Complement

• Two Systems
  – Classical Pathway— antibody mediated
  – Alternative Pathway— antibody independent— properdin activated

• Protein reactivity
  – C1q → C1r → C1s → C4 → C2 → C3 → C5 → C6 → C7 → C8 → C9

• Many proteins are zymogens— enzymes that require proteolytic cleavage in order to become activated
  – Cleavage products designated as “a” or “b”
• Inflammation
  – If deficient in certain complement proteins then you are more susceptible to certain infections, autoimmune reactions and immune complex diseases
  – Complement activation leads to
    • Opsonization
    • Cellular activation
    • Lysis
  – There are specific cellular receptors for complement binding
• C3 is major constituent of complement system
  – Present at concentration of ~1g/L
  – Helps to distinguish “self” from “non-self” – non-self surfaces allow for C3 binding, self surfaces limit C3 binding
• **Classical Pathway**
  - Only Ab that is complexed with Ag can bind to C’
  - C1q has six domains, and 2 or more of these domains must bind to Fc region of Ab (C_{\text{H}}2 domain of IgG or C_{\text{H}}3 domain of IgM)

  - C1 is a pentamolecular Ca++-dependent complex comprised of C1q, 2C1r, and 2C1s molecules
  - Binding of C1q to Fc region causes conformational change, and a single C1r molecule autocatalytically activates and cleaves the other C1r zymogen
  - The 2 C1s molecules are then cleaved by C1r into serine esterases

• **Amplification and Concentration responses**
  - C1s cleaves C4 into C4a and C4b (4b is unstable)
  - Surface bound C4b allows binding of C2
  - The C4b-2 complex is cleaved by C1s \(\rightarrow\) C2a and C2b
  - The C4b-2a complex = C3 convertase in the Classical
– A C4b-2a-3b complex is formed = C5 convertase which proteolytically degrades C5 \( \rightarrow \) C5a and C5b
– The C5b then combines with C6 to initiate the formation of the membrane-attack complex (MAC) which is C5b-6-7-8-9
– MAC complex displaces membrane phospholipids and forms large membrane channels and leads to cell lysis

- **Regulation of Classical pathway**
  – Serine proteinase inhibitor (serpin)- inhibits C1r and C1s molecules (inhibits formation of C3 convertase)
  – Found in blood plasma

- **Alternative Pathway**
  – Native C3 in plasma undergoes continuous low grade hydrolysis and the production of C3i, which acts as a binding site for for Factor B (FB)
  – FB (bound to C3i) \( \rightarrow \) by FD \( \rightarrow \) Ba and Bb
  – C3iBb = C3 convertase producing C3b which combines with Bb producing C3bBb