Lecture 2: Introduction to Complement

Key part of the innate immune response and important effector arm of humoral (acquired) immunity.
- >30 proteins from liver and inflammatory cells; short half-lives; tightly regulated enzymatic cascades.
- Regulation is finely tuned and very tight to prevent host damage.
- Up-regulated in the acute phase response during substantial inflammation.

Major roles:
1. Opsonization of pathogens with C3b.
2. Activation of Mast cells via C3a, C5a → inflammation.

Some Definitions:
- Convertases & Split products:
- C3bBb

Complement Fixation:
- Anaphylatoxin:
  (phyllaxis—prevention against infection
  Anaphylaxis = opposite of prevention)

Overview:
Alternative Pathway
- First pathway to become involved in pathogen destruction. Spontaneous activation, amplification occurs if foreign substances (e.g. pathogens) are present.

Lectin Pathway
- Converges with classical pathway at C3 convertase. Triggered by terminal mannose residues on bacteria. High levels of mannose binding protein complex produced during inflammatory response.

Classical Pathway
- Activated during inflammatory response via C-reactive protein (host from liver).
- Also triggered by Ag-Ab complexes on microbial surfaces.
Alternative Pathway:
Phase I - Generation of C3 Convertase & C3b opsonization.
A. Generation of Soluble C3 convertase:
1. C3 (soluble) spontaneous hydrolysis of thio-ester, producing iC3.
2. iC3 (soluble) binds factor B, producing iC3-B complex
3. Factor D cleaves B to give Ba + Bb, iC3Bb complex, a soluble C3 convertase.
4. iC3Bb converts soluble C3 to C3b and C3a.

B. Generation of fixed C3 Convertase:
5. C3b fixed by covalent ester bond on pathogen surface.
6. Factor B binds to immobilized C3b, giving C3bB
7. Factor D cleaves B into Bb and Ba, giving immobilized C3bBb (C3 convertase of the alt pathway).
8. C3bBb complex stabilized by properdin.

C. Production of large amounts of C3 split products, fixation of C3b to membrane in vicinity of active C3 convertase.

D. Amplification of catalytic potential by generation of additional C3 convertases.