Lec.10 : Complement System

The term **complement** refers to a set of serum proteins that cooperates with both the innate and the adaptive immune systems to eliminate blood and tissue pathogens.

Like the components of the blood clotting system, complement proteins interact with one another in catalytic cascades.

Most complement components are synthesized in the liver by hepatocytes, although some are also produced by other cell types, including blood monocytes, tissue macrophages, fibroblasts, and epithelial cells of the gastrointestinal and genitourinary tracts.

Complement was discovered by Jules Bordet as a heat-labile component of normal plasma that causes the opsonisation and killing of bacteria. The complement system refers to a series of >20 proteins, circulating in the blood and tissue fluids. Most of the proteins are normally inactive, but in response to the recognition of molecular components of microorganisms they become sequentially activated in an enzyme cascade – the activation of one protein enzymatically cleaves and activates the next protein in the cascade. Complement can be activated via three different pathways, which can each cause the activation of C3, cleaving it into a large fragment, C3b, that acts as an opsonin, and a small fragment C3a(anaphylatoxin) that promotes inflammation. Activated C3 can trigger the lytic pathway, which can damage the plasma membranes of cells and some bacteria. C5a, produced by this process, attracts macrophages and neutrophils and also activates mast cells.

The Major Pathways of Complement Activation

The Classical Pathway (Initiated by Antibody Binding)

The classical pathway is triggered by activation of the C1-complex. The **C1-complex** is composed of 1 molecule of C1q, 2 molecules of C1r and 2 molecules of C1s, or $C1qr^2s^2$. This occurs when C1q binds to IgM or IgG complexed with antigens. (A single pentameric IgM can initiate the pathway, while several IgGs are needed). This also occurs when C1q binds directly to the surface of the pathogen. Such binding leads to conformational changes in the C1q molecule, which leads to the activation of two C1r molecules. C1r is a serine protease. They

then cleave C1s(another serine protease). The $C1r^2s^2$ component now splits C4 and then C2, producing C4a, C4b, C2a, and C2b. C4b and C2a bind to form the classical pathway C3-convertase (C4b2a complex), which promotes cleavage of C3 into C3a and C3b. C3b later joins with C4b2a to make C5 convertase (C4b2a3b complex) to form the final proteolytic complex of the complement cascade which cleavage C5 to C5a and C5b .

The C5bC6C7C8 complex polymerizes C9 to form a tubule (pore), which spans the membrane of the cell being attacked, allowing ions to flow freely between the cellular interior and exterior. By complexing with C9, the osmotic cytolytic reaction is accelerated. This tubule is a hollow cylinder with one end inserted into the lipid bilayer and the other projecting from the membrane.

A structure of this form can be assumed to disturb the lipid bilayer sufficiently to allow the free exchange of ions and water molecules across the membrane. Ions flow out, but large molecules stay in, causing water to flood into the cell. The consequence in a living cell is that the influx of sodium (Na+) ions and H2O leads to disruption of osmotic balance, which produces cell lysis.

Alternative pathway

Microbial and mammalian cell surfaces can activate the alternative pathway in the absence of specific antigen-antibody complexes. Factors capable of activating the alternative pathway include inulin, zymosan (polysaccharide complex from surface of yeast cells), bacterial polysaccharides and endotoxins, and the aggregated IgG2, IgA, and IgE

C3b that is generated from C3 by a C3 convertase enzyme complex in the fluid phase is rapidly inactivated by **factor H** and **factor I,** as is the C3b-like C3 that is the product of spontaneous cleavage of the internal thioester. In contrast, when the internal thioester of C3 reacts with a hydroxyl or amino group of a molecule on the surface of a cell or pathogen, the C3b that is now covalently bound to the surface is protected from factor H-mediated inactivation. The surface-bound C3b may now bind **factor B** to form C3bB. This complex in the presence of **factor D** will be

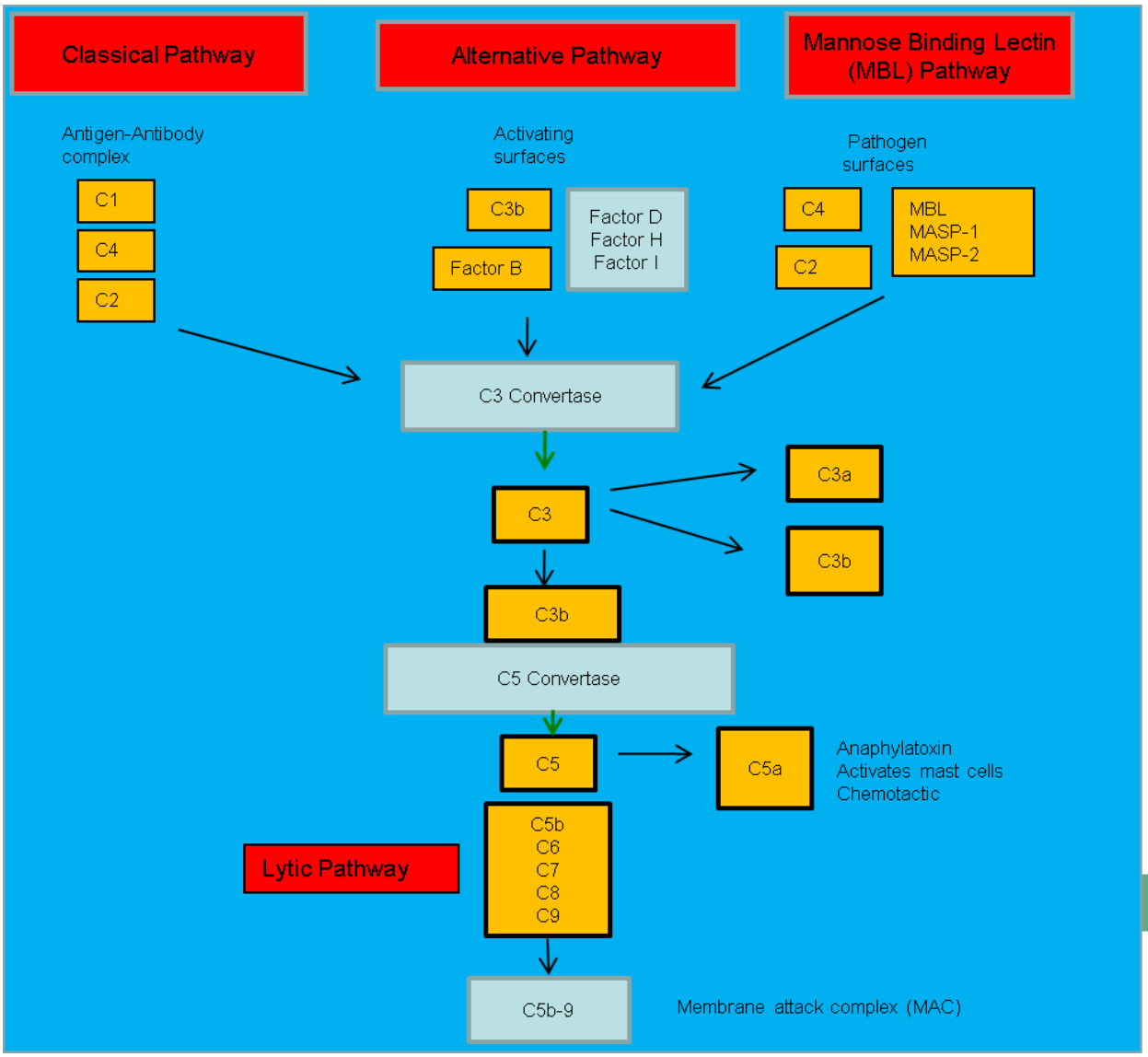
cleaved into Ba and Bb. Bb will remain associated with C3b to form C3bBb, which is the alternative pathway C3 convertase.

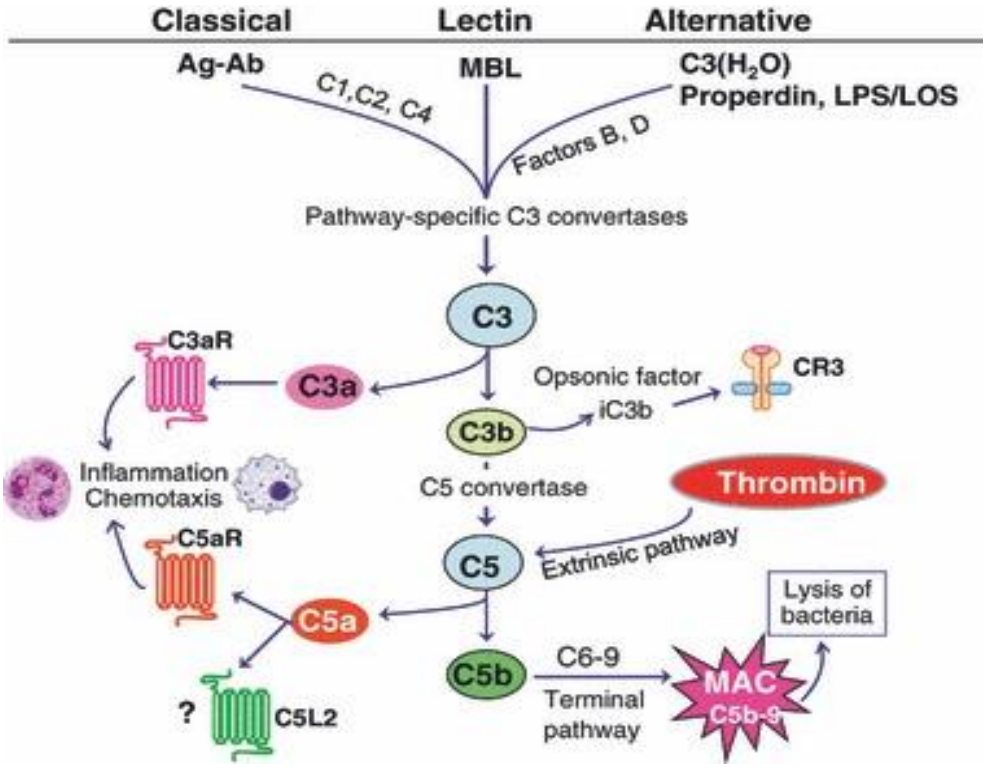
The C3bBb complex is stabilized by binding oligomers of **factor P (Properdin)**. The stabilized C3 convertase, C3bBbP, then acts enzymatically to cleave much more C3, some of which becomes covalently attached to the same surface as C3b. This newly bound C3b recruits more B, D and P activity and greatly amplifies the complement activation.

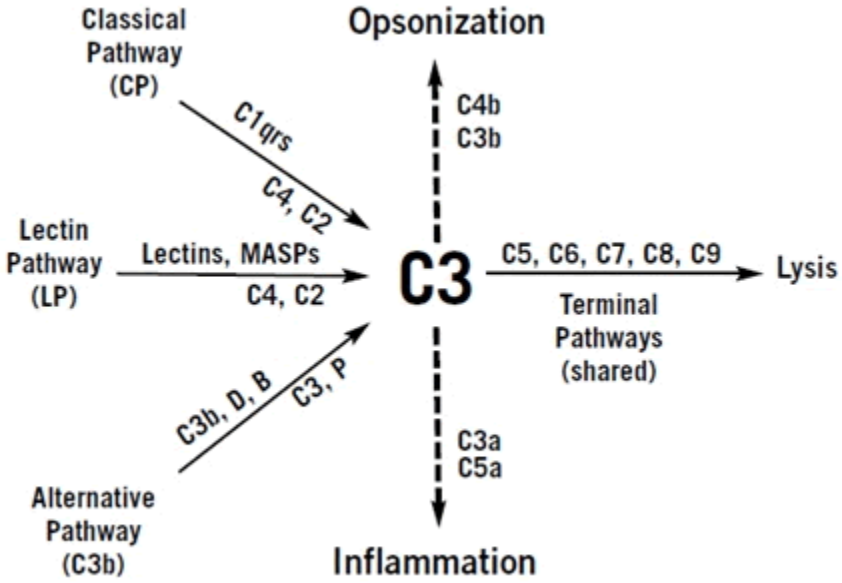
The association of numerous C3b units, factor Bb, and properdin on the surface of an aggregate of protein or the surface of a microorganism has potent activity as a C5 convertase. With the cleavage of C5, the remainder of the complement cascade continues as in the classic pathway.

Mannose – binding lectin Pathway

Mannose – binding lectin Pathway is homologous to the classical pathway (but with the opsonin) mannose-binding lectin (MBL) and ficolins, instead of C1q. This pathway is activated by binding of MBL to mannose residues on the pathogen surface, which activates the MBL-associated serine proteases, MASP-1, and MASP-2 (very similar to C1r and C1s, respectively), which can then split C4 into C4a and C4b and C2 into C2a and C2b. C4b and C2b then bind together to form the classical C3-convertase, as in the classical pathway. Ficolins are homologous to MBL and function via MASP in a similar way.


Classical Pathway
Alternative Pathway
Mannose Binding Lectin (MBL) Pathway
Antigen-Antibody complex
C1
C4
C2
Activating surfaces
C3b
Factor B
Factor D
Factor H
Factor I
Pathogen surfaces
C4
C2
MBL
MASP-1
MASP-2
C3 Convertase
C3
C3a
C3b
C3b
C5 Convertase
C5
C5a
Anaphylatoxin
Activates mast cells
Chemotactic
Lytic Pathway
C5b
C6
C7
C8
C9
C5b-9
Membrane attack complex (MAC)


Classical
Lectin
Alternative
Ag-Ab
MBL
C3(H2O)
Properdin, LPS/LOS
C1,C2, C4
Factors B, D
Pathway-specific C3 convertases
C3
C3aR
C3a
Opsonic factor
iC3b
CR3
C3b
Inflammation
Chemotaxis
C5 convertase
Thrombin
C5aR
C5
Extrinsic pathway
Lysis of bacteria
C5a
C5b
C6-9
Terminal pathway
MAC
C5b-9
?
C5L2


Classical Pathway (CP)
Opsonization
C1qrs
C4, C2
C4b
C3b
Lectin Pathway (LP)
Lectins, MASPs
C4, C2
C3
C5, C6, C7, C8, C9
Lysis
Terminal Pathways (shared)
C3b, D, B
C3, P
C3a
C5a
Alternative Pathway (C3b)
Inflammation

Role of Complement in Disease

The complement system plays a critical role in inflammation and defense against some bacterial infections. Complement may also be activated during reactions against incompatible blood transfusions, and during the damaging immune responses that accompany autoimmune disease. Deficiencies of individual complement components or inhibitors of the system can lead to a variety of diseases which gives some indication of their role in protection against disease.

Complement triggers the following immune functions

- Opsonization promote **Phagocytosis**
- Chemotaxis
- Inflammation by attracting macrophages and neutrophils
- lysis, apoptosis by rupturing membranes of foreign cells