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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 permanent
 - 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 nucleophilic 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 hydrophobic 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 form membrane attacking complex
 - Important in neisserial defense
 - Increased risk of neisserial infection
 - Deficiencies in MBP
 - Recurrent pyogenic infection
 - 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