Complement Reactions

The complement activation occurs via three pathways; which are:

1. **Classical pathway**
2. **Alternative pathway**
3. **Lectin pathway (or mannose binding lectin pathway)**

The early step of complement system varies in different pathways. However, all the pathways form enzyme complexes; C3 convertase, which cleaves C3 into C3a and C3b; and the C5 convertase, which cleaves C5 into C5a and C5b.C3b, thus formed, binds C3 convertase to form C5 convertase.

C5 convertase, generated by the alternative, classical, or lectin pathway, initiates the activation of late components of the complement system to form membrane attack complex (MAC) and ultimately kills the pathogen

This occurs through three pathways; **Classical pathway**, activated by antigen-antibody reaction, **Alternative pathway**, activated on microbial cell surfaces, and **Mannose binding Lectin pathway**, activated by a plasma lectin that binds to mannose residues on microbes.

1. **Classical Pathway**

The classical pathway begins with the formation of antigen-antibody complex (immune complex). When an antigen enters the body, the antibody (IgM/IgG) binds to it. This induces conformational changes in the Fc portion of the antibody which exposes a binding site for C1 protein. Hence, the antibody activates the complement system only when bound to an antigen.

C1 is a large, multimeric, protein complex composed of one molecule of C1q and two molecules each of C1r and C1s subunits. C1q binds to the antigen bound antibody (Fc portion). C1r and C1s are proteases which help to cleave C4 and C2.

The immune complex bound to C1 calls another protein C4 which is cleaved into C4a and C4b. C4a goes away whereas activated C4b attaches to the target surface near C1q. Now, C4b attracts C2 which is also cleaved into C2a and C2b. C2a binds C4b forming the C4b2a complex whereas C2b goes away. The active

C4bC2a activates C3. The C4b2a complex is also known as **C3 convertase** as this converts C3 into an active form by separating C3a and C3b. One molecule of C4b2a can cleave a large number of C3 molecules. C3b binds to the microbial surface or to the convertase itself.

C3b when binds to C3 convertase forms C4bC2aC3b (**C5 convertase**) which activates C5.

C5 convertase cleaves C5 into C5a and C5b. C5a diffuses away but C5b is stabilized by binding C6. Then C5bC6 binds to C7. C5bC6C7 complex is then inserted into the phospholipid bilayer of the cell membrane which further binds C8. These all (C5b678) activate C9 to form a macromolecular structure called the **membrane attack complex (MAC)**. This makes hole in the bacterium, as a result, the intracellular contents leak out and unwanted substances get in. Thus, the cell cannot maintain its osmotic stability and the

lysis occurs by an influx of water and loss of electrolytes.

This is more effective in Gram negative bacteria than in Gram positive bacteria because MAC formation is easy in the outer membrane in Gram negatives whereas it is difficult in the rigid thick layer of peptidoglycan in Gram positives.

Some of the C3b molecules do not associate with C4b2a; instead these molecules coat immune complexes or microbial cell surfaces and work as opsonins. This process is called opsonization in which opsonin molecule binds one side to the particulate matter i.e. in bacteria, tumor cell, RBC and on the other side they bind to the receptor of phagocytic cell(like, neutrophils and macrophages) which enhance the process of phagocytosis.

Smaller complement subunits diffuse from the site and can initiate localized inflammatory responses by binding to specific receptors.

2. **Alternative Pathway**

Unlike classical pathway, alternative pathway, does not require Ag-Ab complex for the initiation of complement pathway. It is initiated by cell surface constituents that are foreign to the host. These surface molecules may be **lipopolysaccharide** etc.

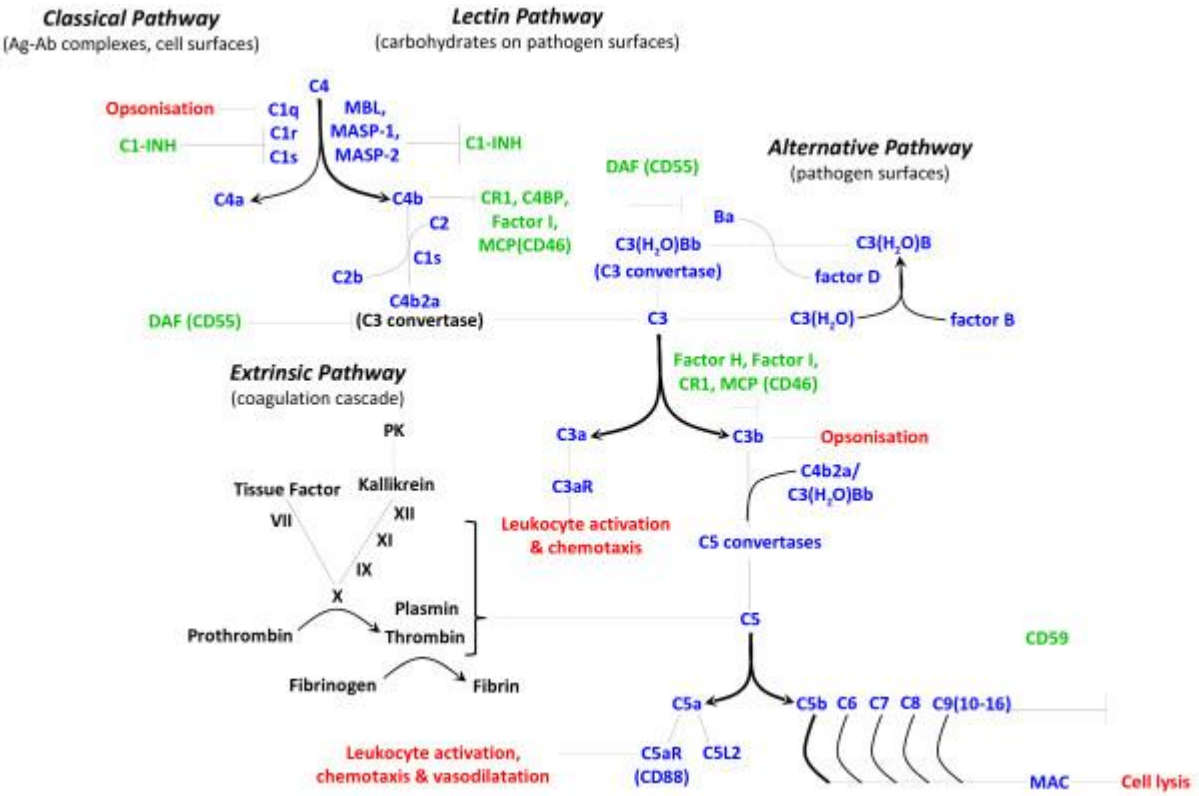
When a bacterium enters the host body, as a result of inflammation, complements reach towards the site, where C3 molecules directly touch antigen and become active. In this pathway, serum C3 containing an unstable thioester bond undergoes slow spontaneous hydrolysis to yield C3a and C3b. C3b binds the surface of foreign cell and then binds to another serum protein called factor B. Now the factor B exposes the site which serves as the substrate for enzymatically active serum protein D. Then factor D cleaves B into Ba and Bb forming C3 convertase (C3bBb). C3 convertase then forms C5 convertase which ultimately forms a MAC as in classical pathway.

3. **Mannose binding Lectin (MBL) Pathway**

Some bacteria can activate complement system without having antibody and endotoxin. This occurs through MBL pathway which is activated when circulating lectin (MBL) binds to mannose residues on glycoproteins or carbohydrates on the surface of microorganisms. Microorganisms inducing MBL pathway are bacteria, such as Salmonella, Listeria, and Neisseria strains, some fungi and some viruses including HIV-1. MBL is an acute phase protein and its concentration increases during inflammation. The lectin recognizes and binds the carbohydrate of the target cell which then activates complements.

MBL pathway resembles classical pathway as it proceeds through the action of C4 and C2 to produce activated proteins of the complement system. MBL works same as C1q which it resembles in structure.

After the MBL binds to carbohydrate residues on the surface of a cell or pathogen, two components, MASP-1 and MASP-2 bind to MBL. MASP stands for MBL-associated serine proteases. Two proteases form a tetrameric complex similar to the one formed by C1r and C1s and cleaves C4 and C2 forming C3 convertase. The process now continues to form of C5 convertase and the MAC as in classical pathway.


Classical Pathway
(Ag-Ab complexes, cell surfaces)
Lectin Pathway
(carbohydrates on pathogen surfaces)
Alternative Pathway
(pathogen surfaces)
Extrinsic Pathway
(coagulation cascade)
C4
Opsonisation
C1q
C1r
C1s
C1-INH
MBL,
MASP-1,
MASP-2
C1-INH
C4a
C4b
CR1, C4BP,
Factor I,
MCP(CD46)
C2
C1s
C2b
C4b2a
(C3 convertase)
DAF (CD55)
DAF (CD55)
Ba
C3(H2O)Bb
(C3 convertase)
C3(H2O)B
factor D
C3
C3(H2O)
factor B
Factor H, Factor I,
CR1, MCP (CD46)
C3a
C3b
Opsonisation
C3aR
Leukocyte activation
& chemotaxis
C4b2a/
C3(H2O)Bb
C5 convertases
PK
Tissue Factor
Kallikrein
VII
XII
XI
IX
X
Prothrombin
Plasmin
Thrombin
Fibrinogen
Fibrin
C5
CD59
C5a
C5b
C6
C7
C8
C9(10-16)
Leukocyte activation,
chemotaxis & vasodilatation
C5aR
(CD88)
C5L2
MAC
Cell lysis