Complement System

The term *complement* refers to the ability of a system of some nonspecific proteins in normal human serum to complement, i.e., augment the effects of other components of immune system, such as antibody. The complement system, which is an important component of the human innate host defense system, consists of approximately 20 proteins that are present in normal human serum.

The complement system is an extremely powerful system comprising of rapidly acting glycoproteins, several proenzymes, and components, and it exists in an inactive state in the plasma. All normal individuals always have complement components in their blood.

Properties of Complement:

1. It is present in sera of all mammals including humans and in lower animals including birds, amphibians, and fishes.

2. These are heat-labile substances that are inactivated by heating serum at 56°C for 30 minutes.

3. These are glycoproteins and are synthesized primarily by liver cells and to a very less extent by macrophages and many other cell types.

4. The complement usually does not bind to the antigen or antibody but only to antigen–antibody complex.

5. The importance of the complement lies in the fact that it contributes to both the acquired and innate immunity of an individual.

Effects of complement

There are four main effects of complement:

1- It causes lysis of cells (such as bacteria, viruses and tumor cells).

2- It generates mediators that participate in triggering specific cell functions, inflammation, and secretion of immunoregulatory molecules.

3- It facilitates opsonization, the process by which bacteria are more readily and more efficiently engulfed by phagocytes.

Activation of Complement

Complement activation takes place through any of the following three pathways:

1. The classical pathway

2. The alternative pathway

3. The lectin pathway

alternative and lectin pathways are important in the innate immunity of the host. These two are also more important when the human host is infected by a microorganism for the first time, because the antibody required to trigger the classical pathway is not present.

All the three activation pathways lead to activation of C3, resulting in the production of C3b. Hence, C3b is considered as the central molecule in the activation of the complement cascade.

The final steps that lead to the formation of a membrane attack complex are same in all the pathways. When these complement components are activated, a sequential, rapid cascading pattern ensues. This is because once a complement component is activated, it is either cleaved or becomes bound to a previously activated component or complex of complement components. Also, each component or complex of components, once activated, generally amplifies the cascading process by activating many molecules of the next component in the series.

The C3b has two important functions to perform:

1- It combines with other components of the complement to produce C5 convertase, the enzyme that leads to the production of membrane attack complex.

2-It opsonizes bacteria due to the presence of receptors for C3b on the surface of the phagocytes.

Classical Pathway of Complement Activation

The classical pathway is a chain of events in which complement components react in specific sequences as a cascade resulting in cell lysis. It is activated by antibody bound to antigen.

Steps of activation of classical pathway:

The classical pathway of complement activation usually begins with the formation of soluble antigen–antibody complexes (immune complexes) or with the binding of antibody to antigen on a suitable target, such as a bacterial cell.

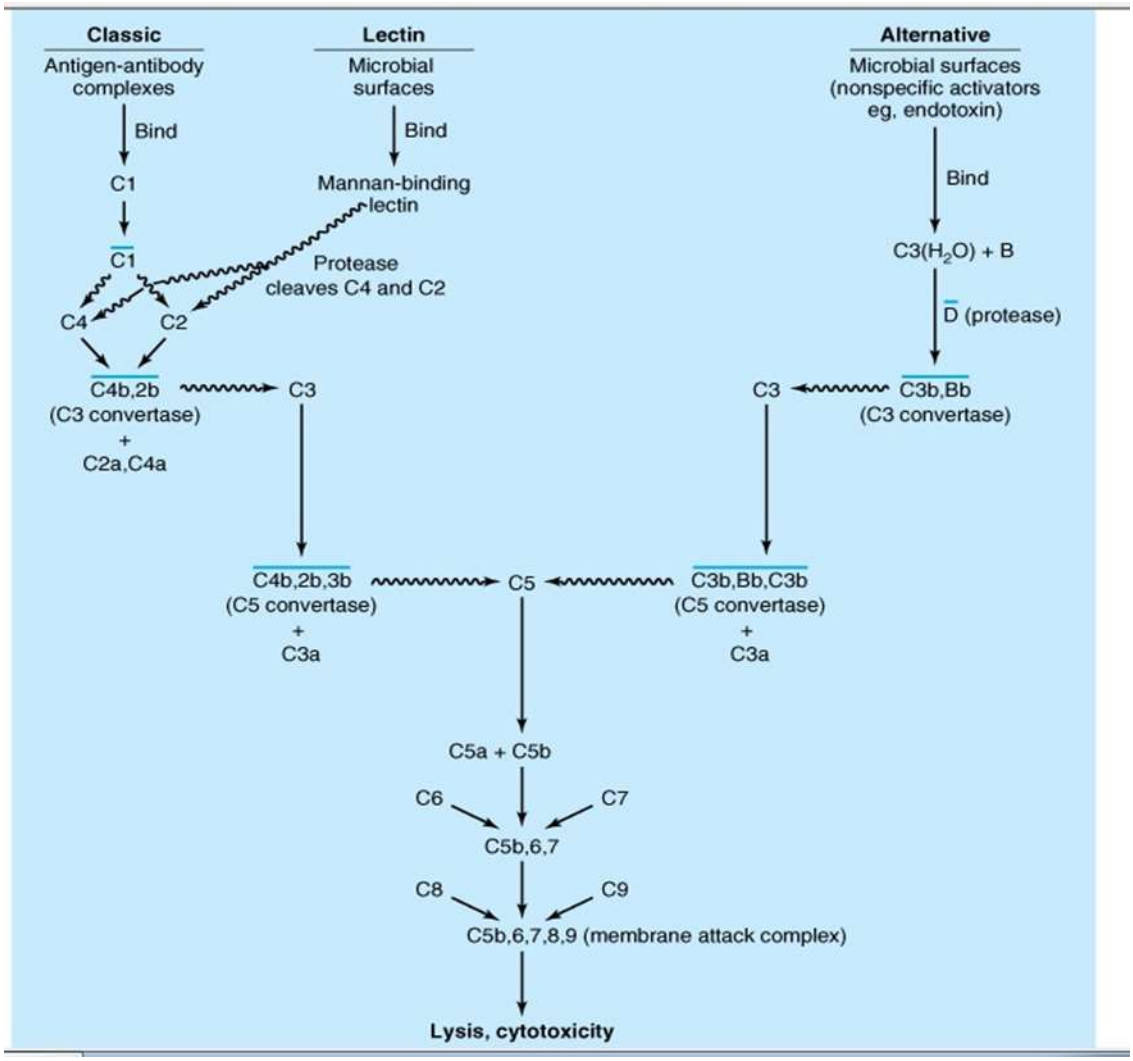
Alternative Pathway of Complement Activation

The alternative pathway was first described by Pillemer in 1954. It differs from the classical pathway in (*a*) the nature of activating substances and

(*b*) the sequence of events itself. The alternative pathway is unique in not requiring antigen–antibody complexes to activate the complement. This pathway does not depend on antibody and does not involve the early complement components (C1, C2, and C4) for activation of the complement. It, therefore, can be activated before the establishment of an immune response to the infecting pathogen.

Lectin Pathway of Complement Activation

The lectin pathway, as the name suggests, is triggered by lectins. Lectins are the proteins that recognize and bind to specific carbohydrate targets. The mannose-binding lectin (MBL) is one such protein that takes part in the lectin pathway of complement activation. MBL is a large serum protein that binds to nonreduced mannose, fructose, and glucosamine on bacterial and other cell surfaces with mannose-containing polysaccharides (*mannans*).



Differences betweenclassical, alternative, and lectin pathways are

Classical pathway	Alternative pathway	Lectin pathway
Chain of events in which components react in specific sequence following activation of C1	Activation of C3 without prior participation of C1,4,2	Activated by binding of mannose-binding lectin to mannose residues on surface of microorganisms
Requires binding of C1 to antigen–antibody complex	Activators are bacterial endotoxins, IgA and IgD, cobra venom factor, and nephritic factor	No role for antibodies; similar to alternate pathway
Cannot be considered as a component of innate immune mechanism	It is a component of the innate immune mechanism	Can be considered as a component of innate immune mechanism

Regulation of Complement System

Since the complement system involves the formation of many biologically active substances, there are many regulatory systems to prevent unwarranted damage to the human host. The activities of the different complement components activated at each stage of the cascade are regulated by several mechanisms. The following are regulators of the complement system:

1. Level of antibody

2. C1 inhibitors

3. Other inhibitory substances

4. Decay-accelerating factor (DAF)

5. Regulation of alternative pathway

Biological Effects of Complement

The main role of complement is to amplify the humoral immune response. The complement through its various products participates in the inflammatory response, opsonization of antigen, viral neutralization, and clearance of immune complexes as follows:

1- Opsonization: Microbes, such as bacteria and viruses are phagocytized much better in the presence of C3b because there are C3b receptors on the surface of many phagocytes.

2- Chemotaxis:C5a and the C5, 6, 7 complex attract neutrophils. They migrate especially well toward C5a. C5a also enhances the adhesiveness of neutrophils to the endothelium.

3- Anaphylatoxin: C3a, C4a, and C5a cause degranulation of mast cells with release of mediators, e.g., histamine, leading to increased vascular permeability and smooth muscle contraction, especially contraction of the bronchioles leading to bronchospasm.

4- Cytolysis:Insertion of the C5b,6,7,8,9 complex into the cell membrane leads to killing or lysis of many types of cells including erythrocytes, bacteria, and tumor cells. Cytolysis is not an enzymatic process; rather, it appears that insertion of the complex results in disruption of the membrane and the entry of water and electrolytes into the cell.