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 cell types (splenic marcorphages)
- 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

Early Steps

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

Late Steps

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

All Step Together …

Important Complement Proteins

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

- **C5a**
  - 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 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 that “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

Complement Effects

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

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 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?