1.2.4

The Complement System

The complement system is another part of our internal and innate defense. Including more than 30 liver proteins circulating in an inactive state in the blood, the complement system stands ready at all times to destroy microbes. The proteins of the complement system are activated in a cascade where each one is activated by the one before it. Through the complement system, microbes are destroyed in three ways: inflammation, opsonization, and bacteriolysis/cytolysis.

Watch the following two videos on the complement system:

1. Complement System Part 1 – Actions

2. Complement System Part 2 – How the System is Activated

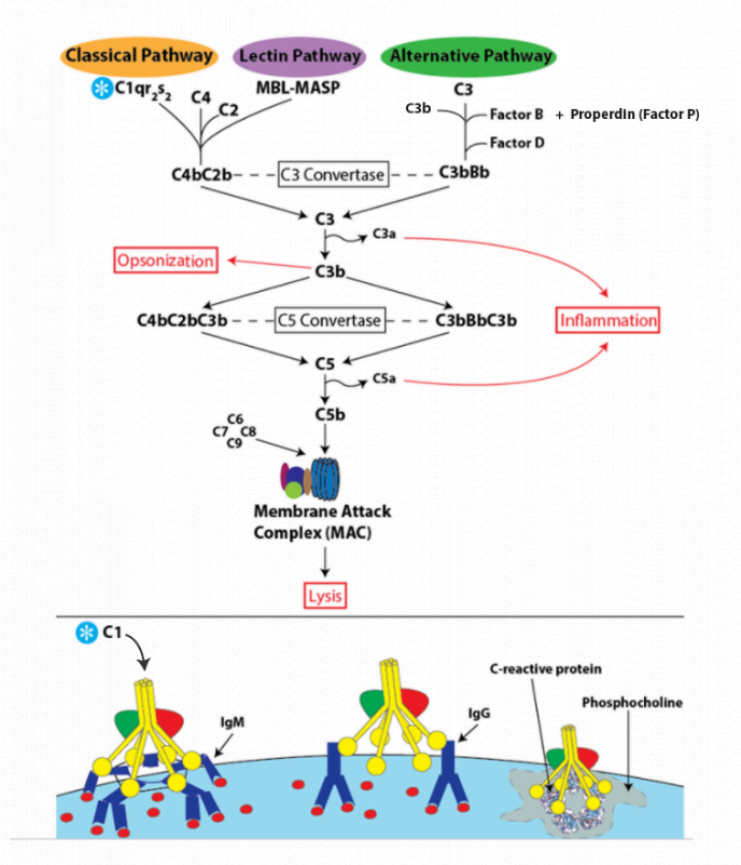

Diagram of the Complement System Image by JS

The complement system can begin in one of three pathways: the classical pathway, the alternative pathway, and the lectin pathway. The complement proteins in each pathway of the complement system all have specific tasks. These proteins become active when they are cleaved (for example C4 becomes activated when it is cleaved into two fragments called C4a and C4b). Before we discuss the specifics of the three starting points to the complement system, we will go over the common pathway all three of them converge on.

The common pathway begins once C3 is activated (cleaved) and becomes C3a and C3b. C3a acts as an anaphylatoxin, which means it causes mast cells to release histamine. Histamine functions to increase inflammation by causing vasodilation, which allows greater blood flow to the area, and endothelial retraction, which allows immune cells to leave the blood and enter the affected tissue. C3a also acts as a chemotactic factor to attract leukocytes. C3b acts as an opsonin, which means it binds to pathogenic or damaged cells and makes it easier for phagocytic immune cells to recognize them. Opsonization is like putting jam on toast. Macrophages and neutrophils are much more likely to eat a bacterium with C3b on it. If C3b was activated through the classical or lectin pathways it then combines with C4b and C2b to make C5 convertase which will cleave C5 into C5a and C5b. If C3b was activated by the alternate pathway it will participate in making a different C3 convertase. This enzyme will then cleave more C3. Eventually, the increased C3b will join the C3 convertases to make C5 convertase which will cleave C5 into C5a and C5b. Just like C3a, C5a acts as an anaphylatoxin and chemotactic factor. C5b activates other complement proteins involved in bacterial cell lysis. This is where the **membrane attack complex (MAC)** comes into play. C5b binds with C6, C7, and C8 to form a receptor for C9 on the bacterial cell's plasma membrane. Many C9s then come and bind to this receptor and they form a channel that lets in extracellular fluid into the bacteria and causes it to lyse. Together, C5b and C6-C9 are known as the MAC.

Now that we have gone over the general players of the complement system, let's talk about each pathway and how it is activated. The first pathway we will mention is the **classical pathway**. It was the first to be discovered and starts when the variable region of antibodies (IgG and IgM) attaches to an antigen on a microbe. This allows for the activation of C1. Activated C1 cleaves C4 into C4a and C4b. C4b then joins C1 and the complex can cleave C2 into C2a and C2b. C4b and C2b then form a C4b2b complex that is also called C3 convertase, which cleaves C3 into C3a and C3b. Then C4bC2b binds another C3b to form the C5 activation complex (C5 convertase). Once C5 is activated into C5a and C5b, the membrane attack complex can be assembled.

****A note on complement protein nomenclature: the 'b' generally designates the larger fragment while the 'a' generally designates the smaller fragment. However, when C2 was initially characterized it was not according to this convention (i.e. the larger fragment was identified as C2a). Hence, when referring to the classical C3 Convertase, you may see both 'C4b2a' and 'C4b2b' as some scientists are trying to conform to the original nomenclature.*

Another way that the classical pathway can be initiated is through **CRP** and phosphocholine. CRP stands for C-reactive protein, which is found circulating in the plasma. CRP binds to phosphocholine, which is a special type of phospholipid expressed in the membranes of dead or dying cells as well as some pathogens. When CRP recognizes and attaches to phosphocholine it attracts antibodies that are capable of triggering the classical pathway. CRP is made mostly by the liver and has been observed to increase in the plasma under the influence of a variety of pathologies. For this reason, it is often used as a general test to screen for tissue damage and inflammation.

The **alternative pathway** was the second to be discovered and includes complement factors B, D and P (properdin). A certain amount of C3 is spontaneously cleaved in the plasma. C3b attaches to cell membranes and forms a complex with factor B. Factor B is assisted by another protein called factor P. This C3b-B-P complex is now in a configuration that Factor D can work on it to perform a lysis that cleaves factor B into Bb and Ba. Bb attaches to C3b and we have another form of C3 convertase. This new C3 convertase can also cleave C3 to create C3a and C3b. Soon, there is enough C3b that C3bBb joins with another C3b and we have C3bBbC3b or C5 convertase. The fact that C3 can undergo spontaneous cleavage would suggest that it might be possible for C3b to be generated that attaches to healthy tissue cells and starts the complement cascade that could result in damage. Luckily, normal body cells have a variety of membrane proteins that actually interfere with this process. Bacteria, fungi and parasites on the other hand, do not have such interfering membrane proteins so they are much more susceptible to the alternate pathway that results in their destruction and localized inflammation.

The **lectin pathway** was the last to be discovered. Lectin is a protein that recognizes carbohydrate residues. **Mannose-binding lectin or MBL** is made by the liver and binds to mannose on pathogen cell surfaces. MBL acts as an opsonin and also activates the complement cascade. MBL is considered an acute phase protein, which is a protein whose plasma concentration changes in response to inflammation. When macrophages and neutrophils perform phagocytosis on bacteria, they release cytokines that travel through the blood to the liver. The liver is stimulated by these cytokines to create more MBL. MBL is then released into the blood where it is recognized and binds to mannose on pathogen cell surfaces. This binding results in an attraction for mannose associated serine protease (MASP), which is also derived from the liver. The MBL-MASP complex acts as an enzyme that can cleave C4 into C4a and C4b after which C4b can cleave C2 and soon, we have C4bC2b and the same C3 convertase arises that occurred in the classical pathway.

MBL has been shown to bind to *Candida albicans* (fungi that causes yeast infections), streptococci, and Salmonella.