The Complement System

This system includes over than 20 proenzymes (glycoproteins) components inactive state found in the blood. When the complement components are activated, serial, rapid cascad events occur. Historically, the term complement (C) was used to a heat-labile serum component able to lyse bacteria and its activity is destroyed (or inactivated) by heating serum at 56 C ^{o} for 30 min.

1. **Synthesis and metabolism of complement components.** Complement glycoproteins are synthesized by liver cells (hepatocytes) and macrophages and many other cells (e.g. gut epithelial cells). All normal individuals have complement components in their blood. The synthetic rates for the complement glycoproteins increase when complement is activated and consumed.

2. Activation of the complement system.

This system can be activated by:

a) Antigen-antibody complexes containing IgG or IgM activate complement by the **classical pathway** that starts with C1 (complement 1).
b) Membranes and cell walls of microbial organisms (e.g. Lipopolyccharides layer [LPS] of gram –ve bacteria) and many other substances can activate complement by the **alternative pathway.**
c) Proteolytic enzymes released either from microbes or from host cells during immune defense mechanisms, can also activate the complement system by breaking down critical components.

3**. The complement cascade induction.** When the complement component is activated, it continues activating the next component by:

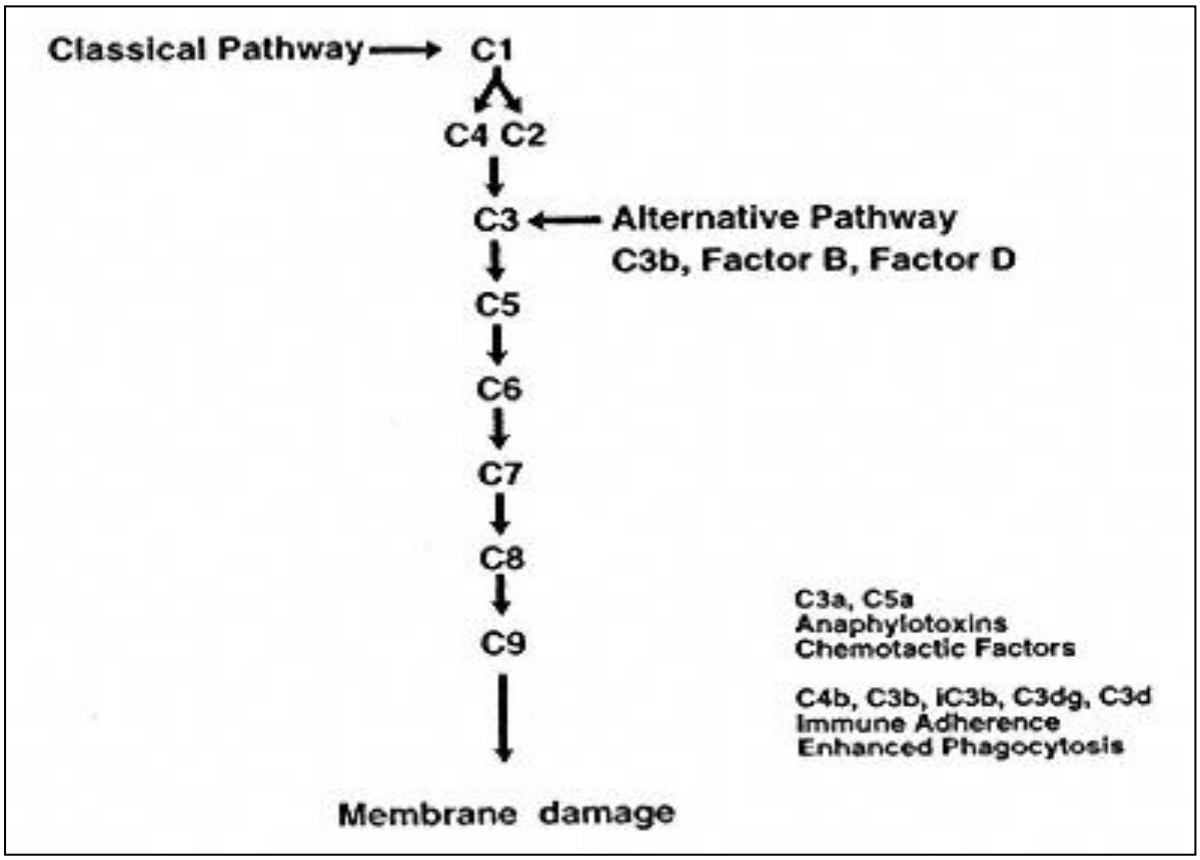
- either cleaves.
- or becomes bound to an activated component or complex of complement components.

4. **Function of the complement system:**

The complement system has role in both specific and non-specific immunity. The functions of the complement system are:

1) Binding and neutralizing foreign substances that activate it.
2) Induce the ingestion of complement-coated substances by phagocytic cells (help in the **opsonization** process when C3b and C4b linked with the surface of microorganisms and attach to Complement receptor on phagocytic cells then induce phagocytosis).
3) Activation of many cells including PMNs cells and macrophages.
4) Have roles in regulation of antibody responses.
5) Clearance of immune complexes and apoptotic cells.
6) Have roles in inflammation and tissue damage.
7) Some components (C3a, C4a and C5a), have role in Anaphylaxis (a dangerous case of type I hypersensitivity), hence they are called **anaphylotoxins**.
8) Some complement components acts as chemotactic factors e.g. C5a.

5. Complement Pathways



(The sequence of complement components activation)

A. Classical Pathway:

1) C1activation

C1, a multi-subunit protein containing three different proteins (C1q, C1r and C1s), binds to the Fc region of IgG and IgM antibody molecules that have interacted with antigen (it does not bind to free Ab), binding requires calcium and magnesium ions. The binding of C1q results in the activation of C1r which in turn activates C1s. The result is the formation of an activated "C1qrs", which is an enzyme that cleaves C4 into two fragments C4a and C4b.

2) C4 and C2 activation (generation of C3 convertase).

The C4b fragment will stay (usually binds to the binds to the membrane of bacteria) and the C4a fragment is released. Activated "C1qrs" also cleaves C2 into C2a and C2b. C2a binds to the membrane in association with C4b, and C2b is released. The resulting C4bC2a complex is a C3 convertase (acts as enzyme), which cleaves C3 into C3a and C3b.

3) C3 activation (generation of C5 convertase):

C3b binds to the membrane in association with C4b and C2a, and C3a is released (which acts as anaphylaxis protein and a chemotactic factor). The resulting C4bC2aC3b is a C5 convertase. The generation of C5 convertase is the end of the classical pathway. Many products of the classical pathway have biological activities that support the host defenses as in the table (1).

B. Lectin Pathway

The lectin pathway is very similar to the classical pathway. It starts with the binding of mannose-binding lectin (MBL) to bacterial surfaces. Many serial events happens resulting C4bC2aC3b formation, which is the C5 convertase. The generation of C5 convertase is the end of the lectin pathway.

Table (1) Biological Activity of classical pathway products	
Component	**Biological Activity**
C2b	**Prokinin**; have role in kinin system, causes edema
C3a	**Anaphylotoxin**; can activate basophils and mast cells to degranulate resulting in increased vascular permeability and contraction of smooth muscle cells, which may lead to **anaphylaxis**
C3b	**Opsonin**; induces phagocytosis by binding to complement receptors. Activation of phagocytic cells
C4a	**Anaphylotoxin** (weaker than C3a)
C4b	**Opsonin**; induces phagocytosis by binding to complement receptors

C.Alternative Pathway

Activation of this pathway starts spontaneously and C3 will be cleaved by the help of Factor B, Factor D, properdin and Mg^{+2} ions. Cleavage of C3will release C3a (which acts as anaphylaxis protein) and C3b. when C3b is formed, Factor B will bind to it and will be cleaved by Factor D. The resulting C3bBb complex is a C5 convertase and this is the end of the alternative pathway. Generation of C3b is essential for the activation of the alternative pathway.

The component C3b can be formed due to:

a. During normal C3 turnover in blood
b. In the presence of bacterial proteases
c. During classical pathway activation (for this reason activation of the classical pathway is always associated with activation of the alternative pathway which generating more activated C3).

The alternative pathway of complement activation is important especially during the early phase of an infection, when the concentrations of

specific antibody are very low and classical pathway activation is limited and in the presence of large numbers of bacteria. The alternative pathway provides the non-specific resistance against infection without the need to antibodies and hence provides a first line of defense against a number of infectious agents.

D. Membrane attack complex Formation:

Lytic pathway is the end of all the complement system pathways, C5 convertase from all pathways (classical, lectin or alternative) cleaves C5 into C5a and C5b. Then C5b rapidly binds with C6, C7, C8 and C9 molecules. Pores will be formed in the membrane and lysis occurs due to physical damage to the membrane. The complex of C5bC6C7C8C9 is called the membrane attack complex (MAC).

C5a formed in the lytic pathway is the most active anaphylotoxin. It is a chemotactic factor for neutrophils and stimulates the respiratory burst in them and it stimulates inflammatory cytokine production by macrophages.

Complement deficiencies and diseases

Component	Disease	Mechanism
C1, C2, C4	SLE	Opsonization of immune complexes help keep them soluble, deficiency results in increased precipitation in tissues and inflammation
Factors B or D	Susceptibility to pyogenic (pus-forming) bacterial infections	Not enough opsonization of bacteria
C3	Susceptibility to bacterial infections	Lack of opsonization and inability to utilize the membrane attack pathway
C5, C6, C7 C8, and C9	Susceptibility to Gram-negative infections	Inability to attack the outer membrane of Gram-negative bacteria