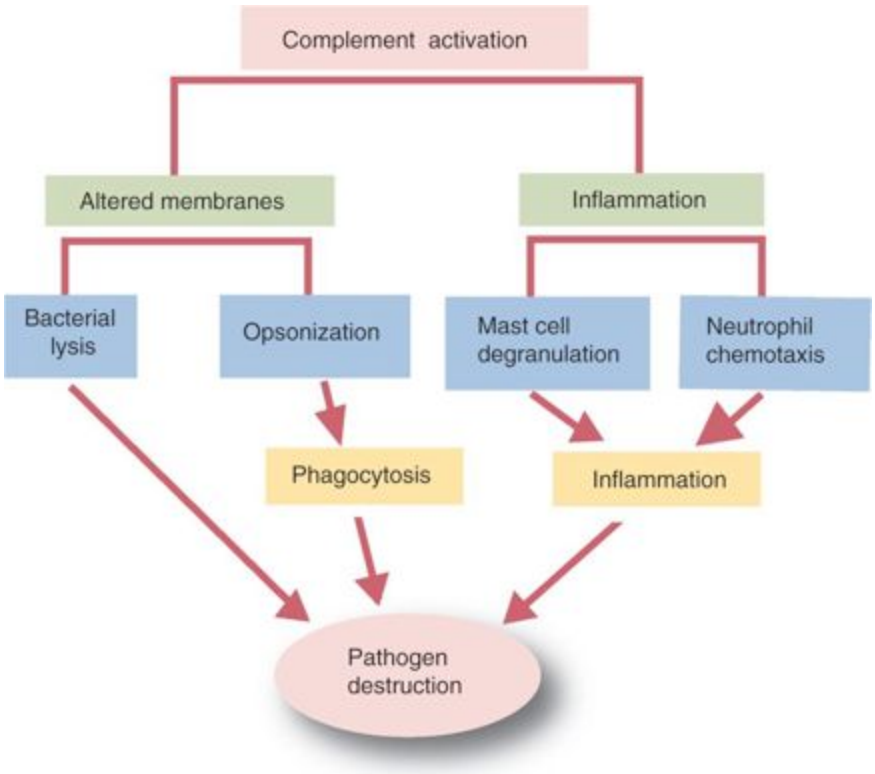
Main Points

- The complement system is activated by two innate pathways: the alternative pathway and the lectin pathway
- The complement system is activated by antibodies bound to antigen—the classical pathway
- Complement components, especially C3b, bind covalently to invading microbes and so opsonize them
- Complement components may form a membrane-attack complex and punch holes in microbes
- The complement system plays a key role in triggering inflammation through the release of the potent chemoattractant C5a



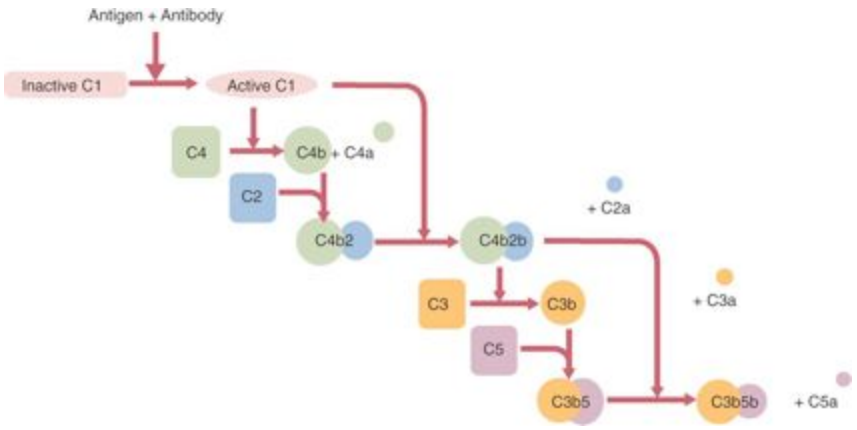
Production

- Most Complement is produced in liver or macrophages.
- A large amount is stored in neutrophils

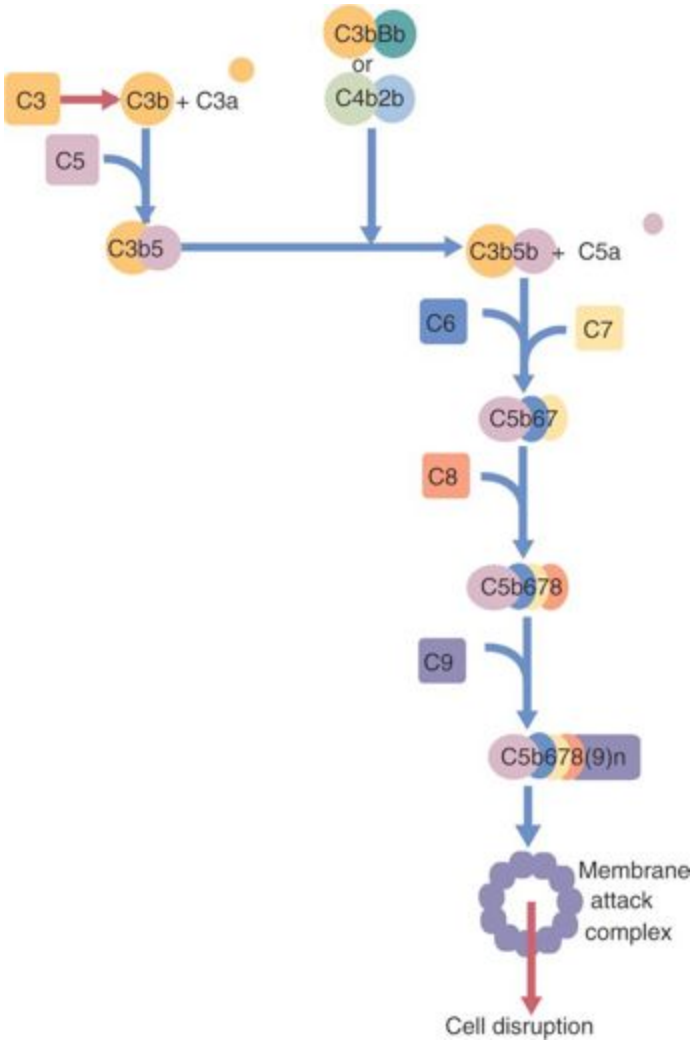
Activation of Complement

- Classical
    - Activated by antibodies bound to surface of organism
        - Must have aquired immune response

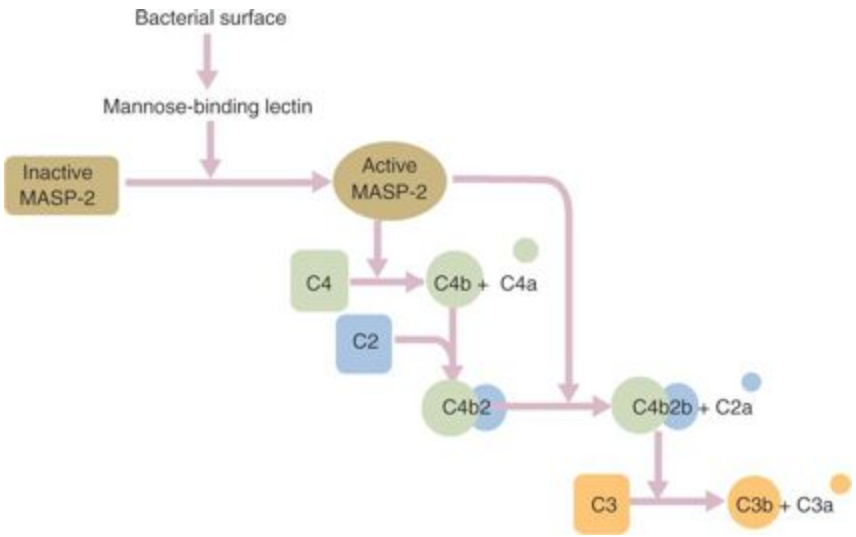
- When antibodies bind to pathogen, expose Fc regions. When multiple Fc regions are exposed in close proximity, classical complement pathway is activated. C1 binds to at least 2 Fc regions (either multiple IgG or single IgM).
    - IgM is much more efficient at classical activation
- Activated C1s (part of C1) can activate C4 and C2 and proceed to MAC (see below).



- Alternative
    - Activated directly by microbial carbohydrates (PAMPs)
    - C3 is most important protein
        - Breaks down to C3a and C3b
            - iC3b is made from C3b and acts as ligand of receptors found of circulating leukocytes, stimulating phagocytosis and activation of inflammatory cells
                - Further broken down to C3dg which promotes antibody production
            - Surface bound C3b also binds C5 breaking it to C5a and C5b
                - Will incorporate C6 and C7, C8 and C9 and lead to membrane attack complex which is a tubular structure made up of a ring of C9 inserted into bacterial membrane and kill organism by osmotic lysis.



- Lectin
    - Activated directly by microbial carbohydrates (PAMPs)
    - Serum lectins bind to microbial (bacterial, fungal, protozoal, viral) carbohydrates and trigger splitting of C4 to C4a and C4b.
        - C4b binds to microbial surface and acts via pathway including C2 and C3 and C5 and progress to MAC



Complement regulation

- C1-inactivator regulates classical pathway.
- CD55, Factor H, C4-binding protein, CD35 and CD46 all accelerate decay of active complement proteins
- CD59 (protectin) inhibits C5b678 insertion and C9 polymerization to prevent MAC

Complement Receptors

- CR1 (CD35), CR2, CR3, CR4, and CRIg
    - CR1 is main one - 90% is on RBCS
        - Binds circulating immune complexes, coating RBC which goes to liver or spleen for removal.
        - Deficiency can lead to immune complex accumulation in tissues
    - CR3 deficiency in dogs leads to immune complex mediated kidney disease

Non-MAC functions of complement

- Opsonization
    - Bound C3b and C4b activate phagocytic cells which have CR1 or CRIg.
    - If not phagocytosed, then neutrophils may secrete lysosomal enzymes and oxidants leading to inflammation - Type III hypersensitivity reaction
- Chemotaxis
    - Activation of any complement pathway leads to production of potent chemotactic peptides.
- Inflammation
    - C3a and C5a stimulate platelets to release histamine and serotonin and cause mast cell degranulation
- Immune regulation
    - If antigen molecule binds to B cell, C3d will significantly potentiate B-cell receptor signaling and maturation of B cell

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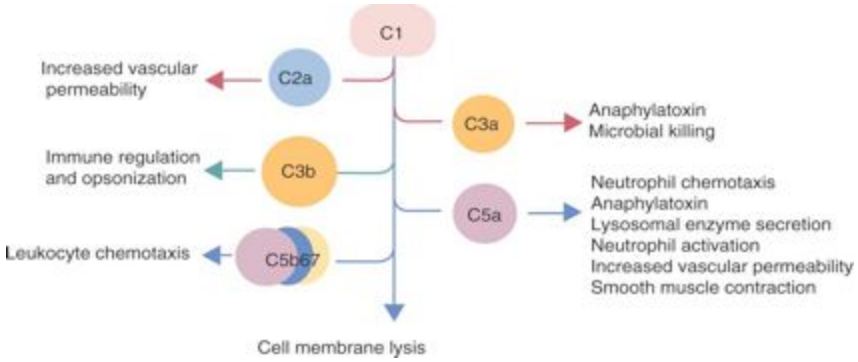

Complement Deficiencies

- Canine C3 Deficiency
    - Colony of brittany spaniels
    - Cause recurrent sepsis, pneumonia, pyometra, wound infections
    - Can also develop amyloidosis, immune complex kidney disease

Questions

1. Which of the following factors polymerizes to form the tubular portion of the membrane attack complex?
    a. C5
    b. C6
    c. C7
    d. C8
    e. C9

2. Explain why IgM is a more potent activator of the classical complement pathway than IgG

3. Complement components are cleared from the circulation mainly by:
    a. Direct phagocytosis by kupffer cells in the liver
    b. Filtered freely through the glomerulus
    c. Binding by CR1 on RBCs and removal in liver and spleen
    d. Binding by CRIg and removal by phagocytic cells in circulation

4. Which complement activation pathway requires adaptive immune response
    a. Classical
    b. Lectin
    c. Alternative
    d. Schnitzlepuss

5. The main regulator specific to the classical pathway is _____, which the regulator common to all pathways is _____. (Choose 2, in order)
    a. C-1 inactivator
    b. CD55
    c. Factor H
    d. CD59 (protectin)

Answers

1. Which of the following factors polymerizes to form the tubular portion of the membrane attack complex?
    a. C5
    b. C6
    c. C7
    d. C8
    e. **C9**

2. Explain why IgM is a more potent activator of the classical complement pathway than IgG
    a. Multiple Fc sites are required to bind C1. IgM can bind to C1 alone, while there needs to be at least 2 IgGs in close proximity to bind.

3. Complement components are cleared from the circulation mainly by:
    a. Direct phagocytosis by kupffer cells in the liver
    b. Filtered freely through the glomerulus
    c. Binding by CR1 on RBCs and removal in liver and spleen
    d. Binding by CRIg and removal by phagocytic cells in circulation

4. Which complement activation pathway requires adaptive immune response
    a. Classical
    b. Lectin
    c. Alternative
    d. Schnitzlepuss

5. The main regulator specific to the classical pathway is **C-1 inactivator**, which the regulator common to all pathways is **CD59 (protectin).** (Choose 2, in order)
    a. C-1 inactivator
    b. CD55
    c. Factor H
    d. CD59 (protectin)