Objectives
- Identify functions of complement
- Recognize the similarities and differences of the three complement pathways
- Identify important complement components & their functions
- Identify deleterious effects of complement activation and deficiency

Complement (C')
- Series of approximately 30 heat-labile proteins
- Normally inactive in the serum
  - Inactive complement proteins known as zymogens
- Can be sequentially activated in a controlled sequence
  - Amplification of the reaction occurs at each step
- Production of biologically active fragments for lysis or killing of the target

Complement Proteins
- Synthesized in the liver and by several cells types (splenic macrophages)
- Plays an essential role in inflammation and in facilitating antibody effectiveness
- Severe infections or autoimmune diseases can result from complement deficiencies (rare in the population)

Functions of Complement
- Essential role in inflammation
- Assists antibodies in effector functions (Antibody Dependent Cell-mediated Cytotoxicity- ADCC)
- Assist in clearing immune complexes
- Opsonization and facilitation of phagocytosis
- No antigen specificity
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

Complement Activators

<table>
<thead>
<tr>
<th>Activators</th>
<th>Description</th>
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<tbody>
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Early Steps

- The initial steps vary between pathways
- Dependent on activating substance
- C3 convertase quickly forms in all paths to cleave C3

Watch this well-done animation on the activation of complement, the steps in the complement pathways, & the functions of complement.

Late Steps

- Late steps (after C5 convertase) are same in all pathways
- Lead to formation of MAC

Important Complement Proteins

- **C3**
  - Most abundant complement protein
  - Common to all three pathways
  - a & b fragments have important biologic effects
- **C3a**
  - Anaphylatoxin that promote inflammation
- **C3b**
  - Binds the microbial surface thus acting as an opsonin
  - C3b also a component of the C3 & C5 convertases
Important Complement Proteins

- **C5a**
  - Biological effects of C5a and C5a-des Arg
  - 1. promotes mast cell degranulation
  - 2. promotes neutrophil migration
  - 3. promotes monocyte/macrophage migration
  - 4. promotes lymphocyte activation
  - 5. promotes eosinophil degranulation

- **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

Membrane Attack Complex

- Watch this short animation of the formation of the MAC & subsequent cell lysis.
  - Source: Gary Kaiser.

Functional Proteins

- Overview of how complement effects innate immunity & inflammation

Complement Effects

- Lysis (destruction of target cell)
  - Membrane Attack Complex
  - Antibody makes complement more efficient and guides complement deposition
- Opsonization (enhanced phagocytosis)
  - Due to the formation of C3b and C5b (larger fragments than “a” fragments)
  - C3b and C5b bind substrate
  - Attract phagocytes to microbes coated with complement
Complement Effects

- **Activation of the inflammatory response**
  - Anaphylatoxins C3a and C5a promote inflammation
  - C3a and C5a are freely soluble in solution
  - Increased cellular attraction and activation
  - Increased vascular permeability

- **Induction and enhancement of antibody response**
  - Complement receptors on APC and B lymphocytes enhance antigen presentation
  - Accessory role in antibody response

- **Viral neutralization**
- **Clearance of immune complexes**
  - Efficient removal from tissue by phagocytic cells
  - Solubilize immune complexes

- **Removal of immune complexes**

Especially note the Complement Mediated Inflammatory Responses!!

Deleterious Effects of Complement

- **Systemic Activation**
  - Triggered by Gram Negative organisms
  - Leads to septicemia, anaphylatoxins and shock

- **Activation by unrelated tissue necrosis**
  - Ischemia (myocardial infarction)

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)**
Complement Deficiencies

- Clinical symptoms are determined by the Complement Pathway affected
  - Can be acquired or inherited
  - No specific treatments
  - Antibiotics and immunizations used to reduce risk of disease

C2 & C4 Deficiencies

- C2 deficiency is most widely reported deficiency of all components in complement pathways
- Immune complex disorders are the main problem with a deficiency of C2
- Complete C4 deficiency is rare
- Almost all the patients with complete C4 deficiency have discoid or systemic lupus erythematosus (with or without associated glomerulonephritis)

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
  - Especially Gram-negative bacteria such as meningococci and pneumococci

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
  - ‘African 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
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?