **Steps of Alternative pathway :**

Spontaneously cleavage of C3 into C3a and C3b, C3b will bind to the surface of cell wall of microbial cell.

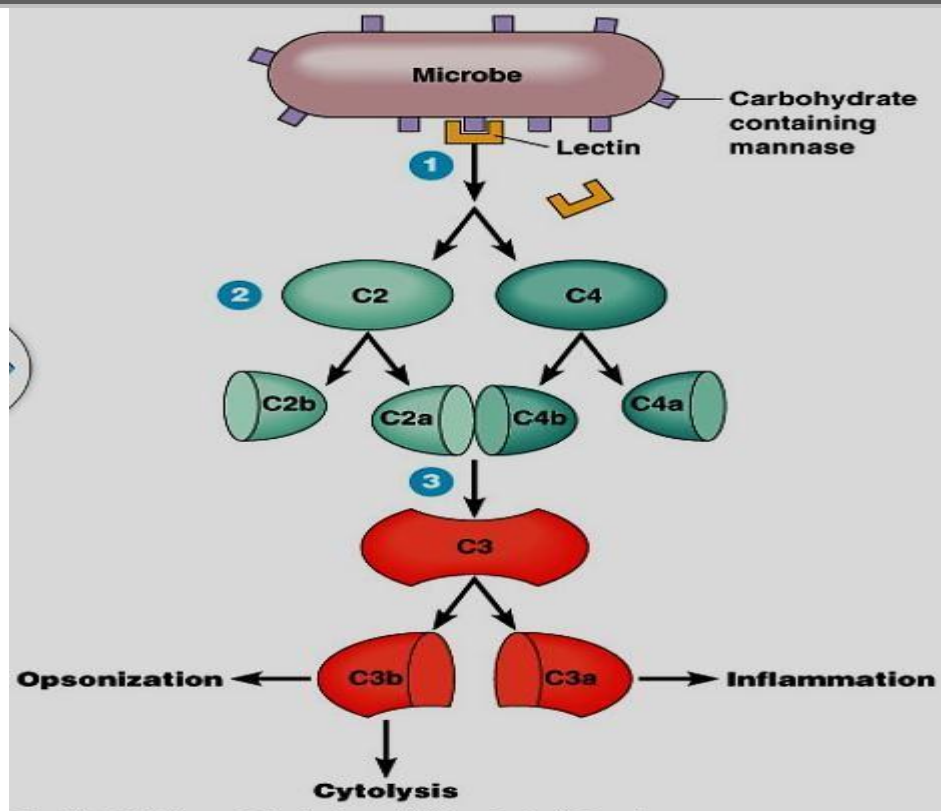
- C3b will bind with B factor in the presence of D factor cleavage into Ba and Bb to form C3bBb which has C3 convertase activity.
- C3 will cleave into C3a and C3b to form C3bBb3b binding with properdin stabilizes.
- C3bBb3bp has C5 convertase activity cleave C5 and form C5b6789 which leading to form MAC.

## **"Lectin complement pathway"**

Or Mannose – binding lectin pathway (MBL pathway) because lectin activates complement binds to mannose residues, like the alternative pathway dose not depend on antibody for it is activation. The lectin pathway is homologous to classical pathway but with opsonization. Lectins are proteins in serum that recognize and binding to specific carbohydrate target mannose residues on the surface of microorganisms ...leading to:

- Activation of C1 which cleave C4 into C4a and C4b also C2 into C2a and C2b and form **C4b2a** complex.
- **C4b2a** complex has C3 convertase activity to cleavage C3 into C3a and C3b and form **C4b2a3b** complex.
- **C4b2a3b** complex has C5 convertase activity to cleave C5 into C5a and C5b, C5b bind and form C5b6789 and form **MAC**.

➤



### " Lectin Complement Pathway"

#### Regulation of complement system :

The complement system has the potential to be extremely damaging to host tissues, meaning its activation must be tightly regulated. The complement system is regulated by complement control proteins which are present at a higher concentration in the blood plasma than the complement proteins themselves. A number of regulatory mechanisms have evolved to restrict complement activity to designated targets, it is required passive and active regulatory mechanism.

#### ➤ **Regulation before assembly of convertase activity:**

- C1 inhibitor bind to C1r2s2 causing dissociation from C1q.
- Factor H prevent binding of C3b and factor B.

#### ➤ **Regulation after assembly of convertase:**

- C3 convertase dissociated by complement receptor 1 CR1, factor H and decay – accelerating factor (DAF) (CD55) which is glycoproteins.

#### ➤ **Regulation at assembly of MAC:**

- S protein prevent insertion of C5b67 MAC component into the membrane.
- Homologous restriction factor (HRF) (CD59) bind to C5b678 preventing assembly with C9 and block the formation of MAC

**Complement deficiencies :**

Genetic deficiencies have been described for each of the complement components, homozygous deficiencies in any of the classical pathway like C1q, C1r, C1s result immune- complex disease such as systemic lupus erythematous. Individuals with C3 deficiency suffer from recurrent Neisseria infection and Individual with MAC deficiency developed meningococcal and gonococcal infection.

- ☒ What is the history of the Complement system?
- ☒ What are the basic functions of the Complement system?
- ☒ What are the components of the Complement system, and how are they classified?
- ☒ What are the biochemical pathways that activate the Complement system?
- ☒ What are the steps involved in the Classical complement pathway?
- ☒ How is the Membrane Attack Complex (MAC) formed?
- ☒ What are the steps involved in the Alternative complement pathway?
- ☒ How is the Lectin complement pathway activated, and what are its steps?
- ☒ How is the Complement system regulated to prevent damage to host tissues?
- ☒ What are the consequences of genetic deficiencies in the components of the Complement system?
- ☒ What is the role of C3 convertase in the complement activation pathways?
- ☒ How does the Alternative complement pathway differ from the Classical complement pathway in terms of activation?
- ☒ What specific pathogens or non-pathogens can initiate the Alternative complement pathway?
- ☒ What are the differences between the activation of C3 and C5 convertase in different pathways?
- ☒ How does the regulatory mechanism prevent overactivation of the complement system?
- ☒ What are the roles of specific factors like Factor H, C1 inhibitor, and CR1 In complement regulation?
- ☒ What are the specific immune responses mediated by complement components like C3b and C5a?
- ☒ How does complement deficiency contribute to diseases such as systemic lupus erythematosus or Neisseria infections?
- ☒ What role do mannose residues play in the activation of the Lectin complement pathway?
- ☒ How does the S protein and HRF (CD59) regulate the formation of the MAC?