Innate Immune System

Innate Immunity is present in all individuals at all times and does not increase with repeated exposure to a given pathogen. The response is non-specific, the exposure leads to immediate maximal response to infection and there is no development of immunological memory.

In this section you will find explanations of the mechanisms and cells involved.

The Complement System:

Once you have read this section you will become familiar with the complement system which is a biochemical cascade.

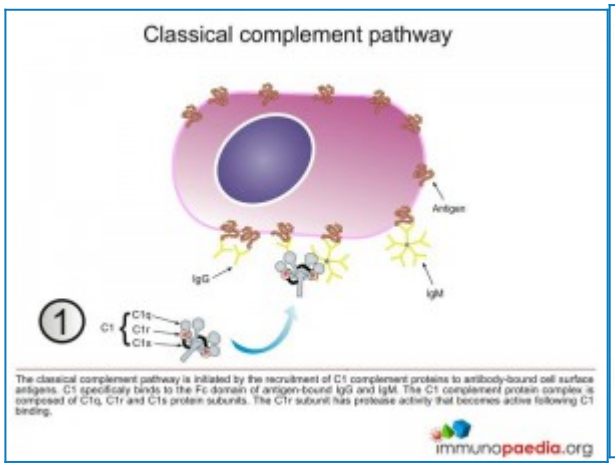
There are three biochemical pathways which can activate the complement system:

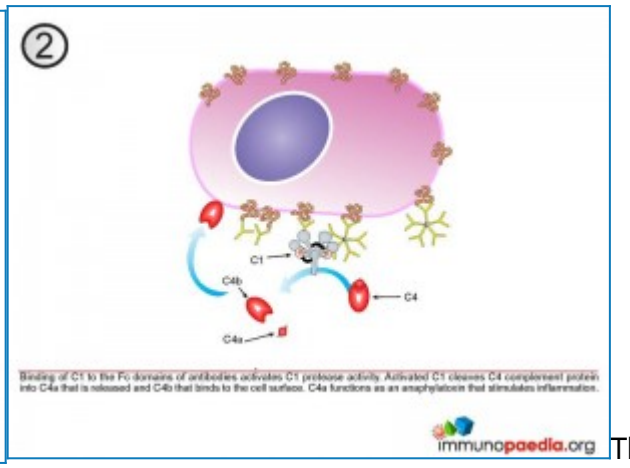
- Classical Pathway
- Alternative Pathway
- Mannose – Binding Lectin (MBL) Pathway

With the aid of our colour graphics you will be able to clearly see how the pathways are activated and the sequence of events which follow.

Click here to view the associated case study

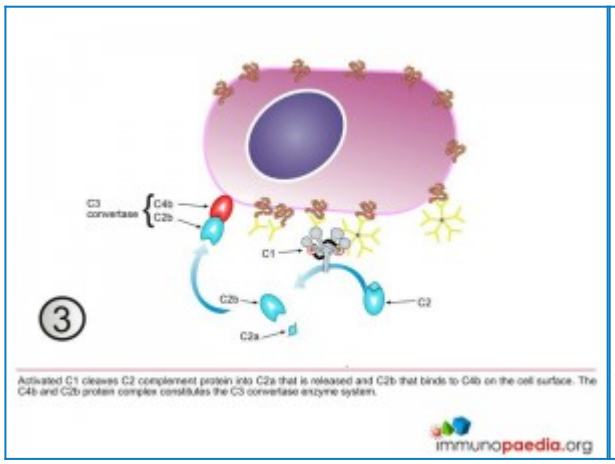
The Classical Pathway

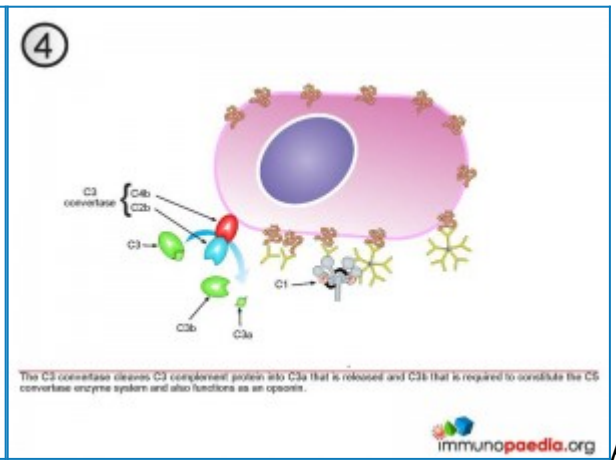




The classical pathway of the complement system is a major effector of the humoral branch of the human immune response. The trigger for the classical pathway is either IgG or IgM antibody bound to antigen. Binding of antibody to antigen exposes a site on the antibody which is a binding site for the first complement component, C1. (Figure 1).

C1 is a macromolecular complex made up of subunits C1q, C1r, and C1s. When the intact macromolecular C1 binds to the exposed regions of at least two antigen-bound antibodies, the C1r and C1s subunits are activated and are responsible for the cleavage of the next two involved complement components, C4 and C2. (Remember, the numbers indicate the order in which the components were discovered, not the order in which they activate in the cascade). C4 is cleaved into two fragments. The larger C4b molecule attaches to the target membrane nearby while the small C4a molecule floats away (Figure 2).

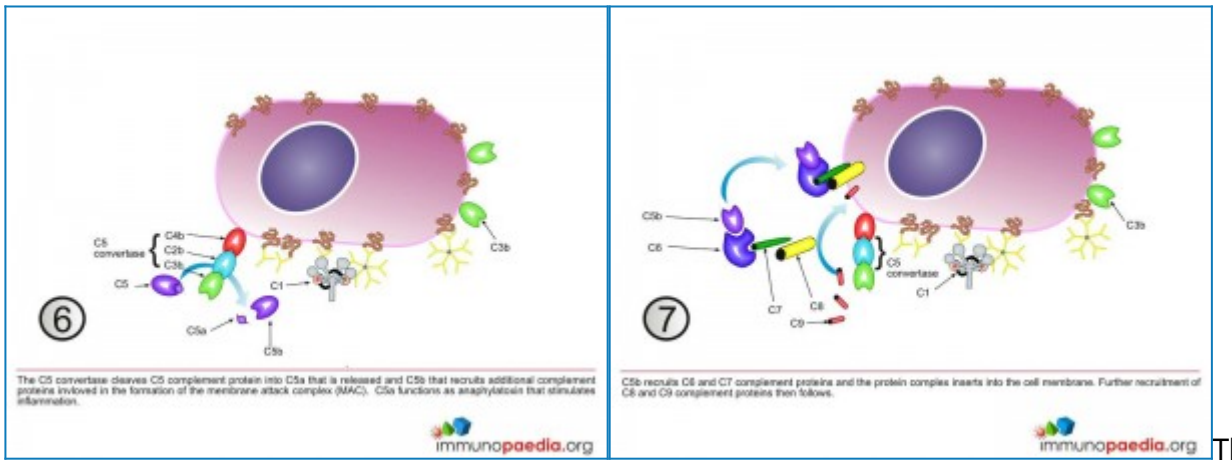




An exposed site on deposited C4b is available to interact with the next complement component, C2. Again, activated C1s cleaves the C2 molecule into two pieces. In this case, the fragment that remains is C2b. The smaller C2a fragment floats away. What remains bound to the membrane is C4b2b, also known as the C3 convertase because its role is to convert the next complement component, C3, into its active form (Figure 3)

The C3 convertase of the classical pathway splits C3 into two fragments, C3a and C3b. The convertase has the ability to cleave multiple C3 molecules, forming hundreds of C3a and C3b fragments. The C3a fragments float away and have a role in inducing an inflammatory response (Figure 4).

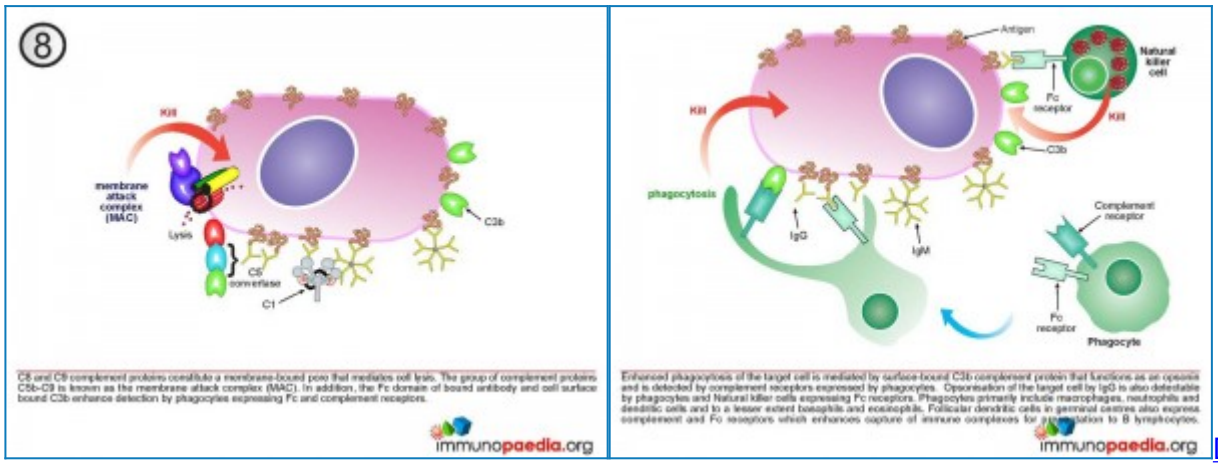
Of critical importance, some of the C3b binds to the C4b2b to form C4b2b3b – known as the C5 convertase (Figure 5).



The C5 convertase, much like the C3 convertase before it, catalyzes the cleavage of hundreds to thousands of C5 complement components into C5a and C5b, before it reverts to inactivity. C5a floats away and contributes to inflammation while the C5b fragment binds to the antigen surface. This binding of C5b is the initial step in the formation of the membrane attack complex (MAC) (Figure 6).

The membrane-bound complement component C5b is bound by the next complement molecule, C6 (Figure 7).

The resulting bimolecular complex then binds C7 and then C8. The C5b-8 complex acts as a receptor for a variable number of membrane-disrupting C9 molecules. The resultant C5b-8 complex and poly-C9 is given the name “membrane attack complex.” The MAC creates a transmembrane pore leading to the lysis of the target cell (Figure 8 and Figure 9).



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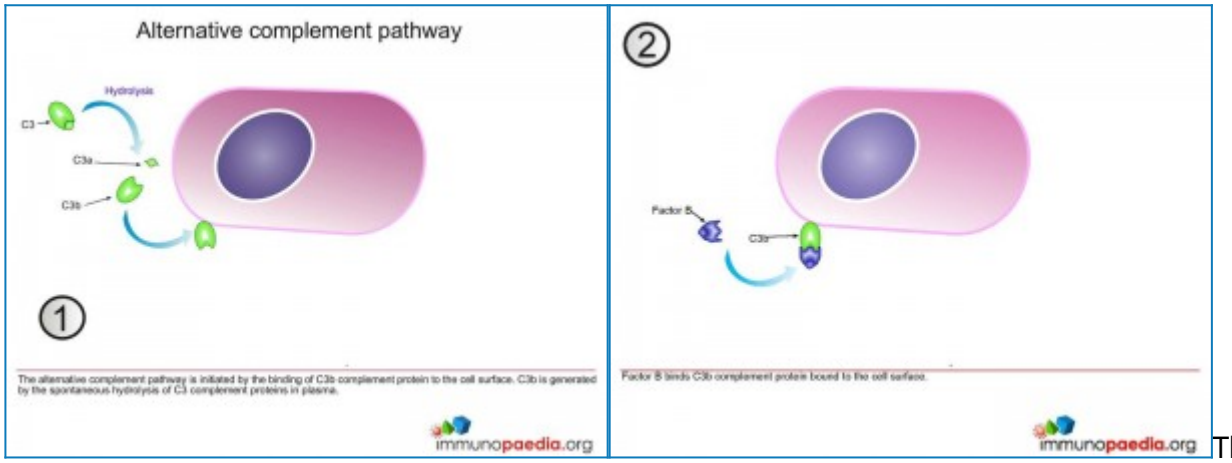
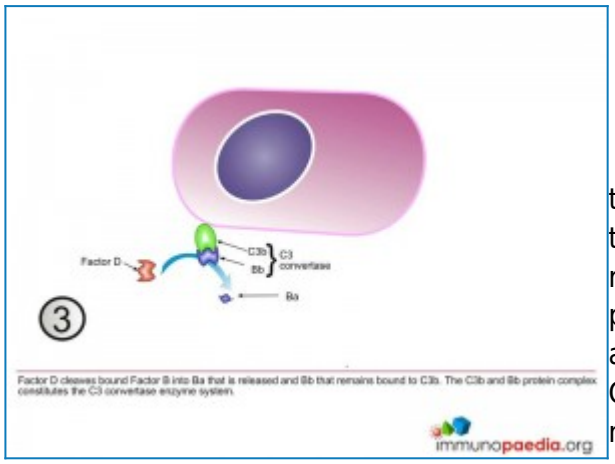
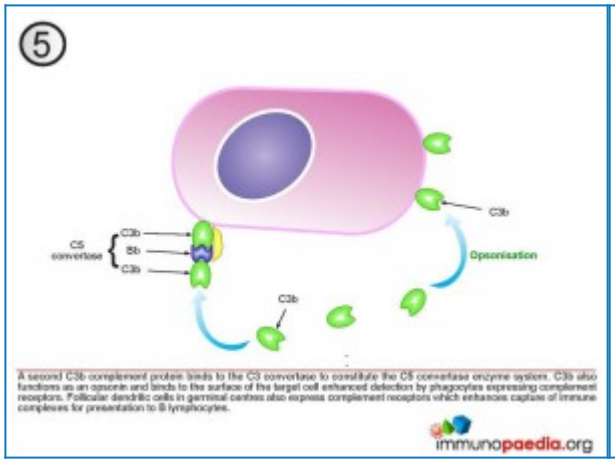
The Alternative Pathway

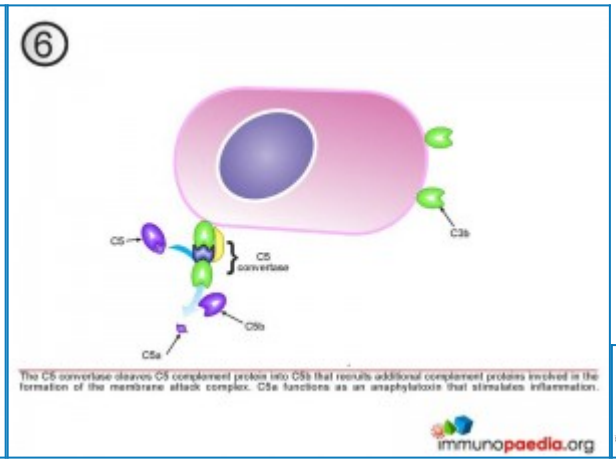


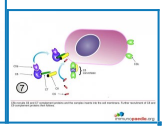
The alternative complement pathway does not require antibody for its activation. Rather, a variety of antigens such as bacterial lipopolysaccharide and components of viruses and other pathogens have



the ability to activate this pathway. It is thought to have the classical pathway, which depends on the relatively recently evolved antibody molecule. Like the classical pathway, the alternative pathway produces both a C3 and a C5 convertase which leads to the production of C5b and then to the formation of the MAC. The specific molecular players and the path followed along the way are, however, different.







The complement component, C3, is spontaneously cleaved at low levels. This means that there are C3a and C3b fragments freely floating in serum. The C3b component can attach to a number of different surfaces, both foreign and host cells alike. C3b is quickly inactivated by the sialic acid found on most mammalian cell surfaces. Microbes, most of which lack sialic acid, are stable sites for C3b deposition (Figure 1).

Membrane-bound C3b fragments are bound by Factor B (Figure 2).

Factor B is then cleaved by Factor D. The fragment Ba floats away, while Bb stays associated with C3b. The resulting C3bBb molecule is the alternative pathways C3 convertase. The C3 convertase of the alternative pathway is, however, not particularly stable (Figure 3).

In order to effectively split a relevant number of C3 molecules, the C3 convertase requires the stabilization of another molecule, properdin (P), which binds to the C3bBb complex and extends the half-life of its activity (Figure 4)

The alternative pathway C3 convertase acts just like the classical pathway enzyme of the same name and cleaves hundreds of C3 molecules into C3a and C3b (Figure 5).

The C3b molecule remains attached to form the alternative pathway C5 convertase, C3bBb3b. This enzyme cleaves C5 into C5a and C5b. The C5 convertase, much like the C3 convertase before it, catalyzes the cleavage of hundreds to thousands of C5 complement component into C5a and C5b before it reverts to inactivity. C5a floats away and contributes to inflammation while the C5b fragment binds to the antigen surface. This binding of C5b is the initial step in the formation of the membrane attack complex (MAC) (Figure 6).

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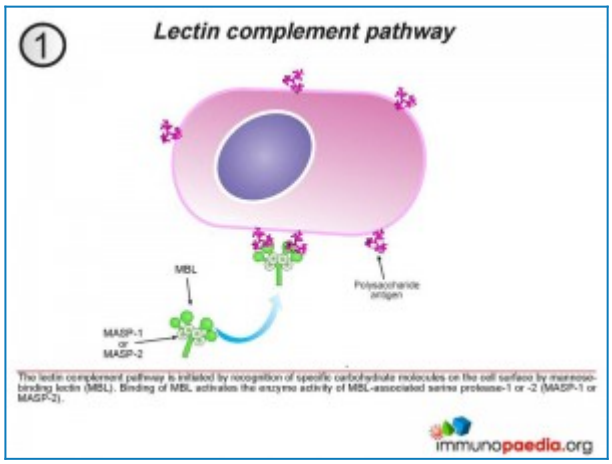
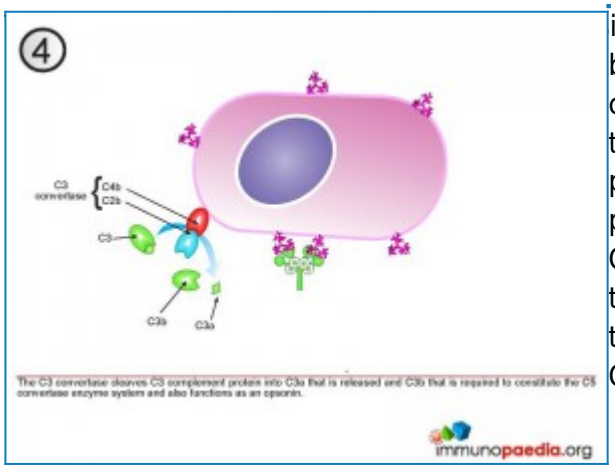
The Mannose-Binding Lectin (MBL) Pathway





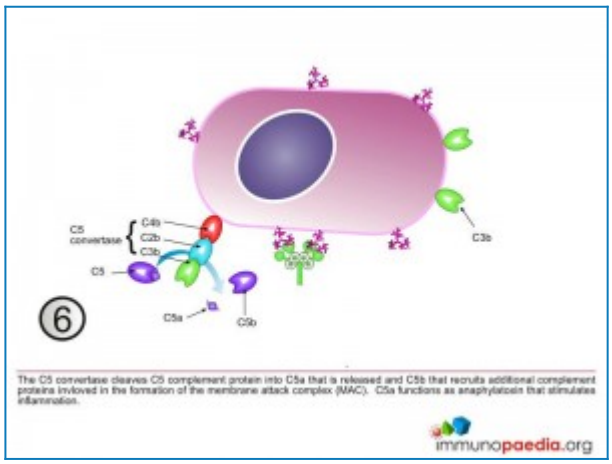
ical pathway. It is initiated by the binding of mannose-binding lectin (MBL) to bacterial surfaces with mannose-containing polysaccharides (mannans). Binding of MBL to a pathogen results in the association of two serine proteases, MASP-1 and MASP-2 (MBL-associated serine proteases). MASP-1 and MASP-2 are similar to C1r and C1s, respectively and MBL is similar to C1q. Formation of the MBL/MASP-1/MASP-2 tri-molecular complex results in the activation of the MASPs and subsequent cleavage of C4 into C4a and C4b (Figure 1).

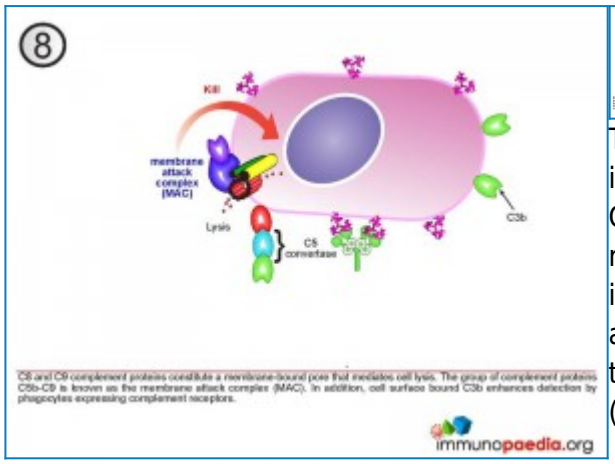
The C4b fragment binds to the membrane and the C4a fragment is released into the microenvironment (Figure 2, only MASP-2 shown).

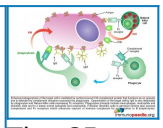
Activated MASPs also cleave C2 into C2a and C2b. C2a binds to the membrane in association with C4b and C2b is released into the microenvironment. The resulting C4bC2a complex is a C3 convertase, which cleaves C3 into C3a and C3b (Figure 3).

C3b binds to the membrane in association with C4b and C2a and C3a is released into the microenvironment (Figure 4).

The resulting C4bC2aC3b is a C5 convertase. The generation of C5 convertase is the end of the lectin pathway (Figure 5).







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