Tikrit University
College of Veterinary Medicine

Lect. 7-Immunology

Subject name: Humoral Factors
Complement system
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Lecturers link

Complement system

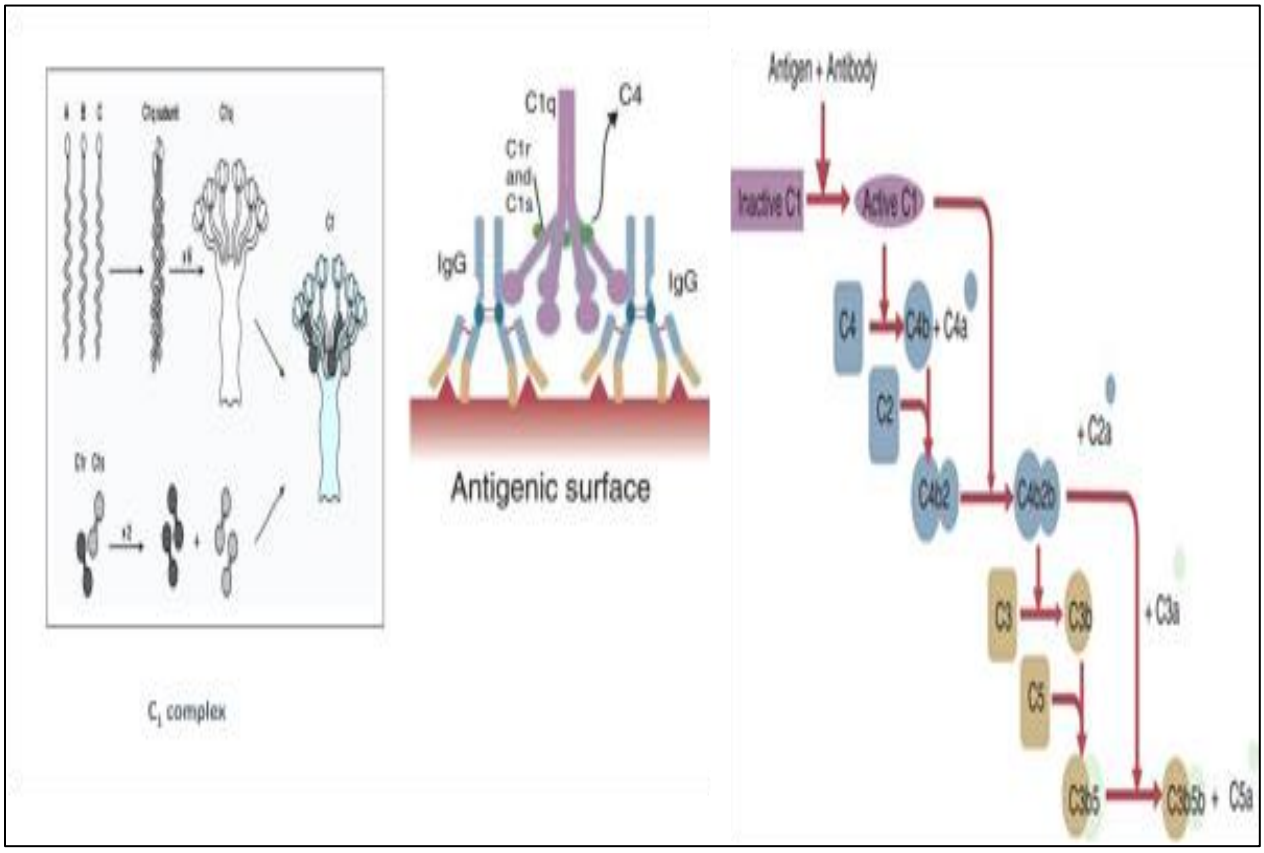
1. **The complement system is one of the major effector mechanisms of humoral immunity and as well as of innate immunity.**
2. **Complement components are synthesized at various sites like liver macrophages and constitutes about 10% of the globular fraction of serum Heat labile (56°C in 30 minutes) serum (plasma) protein..**
3. **Complement system is normally inactive but activated under certain condition like microbial infection and generates effector mechanism to destroy the activator (i.e the microbes).**
4. **The complement system is composed of at least 30 different complement proteins. are called zymogens (proenzymes). The complement proteins are labeled numerically with the prefix C (C1, C2, C3 --- C9) or designated by letters of the alphabet (B, D, P etc).**
5. **Activation of complements involve the sequential proteolysis of proteins to generate enzymes with proteolytic activity.**
6. **Peptide fragments formed by activation of a component are indicated by small letter (C3a, C3b etc). The complement fragments interact with one another to form functional complexes and indicated by a bar over the number or symbol.**
7. **The products of activated complement attach covalently to microbial cell surfaces or antibody coated microbes or other antigens and cause lysis of the target cells (e.g.microbe).**

There are three major pathways for complement activation:

A. The Classical Pathway –

1. **Activated by certain antibodies bound to antigens.**
2. **In classical pathway, first complement component is C_1 complex composed of . three separate proteins C_{1q}, C_{1r} and C_{1s}**
3. **The classical pathway is activated of C_{1q} that made up of an umbrella like radial array of six chains that are connected to central stalk and each chain has globular head, recognizes and binds to Fc region of immunoglobulin heavy chain of IgG and IgM.**

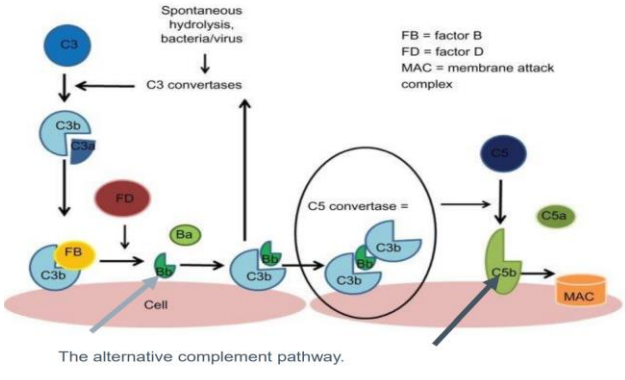
4. **C_1r and C_1s are serine esterases containing two molecules of each and located between C_1q strands.**
5. **Binding of C_{1q} to two or more Fc regions leads to enzymatic activation of C_1r that cleaves and activates C_1s.**
6. **Active C1s cleaves C4 into C4a and C4b. C2 then binds to C4b to form the complex C4b2.(C4bC2). C4b in the presence of Mg2_ splits C2 into C2a and C2b larger fragment (C2a) attached to C4b resulting C4bC2b.**
7. **<u>The C4bC2b. complex possesses enzymatic activity and is called C3 convertase, which converts C3 into an active form.</u>**
8. **The C3 convertase activate C3 into C3a and C3b. Some of the C3b binds to C4b2a to form C4b2a3b called *C5 convertase* and the latter activates C5. Subsequent reactions lead to formation of the terminal complement complex and microbial killing.**



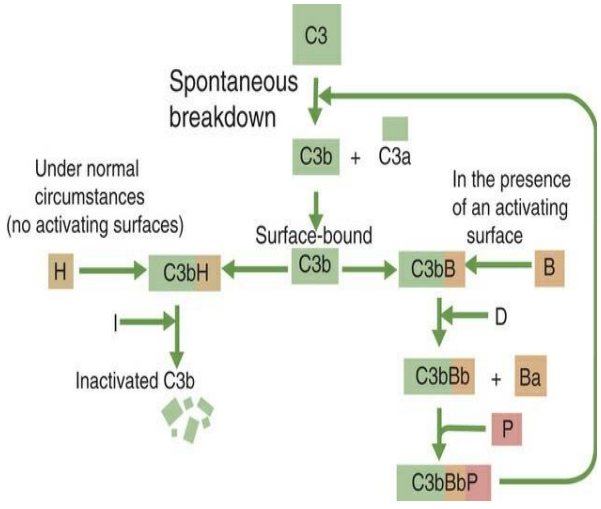
B. Alternative pathway

1. **In alternative pathway C3 is activated and form a stable attachment of C3b to microbial cell surface <u>without the involvement of antibody.</u>** The initial component of the alternative pathway involves four serum proteins: **<u>C3b, factor B, factor D, and properdin</u>**

2. **Normally C3 in plasma breaks down spontaneously into C3a and C3b. The newly formed C3b binds covalently through thioester bonds to the surface of cells including microbes including bacterial cell walls, bacterial lipopolysaccharides(endotoxin), viruses, aggregated IgA, cobra venom etc. permit activation of C3b.**
3. **The B factor is split into two fragments, Ba and Bb, by another serum protein called factor D . the Bb binds to C3b forming the C3bBb complex, which possesses the C3 convertase activity. The interaction between C3b and factor B is stabilized by Mg2,**
4. **The C3bBb complex activates more C3, leading to the formation of more C3bBb, which in turn is capable of activating C5 and the MAC.**
5. **<u>The C3bBb complex has a half-life of only 5 minutes, but by binding with properdin it forms PC3bBb complex, which is relatively heat stable</u>.**
6. **The alternative pathway then proceeds from C3 to produce finally the MAC, in the same way as occurs in the classical pathway**.



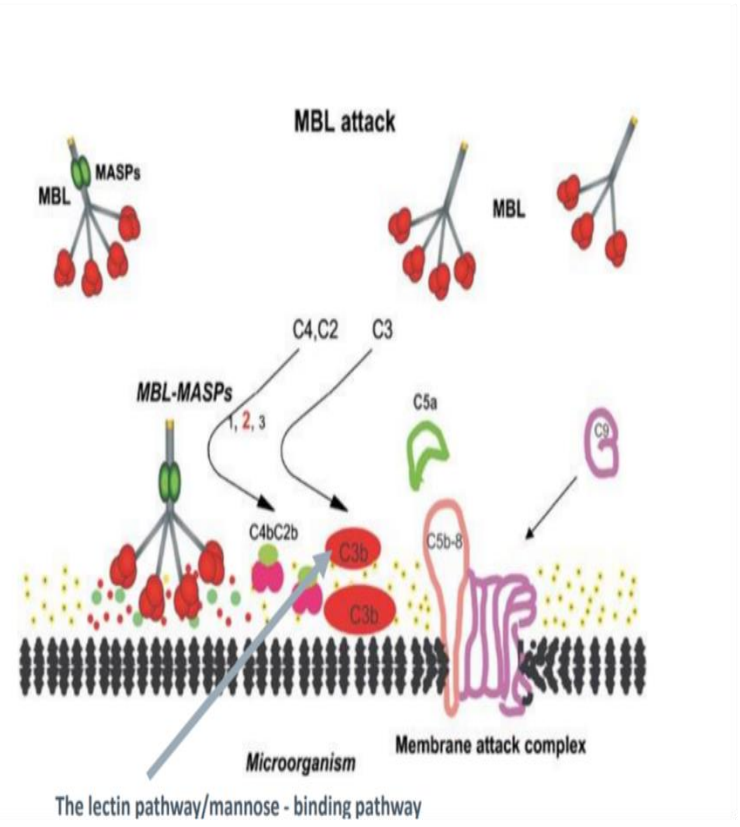
The alternative complement pathway.

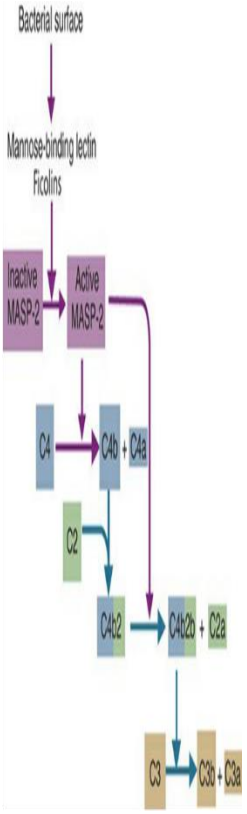


C. The lectin pathway,

1. **The lectin pathway, as the name suggests, is triggered by lectins. Lectins are the proteins that recognize and bind to specific carbohydrate targets. One such protein is the mannose-binding lectin (MBL) that takes part in the lectin pathway of complement activation.**

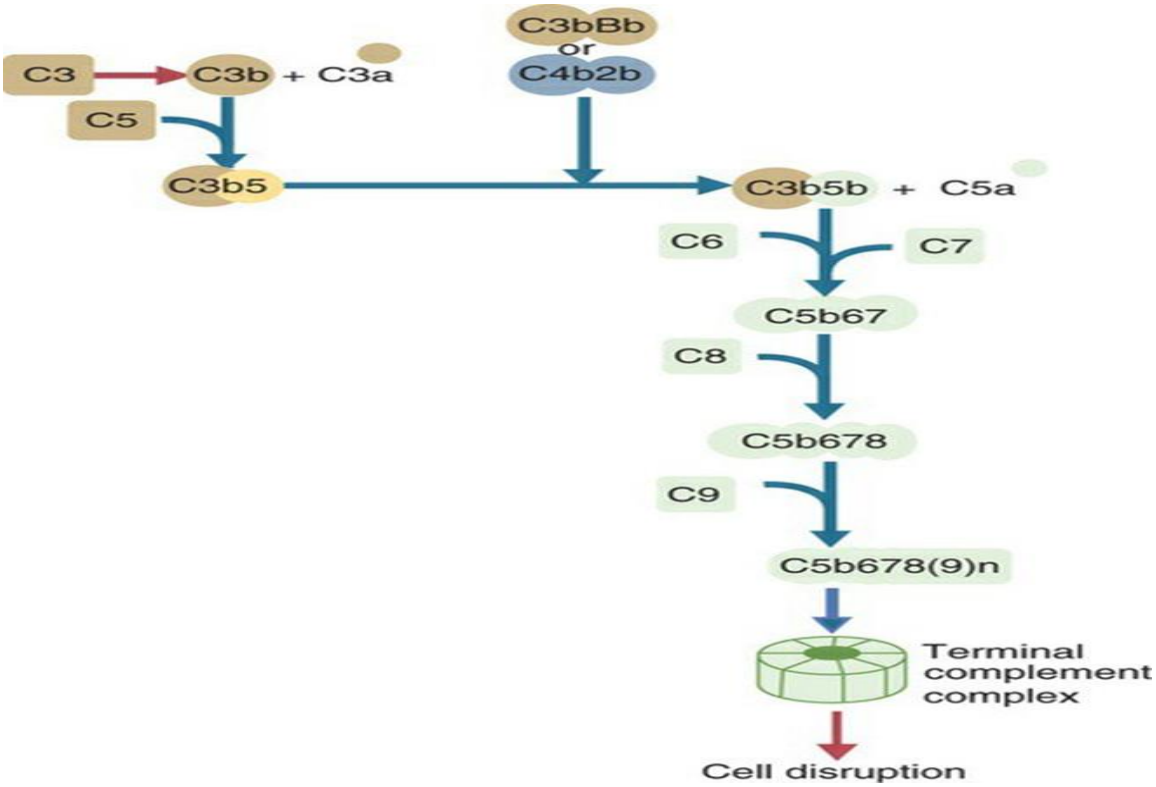
2. **The mannose binding protein or lectin pathway is homologous to the classical pathway, <u>but with the opsonin, mannose-binding lectin (MBL), instead of C1q.</u>**
3. **This pathway is activated by binding mannose-binding lectin <u>MBL</u> to mannose residues on the pathogen surface, which activates the MBL-associated serine proteases (MASP), very similar to C1r and C1s which can then split C4 into C4a and C4b and C2 into C2a and C2b.**
4. **C4b and C2a then bind together to form the C3-convertase, as in the classical pathway. Subsequently, it proceeds to produce MAC in the same way as that occurs in the classical and alternative pathways.**





Mechanism of membrane attack pathway

1. **Once C5 binds to C3b, C5convertase generated by classical pathway (C4b2a), alternative pathway (C3bBb) or mannose binding pathway cleaves C5 to small peptide C5a (released) and C5b, which attach to C3b.**
2. **This cleavage exposed a site on C5b and binds C6 and C7 to form C5b67.**
3. **The C5b67 can remove itself from C3b and insert into the lipid bilayer of nearby cell or microbial membrane.**
4. **Once it is inserted into lipid bilayer, it binds to one C8 molecule and multiple C9 molecules (about 12 to 18) to form a complex C5b6789 of tubular transmembrane pore called the membrane attack complex (MAC).**
5. **The MAC form a large doughnut shaped structure that inserts itself into a cell membrane and forms a transmembrane channel and cause osmotic lysis of the target cell.**



Terminal pathway of complement activation

Comparison of classical, alternative, and lectin pathways

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

- **The complement system has five major antimicrobial functions.**

The main role of complement is to amplify the humoral immune response. The complement through its various products participates in

1. **Chemotaxis:** C5a is a chemotactic molecule causes leukocytes to migrate to a tissue in which an antigen–antibody reaction is taking place. At that site, a phagocytic cell recognizes opsonized particles and ingests them.

2. **Hypersensitivity Reactions:** Complement participates in hypersensitivity reactions. The C3a, C4a, and C5a components stimulate degranulation of mast cells with release of mediators, such as histamine.

3. **Opsonization** of antigen: Bacteria and viruses are easily phagocytosed by phagocytic cells in the presence of complement component C3b. This is because the receptors for the C3b component are present on the surface of many phagocytes.

4. **Cytolysis: Complement** mediates cytolysis. Insertion of C5b–9 complex (MAC) into the cell membrane leads to killing or lysis of erythrocytes, bacteria, and tumor cells. The insertion of the MAC complex results in disruption of the membrane, there by leading to entry of water and electrolytes into the cell.
5. **Enhancement of Antibody Production:** The binding of C3b to the surface receptors on the activated B cells markedly enhances the production of antibodies in comparison to that of B cells activated by antigen alone