Complement
The complement system is involved in various aspects of innate and adaptive immunity. Here’s a breakdown:

**Innate immunity**:
- Opsonization
- Lysis of pathogens
- Chemotaxis
- Inflammation
- Cell activation

**Disposal system**:
- Clearance of immune complexes and apoptotic cells

**Adaptive immunity**:
- Augmentation of antibody response
- Promotion of T-cell response
- Elimination of self-reactive B cells
- Enhancement of immunologic memory

This diagram illustrates the interactions of different immune cells and their roles in the complement system.
Complement pathways:

- Classical pathway
- Alternative pathway
- Lectin pathway
White Board Schematic
C3 plays a central role in complement activation
Complement proteins

- Classical pathway
  - C1q  C1r  C1s  C4  C2
- Alternative pathway
  - D  C3  B
- Lectin pathway
  - MBL  MASP-1  MASP-2
- Membrane attack complex (MAC)
  - C5  C6  C7  C8  C9
- Membrane regulatory proteins
  - CD55  CD46  CD59
C1q binds antigen-bound antibody. C1r activates auto-catalytically and activates the second C1r; both activate C1s.
C1s cleaves C4 and C2. Cleaving C4 exposes the binding site for C2. C4 binds the surface near C1 and C2 binds C4, forming C3 convertase.
C3 convertase hydrolyzes many C3 molecules. Some combine with C3 convertase to form C5 convertase.
The C3b component of C5 convertase binds C5, permitting C4b2a to cleave C5.
C5b binds C6, initiating the formation of the membrane-attack complex.
1. C3 hydrolyzes spontaneously; C3b fragment attaches to foreign surface.

2. Factor B binds C3a, exposes site acted on by factor D. Cleavage generates C3bBb, which has C3 convertase activity.


4. Convertase generates C3b; some binds to C3 convertase, activating C5' convertase. C5b binds to antigenic surface.
After assembly of convertase

C3 convertases are dissociated by C4bBP, CR1, factor H, and decay-accelerating factor (DAF).

Dissociation of convertase; remaining C4b or C3b cleaved by factor I.
Complement pathway activators

✓ Classical pathway
  ✓ IgM-containing immune complexes
  ✓ IgG-containing immune complexes
  ✓ Mannose-binding lectin (MBL)
  ✓ C-reactive protein (CRP)
  ✓ Serum amyloid P (SAP)
  ✓ Myocardial damage products
  ✓ Membranes of apoptotic cells
  ✓ C4 nephritic factor (C4Nef)
  ✓ Myelin
Alternative pathway

- Tickover
- Amplification from classical pathway C3b fixation
- Repeating polysaccharides
- Endotoxin
- Virally infected cells (measles, influenza, Epstein-Barr virus)
- IgA-containing immune complexes
- Some Ig light Chains
- C3 nephritic factor (C3Nef)
- Cobra venom factor (CVF)
- Zymosan (yeast cell wall)

Lectin pathway

- Repeating simple sugars
Comparison of the classical and alternative complement pathways

Antigen/antibody Complexes (adaptive) -> Classical pathway

C3

microorganisms

Alternative pathway (innate)

C3a, C3b

C5-C9
Terminal sequences
Soluble regulatory proteins

*Positive regulation*
Properdin

*Negative regulation*
C1-INH  C4-bp  Factor H  Factor I  Carboxypeptidase  S protein  Clusterin

Receptors
CR1  CR2  CR3  CR4  C1qR  C5aR  C3aR
<table>
<thead>
<tr>
<th>Activity</th>
<th>Components and fragments</th>
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</thead>
<tbody>
<tr>
<td>Increase of vascular permeability</td>
<td>C₅a, C₃a, C₅a₇₅Arg, C₄a</td>
</tr>
<tr>
<td>Smooth muscle contraction</td>
<td></td>
</tr>
<tr>
<td>Degranulation of mast cells and basophils</td>
<td></td>
</tr>
<tr>
<td>Neutrophil activation and chemotaxis</td>
<td>C₅a, C₅a₇₅Arg</td>
</tr>
<tr>
<td>Stimulation of prostaglandin and leukotriene production</td>
<td></td>
</tr>
<tr>
<td>Opsonization of bacteria and immune complexes leading to phagocytosis</td>
<td>C₃b, C₄b</td>
</tr>
<tr>
<td>Stimulation of the respiratory burst of professional phagocytes</td>
<td>C₃b, C₅a, C₅a₇₅Arg, C₁q</td>
</tr>
<tr>
<td>Lysis of bacteria and foreign cells</td>
<td>C₅b₆₇₈(9)ₙ</td>
</tr>
<tr>
<td>Solubilization of circulating immune complexes</td>
<td>C₃b, CR1</td>
</tr>
</tbody>
</table>
Complement-fixing potential of antibodies

- Classical pathway:
  IgM > IgG3 > IgG1 > IgG2 >> IgG4

- IgA can activate the alternative pathway

- IgE will activate complement only in unusual circumstances
Anaphylatoxins and disease

- **Target**
  - Smooth muscle
  - Mast cells
  - Blood capillary wall
  - Vascular endothelium
  - Leukocytes
  - Platelets
  - Immune response

- **Effect**
  - Contraction
  - Histamine release
  - Increase in vascular permeability
  - Increased adhesiveness for leukocytes
  - Adhesion, aggregation, chemotaxis, release of lysosomal enzymes, generation of oxygen radicals
  - Aggregation, release of serotonin
  - C3a: suppression
  - C5a: enhancement
Complement as an effector pathway in disease

- Vasculitis and immune complex diseases
- Rheumatologic disease
- Pulmonary disease
- Renal disease
- Platelet diseases
- Hemolytic disease
- Myocardial disease
- Blood vessels disease
- Cutaneous disease
- Systemic lupus erythematosus (SLE)
- Reproduction and pregnancy
- Myositis
- Neurologic disease
# Summary of complement deficiency states

<table>
<thead>
<tr>
<th>Component</th>
<th>Mode of inheritance</th>
<th>Primary disease associations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>ACD</td>
<td>Autoimmune&gt;&gt;infection</td>
</tr>
<tr>
<td>C4</td>
<td>ACD</td>
<td>Autoimmune&gt;&gt;infection</td>
</tr>
<tr>
<td>C2</td>
<td>ACD</td>
<td>Autoimmune&gt;&gt;infection</td>
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<tr>
<td><strong>Lectin pathway</strong></td>
<td></td>
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<tr>
<td>MBL</td>
<td>ACD</td>
<td>Infection&gt;&gt;autoimmune</td>
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<tr>
<td>MASP1/MASP2</td>
<td>NA</td>
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<tr>
<td><strong>Alternative pathway</strong></td>
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<tr>
<td>Factor B</td>
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<tr>
<td>Factor D</td>
<td>ACD</td>
<td>Infection</td>
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<tr>
<td>Properdin</td>
<td>X-linked</td>
<td>Infection&gt;&gt;autoimmune</td>
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<tr>
<td><strong>Shared components</strong></td>
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<tr>
<td>C3</td>
<td>ACD</td>
<td>Infection&gt;&gt;autoimmune</td>
</tr>
<tr>
<td>C5</td>
<td>ACD</td>
<td>Infection&gt;&gt;autoimmune</td>
</tr>
<tr>
<td>C6-9</td>
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<td>C1qR</td>
<td>NA</td>
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</tr>
<tr>
<td>CR1/CR2</td>
<td>Acq</td>
<td>Autoimmune and Immune complex</td>
</tr>
<tr>
<td>CR3/CR4</td>
<td>ACD</td>
<td>Leukocyte adhesion disease</td>
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<tr>
<td>C5aR</td>
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<tr>
<td>C3aR</td>
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<tr>
<td><strong>Regulatory proteins</strong></td>
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<tr>
<td>C1-INH</td>
<td>AD</td>
<td>HAE</td>
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<tr>
<td>DAF</td>
<td>ACD(Inab)Acq(PNH)</td>
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<tr>
<td>MCP</td>
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<tr>
<td>CD59</td>
<td>Acq</td>
<td>PNH</td>
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<tr>
<td>Factor H</td>
<td>ACD</td>
<td>Infection~autoimmune</td>
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<tr>
<td>C4-bp</td>
<td>ACD</td>
<td>Autoimmune~infection</td>
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<tr>
<td>Factor I</td>
<td>ACD</td>
<td>Infection~autoimmune</td>
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C5aR signaling promotes metastasis to the lungs of breast tumor–bearing mice.

C5aR blockade enhances CD4+ and CD8+ T-cell responses.


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C5aR-mediated immunosuppression in the lungs of breast tumor-bearing mice.

C5aR impact T-cell polarization by regulating lung MDSCs. A, Th1/Th2 ratio calculated from IFNγ (Th1)- and IL4 (Th2)-expressing CD4+ T cells obtained from the lungs of breast tumor-bearing WT and C5aR−/− mice. *, P = 0.0245 (t test with Welch correction).
C5aR-mediated inflammation facilitates metastases.


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MDSC infiltration and C3 deposition and expression in lymph nodes of patients with breast cancer.