Slide 1

SLIDE 1 This presentation will conclude our discussion of Innate Immunity. We will focus on the complement system and how it influences inflammation. We will cover the functions of complement, components of each pathway, and select complement deficiencies. In part one of the presentation this week, we discussed specific physiological changes that occur during inflammation (such as capillary permeability and cell migration) as part of the innate immune response. Now, we will briefly concentrate on how complement stimulates inflammation and improves immunity.

Slide 2

SLIDE 2 Learning objectives for this week’s material. Important topics to know for this presentation include the similarities and differences of the three complement pathways and the functions and deleterious effects of complement activation and deficiency.

Slide 3

SLIDE 3 There are approximately 20 to 30 known complement proteins that are normally found inactive in the blood serum [Do not worry about the exact number for the quiz!!]. These inactive proteins are known as zymogens. With an antigenic stimulus, each of these proteins will be activated sequentially in a controlled process. With each additional protein activated, there is amplification of the complement reaction.
SLIDE 4 Complement proteins are produced in the liver and by certain other cell types. If someone has a malfunctioning liver, the production of complement can be affected. Complement is essential in the inflammatory process and in effectiveness of antibodies. Without insufficient complement, severe infections can result. Complement deficiencies are rare worldwide, and C2 complement deficiency is the most common form of deficiency. Not only can complement deficiencies be inherited, chronic disorders and acute infection can induce complement deficiencies.

SLIDE 5 Complement has many effector functions that are integral to the immune response. It has an essential role in inflammation, improves phagocytosis, and assists antibodies to target microbes for killing.

SLIDE 6 This figure summarizes the functions of complement. All 4 components (lysis, opsonization, inflammation activation, & clearance of immune complexes) are critical to improve the innate immune response.
3 Pathways of Activation

- Classical
  - Triggered when IgM or certain IgG subclasses bind antigens
- Alternative (Properdin)
  - Triggered by the deposition of complement protein, C3b, onto microbial surfaces
  - No antibodies required for activation
- Lectin
  - Triggered by the attachment of plasma mannose-binding lectin (MBL) to microbes
  - No antibodies required for activation

SLIDE 7 The classical pathway requires antibodies for its activation; therefore, the classical pathway will not be activated until antibodies have been produced against an antigen. It may take 5 to 10 days for antibodies to be produced after first being exposed to an antigen. This means that the classical pathway will not be activated with initial exposure to an antigen!! In contrast, the alternative pathway is triggered by the binding of C3b to microbial surfaces. The alternative pathway does not require antibodies; therefore, the alternative pathway can more rapidly respond to antigens than the classical pathway. The Lectin pathway is a third and lesser known pathway of complement activation. This pathway is activated when the protein, mannose-binding lectin, binds to a terminal mannose on microbial surface glycoproteins. This process then activates the classical pathway; but, antibodies are not required in this process!!!
SLIDE 9 The early steps of the complement cascade depend on the type of activator. Antibodies will trigger the classical pathway, whereas microbes will directly activate either the alternative or lectin pathways. The early complement components vary in each pathway. For example, in the alternative pathway, the first component is C3. However, in the classical pathway the first components are C1qrs, C2, & C4. In the lectin pathway, the initial step is MASP, MBL. These early steps of the pathways lead to the formation of the C3 convertase enzymes (made of different protein components in the classical/lectin & alternative pathways). These enzymes cleave C3, the First complement component that is found in all 3 pathways.

SLIDE 10 The late steps of the complement cascade are identical in all 3 pathways after the formation of the C5 convertase. The C5 convertase enzymes are also different in the classical/lectin & alternative pathways. Similarly to the C3 convertases, these enzymes cleave the C5 complement protein into 2 components, C5a & C5b. Note that C9 polymerizes to form the MAC. This end result of the complement cascade is the formation of the membrane attack complex (MAC), which forms pores in the microbial cell membrane leading to cell death.
SLIDE 11 In this diagram, all of the steps of the complement pathways are shown. The classical, lectin, and alternative pathways are illustrated. Note how the Lectin Pathway joins the Classical Pathway. Also notice the interaction of C5a with phagocytes and dendritic cells.

SLIDE 12 C3 is one of the most important components in the complement system. In the diagram, note the central role of C3 in the classical and alternative pathways. The a & b fragments from C3 have important physiologic effects, especially to stimulate inflammation and to coat microbes in order to attract phagocytic cells to rind & destroy the microbe. C3b is the coating protein and is essential to all three complement pathways.

SLIDE 13 C5a protein is a potent anaphylatoxin that strongly promotes inflammation. It is very similar to the C3a component, but it has a greater physiologic effect. C5a activates neutrophils, cell adhesion, migration & chemotaxis (remember these concepts from last week?), as well as mast cell degranulation. Mast cell degranulation (with the release of multiple mediators, such as histamine) can stimulate smooth cell contraction and increases vascular permeability.
Important Complement Proteins

• C5b
  • Initiates the late steps of complement activation (Common Pathway)
• C6, C7, C8, and C9 sequentially bind C5 in the Common Pathway
• C9 polymerizes to form the Membrane Attack Complex (MAC) which forms a pore in the target cell and causes cell lysis

Complement membrane attack complexes (above) punch holes in the membranes of microbial invaders.

Another view of the membrane attack complex creating a pore in the cell membrane.

SLIDE 14 Complement protein, C5b, initiates the Common Pathway. The Common Pathway is the final segment which joins all three complement pathways. The complement proteins in the Common Pathway form the MAC (membrane attack complex) which produces a pore in a bacterial membrane. This pore (usually multiple pores from multiple areas of complement binding) produces lysis of the bacterial membrane.

SLIDE 15 This slide illustrates the MAC (membrane attack complex) formed by the polymerization of C9.

SLIDE 16 This slide illustrates the Classical and Alternative Pathways. Again, notice the several component that lead to the polymerization of C9 and the MAC. Also, notice that there are additional factors (Factor B, Factor D) involved in the Alternative Pathway.
SLIDE 17 The complement system has several important functional properties. Complement can improve phagocytosis of microbes, osmotic lysis of microbes (through the MAC), as well as stimulating inflammation & the recruitment of leukocytes.

SLIDE 18 Beneficial effects of complement include bacterial lysis by the MAC. Antibodies help improve the effectiveness of the complement system. Opsonization or improved phagocytosis via C3b and C5b is another beneficial effect of complement.

SLIDE 19 Complement also activates the inflammatory process. This activation of the inflammatory process can be both a benefit and a detriment. C3a and C5a are known as anaphylatoxins and can produce systemic effects (anaphylactic shock). Complement also enhances the antibody response by improving antigen presentation with receptors on antigen presenting cells & B cells.
SLIDE 20 Complement is also important in the neutralization of viruses and in the clearance of immune complexes by phagocytes.

SLIDE 21 This table summarizes the functions of complement. Especially note the complement components that influence the inflammatory response.

SLIDE 22 As with many immunologic processes, detrimental effects may occur from over activation of complement, which usually plays a beneficial role in the body. For example, systemic activation of the inflammatory response by complement can result in severe damage to the whole body. This damage can be much worse than the damage produced by the initial antigenic stimulus.
**Regulation of Complement**

- Tight regulation of complement system necessary to prevent autoimmunity
- Opsonization by binding to complement receptors on cells
- Recognition of "non-self" by C3b which doesn’t bind to self or is limited in formation
- C3 convertase enzyme also produces inhibition of complement activity (feedback loop)

**SLIDE 23** Complement Pathways are highly regulated to prevent the production of autoimmunity. The limited ability of C3b to recognize ‘self and the C3 convertase enzyme help limit the activation of complement.

**SLIDE 24** This table illustrates more of the regulators of the complement system.

**SLIDE 25** These diagrams illustrate the regulation of complement before and alter the assembly of the convertase enzyme and the assembly of the MAC. Notice the different complement regulators (for example, S protein) from the previous slide (Table 13-2) & how they interact with specific parts of the complement cascade to stop the cascade.
SLIDE 26 Any of the complement factors may be deficient; however, the actual symptoms of the deficiency can depend on the missing complement factor. There are no particular treatments for complement deficiencies, but, vaccinations and prompt medical treatment can reduce the risk of disease. Deficiencies can be acquired or inherited. Inherited deficiency is rare in the general population, with an estimated frequency of 0.03%. Complement deficiencies can be divided into four main classes including (1) increased susceptibility to infection, (2) rheumatologic (autoimmune) manifestations, (3) hemolytic anemia, and (4) angioedema (severe swelling).

SLIDE 27 Deficiency of C2 protein is the most common complement deficiency disorder, with 1 case per 10,000 population. Acquired deficiency may be caused by acute infection or in conjunction with chronic autoimmune disorders. Both genders are equally affected in most complement deficiencies. However, properdin deficiency is X-linked recessive (only males are affected).

SLIDE 28 In C2 deficiencies, skin and joint manifestations are common. This deficiency is frequently found in patients SLE, Henoch-Schonlein vasculitis, polymyositis, and recurrent pyogenic infection. Most individuals with C2 deficiency are asymptomatic (until disease development). Complete C4 deficiency rarely occurs. However, almost all the patients with complete C4 deficiency have discoid or systemic lupus erythematosus (with or without associated glomerulonephritis)
### Slide 29 - C3 Deficiencies

- **C3** is central to all three complement pathways!!
- Usually rare and leads to an inability to form the membrane attack complex (MAC)
- Predisposes person to frequent bouts of pyogenic bacterial infection such as meningococci and pneumococci

### Slide 30 - Meningococcal disease

- Neisseria meningitidis is the most frequently isolated pathogen from patients with bacterial meningitis
- Only humans can harbor *N. meningitidis*
- Susceptibility to meningococcal disease is highest in children aged 3-24 months
- Meningococcal meningitis occurs worldwide
  - Prevalent serotypes vary according to the geographic region
  - "Mediterranean Meningitis Belt" in sub-Saharan Africa
- In 1996, Africa experienced the largest recorded outbreak of epidemic meningitis in history, with over 250,000 cases and 25,000 deaths recorded

SLIDE 29 C3 deficiency is usually rare and, it is inherited in an autosomal recessive pattern. This deficiency predispose individuals to frequent bouts of pyogenic bacterial infections and immune complex diseases.

SLIDE 30 The Classical Pathway protects against meningococcal disease. Meningococcal disease was first described in 1805 when an outbreak occurred in Geneva, Switzerland; however, the causative agent, Neisseria meningitidis was not identified until 1887. In populations with recurrent meningococcal infection, the percent of the population with C3 deficiency is as high as 30%. Twelve subtypes or serogroups of *N. meningitidis* have been identified and four (*N. meningitidis* A, B, C and W135) are known to cause epidemics. Newborns are protected from meningococcal disease by maternal antibodies. However, as these antibodies decrease, the infant becomes at increasing risk of developing meningococcal meningitis. Depending on which complement components are deficient, individuals may be at increased risk of developing bacterial meningitis due to Neisseria meningitidis.
This diagram summarizes the actions of complement during acute inflammation. Complement is multitalented.

In Summary
- Identify the similarities and differences of the 3 complement pathways
- Identify the functions (effects) of complement
- Identify deleterious effects of complement activation
- Identify deleterious effects of complement deficiency

Self-Test Questions
- What is complement?
- What are the 3 pathways of activation?
- Which pathways are not activated by antibodies?
- Which complement components stimulate inflammation?
- Name 2 effects of complement.
- What disease or infection may a person deficient in C3 be pre-disposed to?