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Complement Self-Study Module

Tuesday, February 12, 2008
8:00 AM

- Complement Cascade
  - Proteins produced in liver to direct pathogen destruction; covalently bound and more permenant
  - Once one complement protein binds, multiple proteins bind all directing towards cell injury
- Complement Pathways
  - Classical - begins w/ antigen-antibody binding --> adaptive immune response
  - Lectin - begins w/ non-specific protein binding to antigen --> innate
  - Alternative - begins w/ complement binding --> innate
  - All lead to covalent binding of C3b to pathogen
  - 3 possible outcomes: opsonization, inflammation, lysis
- Activation of complements
  - Most proteins have naming as C#(a/b)
  - Each C protein is cleaved into a/b fragments by convertases
  - "a" fragment may have something to do w/ inflammation
  - "b" fragment is usually covalently bound
- Classical Pathway
  - Antibody binds to antigen
  - C1q binds to antibody (r, s have enzymatic activity)
  - C1q only binds to IgM (pentameric, so only one needed) or IgG (multiple needed)
  - C1q --> C1r --> C1s --> cleavage of C4 to reveal thioester bond on C4b for nucleophlic attack
  - C4b then binds to pathogen; C1s then cleaves C2 into C2a and C2b
  - C2b non-covalently associates w/C4b to make C3 convertase of the classical pathway (C4b,2b)
  - Convertase up to 1000 C3 --> C3a + C3b
  - C3b binds to pathogen surface
- Lectin Pathway
  - Mannose binding protein binds to mannose, structurally similar to C1
    - Non-specific
    - Mannose found on many pathogens
  - Virtually identical to classical pathway for the next steps
- Alternative Pathway
  - Auto activation of C3-->spontaneous C3 cleavage
  - C3b binds to cell surface
  - Factor B associates to C3b and is cleaved by complement D to Ba and Bb
  - C3b,Bb stabilized by properdin
  - C3b,Bb,properdin = C4b,2b
  - Multiple C3b's bind to cell surface = amplification
  - Same is possible for classical and lectin pathways
- Opsonization
  - Macrophages have CR1 which recognizes C3b and C4b (negligible)
  - This makes it easier for phagocytosis to take place
- Inflammation
  - Small fragments released (a fragments)
  - C3a, C5a, C4a (lesser extent) mediate inflammation --> anaphylatoxins
  - Stimulate degranulation of mast cells --> release histamine --> similar to anaphylactic rxn
  - Anaphylatoxins + Mast cell mediators --> aid macrophage adhesion/migration to cell wall
  - C5a works as chemoattractant for neutrophils/monocytes
- MAC complex
  - Complex of proteins to form pore in cell --> open flow of water and ions to eventually cause lysis

of cell
    - C3b + C3 convertase = C5 convertase
    - C5b complexes w/ convertase --> C6, C7, C8
    - C7,C8 have hyrdophobic regions to insert into membrane
    - Up to 20 C9 molecules insert into membrane to form pore
- Immune Complexes can lead to classical pathway activation
    - Circulating RBCs have CR1
    - RBCs bind to immune complexes and carry the complexes out of circulation
    - Classical pathway important in removal of circulating immune complexes
- Other Outcomes
    - Breakdown products --> B cell activation via CR2
- Complement Deficiencies
    - Deficiencies in C1, C4, C2 --> inability to remove immune complexes from circulation
        - Injury by depositing in basement membrane of body tissues
        - Arthritis, renal problems, rash; similar to lupus
        - C2 deficiency is most common (1/10,000)
    - Alternative pathway deficiencies
        - Problems w/ opsonization, phagocytosis
        - Increased risk of pyogenic bacterial infection
    - Deficiencies in C5-9
        - Inability to from membrane attacking complex
        - Important in neisserial defense
        - Increased risk of neisserial infection
    - Deficiencies in MBP
        - Recurrent pyogenic infeciton
        - Failure to thrive
- Regulation
    - Nothing to stop complements from binding to host cells
        - Host cells must have something to prevent
    - DAF - GPI anchored protein
        - Prevents binding of C3b and Bb to make C5 convertases
        - Can also cause dissociation of C5 convertases
        - Inhibits all 3 pathways
        - Defects in GPI anchor --> paroxysmal nocturnal hemoglobinuria prob due to increased susceptibility to complement attack
    - C1-INH
        - C1 inhibitor
        - Deficiency: hereditary angioneurotic edema
            - Too much C4a, C2a
            - Causes edema --> laryngeal particularly problematic b/c of suffocation
            - Treated w/ infusion of C1-INH
    - Protectin (CD-59)
        - GPI anchored
        - Inhibits formation of MAC
    - Membrane Cofactor Protein: Acts as cofactor for proteolytic cleavage of C3b by factor I
    - CR1
        - Membrane bound receptor
        - Protects host cells by inhibiting association of convertases
        - Can act as cofactor for factor I
    - Factor I: Plasma protein that cleaves C4b, C3b
    - Factor H: combines w/ C3b just like factor B but prevents factor B from binding
        - Polyanionic environment of host cells due to sialic acid favors factor H binding
        - Bacteria do not have same environment so factor B binds

    - Serum Carboxypeptidase N (SCPN): Breaks down anaphylatoxins
- Clinical Testing
    - Serum Complement Hemolytic Activity
        - RBCs coated w/ antibodies
        - Dilution of pt. serum added
        - Classical pathway should be activated and RBCs should be lysed
        - More active --> should be able to dilute more
        - Report 50% dilution: half of RBCs lysed