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_H2 domain of IgG or C_H3 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 → 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 → 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) → by FD → Ba and Bb
  - C3iBb = C3 convertase producing C3b which combines with Bb producing C3bBb