Complement Deficiencies

Chapter 16

Complement is the term used to describe a group of serum proteins that are critically important in our defense against infection. There are deficiencies of each of the individual components of complement. Patients with complement deficiencies encounter clinical problems that depend on the role of the specific complement protein in normal function.

Description of the Complement System and Its Pathways

The complement system consists of more than 30 proteins, present in blood and tissues, as well as other proteins anchored on the surfaces of cells. The primary functions of the complement system are to protect from infection, to remove particulate substances, (like damaged or dying cells, microbes or immune complexes) and to help modulate adaptive immune responses. As part of the innate immune system, complement acts immediately to start the process of removal and resolution of the problem. Complement works with the inflammatory cells of the innate immune system and those of adaptive or acquired immunity. It also interacts with proteins of the coagulation and kinin generating systems along with others.

Complement activation is tightly regulated and designed to kill invading microbes while producing minimal "collateral damage" that could result in the destruction of host tissues. Complement proteins in the circulation are not activated until triggered by an encounter with a bacterial cell, a virus, an immune complex, damaged tissue or other substance not usually present in the body.

Complement activation is a cascading event like the falling of a row of dominoes. It must follow a specific order if the end result is to be achieved. The circulating proteins have been grouped into three activation pathways, based on the types of substances and proteins that initiate the activation. If you visualize a trident, the three tines represent the different initiation routes, while the handle represents the lytic mechanism by which this cascade ultimately destroys the threat, no matter which activation pathway started the response. The diagram in *Figure 1* depicts the activation pathways.

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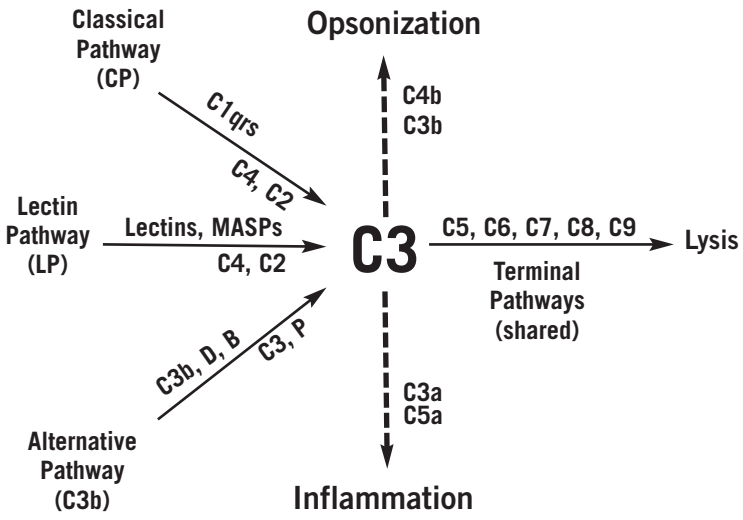

The Classical Pathway (CP) is activated primarily by immunoglobulins (antibodies, including autoantibodies) that are bound to antigens – either in the fluid phase as soluble immune complexes, or on

(Description of the Complement System and Its Pathways continued)

cell membrane surfaces or other tissues. Aggregates of immunoglobulins such as cryoglobulins also activate the CP. Components of the CP are C1q, C1r, C1s, C2 and C4. The CP was the first to be discovered, but is the most recent in evolutionary terms.

The Lectin Pathway (LP) is similar to the CP except for the first two steps. Mannose binding lectin (MBL), the Ficolins, and Collectin can initiate the LP. Associated with these are enzymes referred to as MASPs (MBL-Associated Serine Proteases). C2 and C4 also participate in the LP. The LP is thought to be the most evolutionarily primitive of the complement pathways and the first to react before the adaptive immune response occurs.

The Alternative Pathway (AP) is initiated by fragments of the complement component C3. Other elements of the AP are Factor B, Factor D and properdin. A unique feature of the AP is the presence of the only positive regulator in the complement system, Properdin. Properdin makes it possible for the amplification loop of the alternative pathway to set up a very efficient mechanism for putting lots of C3b onto the surface of the activating cells, protein complexes or particles in the immediate vicinity of the activation site. Because the ability of the C3b to bind to these surfaces decays rapidly, the activation is limited to just the region around the C3 cleavage site. This time-limitation is another control mechanism for the complement pathway.

The Terminal Pathway (TP) is the final set of steps in the complement activation process that forms a membrane lesion or hole (membrane attack complex or MAC) that kills susceptible bacteria or other cells that activate complement on their surfaces. The TP is dependent upon at least one of the other pathways to initiate the process that it then completes. The components of the TP are C3, C5, C6, C7, C8 and C9. A fluid phase form of the MAC, called the Terminal Complement Complex (TCC) can be found in the circulation after complement activation occurs and makes a useful laboratory marker for complement activation.

Control mechanisms to prevent unregulated activity (and tissue damage) are present in each pathway. C1-esterase inhibitor (C1-inh) is a serine protease inhibitor (SERPIN) that acts by forming a complex with active enzymes to trap and inactivate them. It is important in controlling the C1r and C1s activation in the CP, and the MASPs in the LP along with several enzymes in the coagulation system.

The dynamic interplay among the different complement pathways and their control processes involves other plasma protein systems such as enzymes of the coagulation system, enzymes from inflammatory cells, and substances such as histamine released from cells in the local environment. All of these participants affect the outcome of an activation event. Most of the time, the outcome is favorable to the host, with the danger met and the situation returned rapidly to normal. The diseases that accompany uncontrolled activation or inadequate performance of complement's functions are often the result of inherited deficiency or subtle impairment of one or more of the components.

Complement Deficiencies and Their Diagnosis

Clinical indications for possible complement deficiencies include recurrent mild or serious bacterial infections, autoimmune disease, or episodes of angioedema (a painless, but often dramatic, swelling under the skin, or swelling in the intestines, which can be extremely painful). Very rarely angioedema in the brain can be fatal. This swelling does not respond to antihistamines or epinephrine. The list of potential complement-related problems includes renal disease, vasculitis (blood vessel inflammation) and age-related macular degeneration. A history of family members having the same presentation should increase the suspicion of an inherited complement deficiency, most of which are inherited as autosomal co-dominant conditions. All genes, except for those in the Male sex chromosome Y, come in pairs, one inherited from mom and one from dad.

Co-dominance occurs when the contributions of both alleles are visible in the phenotype. In the ABO blood group example, the A and B allele classes are co-dominant in producing the AB blood group phenotype, in which both A-type and B-type antigens are made. By contrast, with traditional dominant–recessive gene combination like eye color, a single brown allele is dominant and if the other parent contributed a blue color allele, the eyes will be brown rather than a mix of brown and blue. In this context it means both the normal and mutant complement proteins are produced in the affected individuals. There is an exception in the case of Properdin, the gene for which is on the X chromosome and is inherited as an x-linked disease. *(See chapter titled "Inheritance.")*

The initial tests done to evaluate a patient's complement system are critical because they can often identify an inherited defect and indicate what further testing must be done to make the diagnosis. The aim of the evaluation process is to clearly define the complement component deficiency with as few tests as possible, while ruling out acquired causes of low complement values. Several screening tests are available that make it easier to find the answers. It is important to know as much as possible about the reason(s) for low or absent complement so that decisions regarding appropriate treatment can be made, including when to use antibiotics and immunizations as well as genetic counseling for inherited deficiencies.

Therapeutics specific for complement deficiencies are still in the developmental stage for most components, but in some cases, such as C1-Inh deficiency, there are currently several drugs available. For uncontrolled complement activation as in PNH or due to dysfunctional FH, there are a few drugs available to treat acute episodes or to prevent recurrence. Therapeutics for complement-derived diseases is in its infancy at this time, but more treatments should become available in the near future.

Deficiencies in the Classical Pathway: C1q, C1r, C1s, C4, C2, C1-Inh

Rapid clearance of immune complexes, dying cells and debris from damaged tissues is a job that is performed efficiently by a normal CP. Primary deficiency of C1q, C1r, C1s or C4 is closely linked to development of systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), thought to be due in part to the inability of complement to clear immune complexes and dying cells. Small complexes are cleared from the circulation when they bind to complement receptors on macrophages in the spleen and liver.

Without complement, the complexes can grow too large to be easily cleared. The resulting aggregates can activate the alternative pathway, allowing C3 to be

(Deficiencies in the Classical Pathway: C1q, C1r, C1s, C4, C2, C1-Inh continued)

deposited into the matrix, with re-solubilized complexes that can be dealt with by the clearance through the liver and spleen. Failing this, these large complexes are no longer soluble, and form deposits in the tissues and become a site of inflammation. Dying cells, if not cleared by non-inflammatory CP activity, may serve as sources of altered self-antigens with the potential for inducing autoantibodies.

C2 deficiency is the most common complement deficiency in Caucasian populations, with frequency estimates between 1 in 10,000 to 1 in 20,000 for homozygous C2-deficient patients. C2 deficiency is found in a slightly higher proportion of SLE patients compared to healthy controls. In primary immunodeficiency, C2 deficiency is found in young children who have recurrent infections, primarily upper respiratory infections with Streptococcus pneumoniae or similar organisms. These children often have frequent ear infections and colds.

Hereditary angioedema (HAE) is a disease caused by deficiency of the CP control protein, C1-Inh. Symptoms generally begin around puberty but can occur earlier. These individuals have recurrent swelling in the extremities, face, lips, larynx or GI tract. The patients describe a sensation of fullness but not pain or itching in the affected area except for those with abdominal swellings who often experience acute abdominal pain. The latter two presentations are of the most concern because suffocation can occur if the airways are obstructed, and the acute swelling of the abdominal region produces intense pain often resulting in exploratory surgery.

The mechanism for production of the swelling involves not the complement enzymes, but the kinin-generating pathway. It is the production of Bradykinin through this pathway that is responsible for the tissue permeability changes that cause the swelling. Acute treatments include C1 inhibitor, a replacement therapy (both plasma derived and recombinant products are available); ecallantide, a kallikrein inhibitor; and icatibant, a bradykinin-2 receptor antagonist. Prophylactic treatments include attenuated androgens and C1 inhibitor.

Deficiencies of the Lectin Pathway Components

MBL, M-ficolin, L-ficolin, H-ficolin, CL-11, MASPs

MBL deficiency is fairly common, affecting approximately 5-30% of individuals. There is some controversy over the importance of the lectins to overall immunity, but most authors agree that the early months of a baby's life are dependent on the ability of the lectin pathway to fight bacterial infections during the period when maternal antibodies decrease and the child's own antibody production is not fully functional. Other studies have shown increased susceptibility to herpes simplex virus-2, influenza A, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Deficiencies of the Alternative Pathway

Factors D, B and Properdin

Factor D deficiency is very rare and has only been described in two families. Both of these families had multiple members with a history of serious infections. Factor B is an acute phase protein and increases during inflammation. There is only one unconfirmed report of this deficiency in humans.

Properdin is the only complement protein that is X-linked. The protein is synthesized by monocytes, granulocytic cells and T-cells. Several mutant forms of the protein have been identified that result in decreased AP function. Properdin deficiency increases the susceptibility to bacterial infections of the Neisseria family of organisms. The most prominent in the group is N. Meningitis, the cause of a serious form of meningitis. Typical family histories include male relatives who have had or died from Neisserial infections.

Alternative Pathway Control Proteins

Deficiencies of factor H are linked with a wide variety of symptoms. Complete deficiency of H leads to uncontrolled activation of the AP and depletion of C3 occurs. This form of factor H deficiency is similar in presentation to the late component deficiencies due to the low or absent levels of C3. Recent data has been published that demonstrates how critical the role for this complement control protein is in maintaining health in a number of tissues. In addition to bacterial infections, deficiency or dysfunction of factor H and the resulting dysregulation of the AP is associated with various forms of kidney disease including atypical Hemolytic Uremic Syndrome (aHUS), as well as age-related macular degeneration (AMD). These diseases are examples of control processes gone awry on the surfaces of the organs affected.

Treatment of Complement Deficiencies

Deficiencies of the early classical and lectin pathway components are primarily accompanied by upper respiratory infections, otitis media, along with lupus-like symptoms. Any complement deficiency should be treated as an immune deficiency, and the patient should be immunized against the likely candidate microbes for their deficiency. Antibody responses should be checked after vaccination, since the inability to activate complement impairs the immune response to some extent. Currently, there are no specific treatments for complement deficiencies. Infection prevention and appropriate treatment of infections (usually with antibiotics), when they do occur is key in the care of patients with these deficiencies. Fresh frozen plasma has been tried in some cases, but carries the risk that the patient may make antibody to the missing complement component, so prolonged use is not advised. Prophylactic antibiotics can be used if the patient experiences repeated infections, and increased vigilance with rapid treatment of problems is another option. Most of these patients eventually make antibodies against the offending bacteria and do not get sick as often.

Boys with Properdin deficiency (X-linked) should be immunized against *Neisseria meningitidis*, in addition to the usual vaccinations of childhood. Often there is a family history of an uncle or other relative who died from Neisserial infection at an early age. Deficiencies of the other alternative pathway components and the terminal pathway proteins are also susceptible to *Neisseria meningitidis* and should be immunized. The vaccine titers should be verified in these individuals as well.