**THE COMPLEMENT PATHWAY**

The complement pathway is an extremely complex groups of serum proteins (20 interacting C1-C9, factor B, factor D) present in the low concentration in the normal serum that in the presence of a specific pathogen or antibody acts up a cascade of triggered reactions ending with the lysine or destruction of the antigen (made by liver).

This amplifies the antibody and is the principle means by which antibodies defend vertebrates against most bacterial infections.

Most of the studies with complement system have been done with anti erythrocyte antibody attached to the red cell membrane.

**CLASSICAL AND ALTERNATING PATHWAY:**

The component can be divided to three groups

1. Early complements: C1, C2, C4….. Classical pathway
2. Late complements: C5, C6, C7, C8, C9…… Cell lysis
3. factor B and Factor D: Alternative pathway
4. C3: The central component

**The Classical Pathway**: Initiated by antigen-antibody complexes typically by IgM and IgG (G1, G2, G3). Classical pathway not only creates a C3 convertase but also generates other several fragments (4a, 2b) which promote phagocytosis and inflammation.

**The alternative pathway or bypass pathway**: Misses the C1, C4, C2 complement and starts at the C3 step. They are directly endotoxin, zymogan and agar. They with factors B and D leads to the formation of a C3 convertase.

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Antibody                             Microbial
Binding                               polysaccharide
C1                                    B factor
C2                                    D factor Alternative
Classical: C4                          Cleavage of C3

C5

C6

C7

C8

C9

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1
THE CLASSICAL PATHWAY: Structure and attachment of C1 to antibody.

The –COOH terminus of polypeptide chain becomes the globular head. The NH₂ terminus, wound together to form the allergen triple helix.

The pathway is as follows,

1) C1q binds to receptor: C1r is activated generating C1s.
2) C1s has esterase activity cleaves C4 → C4a, C4b.
3) 4b2a complex formed which is a proteolytic enzyme capable of binding to forget cell membrane and binds to different sites on cell membrane.
4) C4b2a is the classical C3 convertase which splits C3 → C3a and C3b  
   C3a has anaphylactic and chemotactic properties which allows for tenth amplifications.
5) C3b combines with C4b2a complex forming a C423 complex which is the first component of membrane attach sequence a C5 convertase.
THE ALTERNATIVE PATHWAY:

1) If is this initiating factor/eg bacterial lipopolysaccharides particulate polysachharide. Thus activate molecule, or molecules in the serum which acts as an initiating factor resulting in the binding of the IF to activating material.

2) PRFE is the propteridin receptor forming enzyme which has a C3 convertase activity.

3) If interact with factor D and factor B producing an active B factor B.

4) Feedback amplification results in increased amount of C3bBb. However if this reaction is to be controlled, B is replaced by another component factor H which is susceptible to attack by a C3b inactivator which is biologically inactive.

THE MEMBRANE ATTACK MECHANISM:
a) C5b has bending sites for cell membrane and receptors for C6 and C7.

b) C5b67 is stable and binds firmly to lipids proteins and glycoproteins.

c) The C5b67 has a binding site for C8 and C9 components which comprise the final membrane attach unit.

d) C8 has cytolyses function and cause a circular hole in the membrane.

e) Control of complement sequence is achieved in the presence of inactivators such as C1 inactivator and C3b inactivator (KAF) and also by the inherent ability of most the active components.

If the sequence leads to the inactivation or destruction of the toxins material the alternative pathway will not be activated nor will the antibody bind to the antigen to activate the classical pathway. This within time the sequence will cease.

Complement is also involved in various innate mechanisms. Receptor for C3b and C4b has been identified on lymphocyte associated with antibody mediated responses (B cells), neutrophils, monocytes and macrophages. Phagocytes cells can therefore recognize bind and engulf foreign particles with membrane bound complement components.

C5a and C567 which remained in solution following complement activation is chemo tactic attracting phagocyte and other cells to the site of inflammation

C2 increases vascular permeability

C3a and C5a basic peptides release histamine from the mast cells which secretes histamine and enhances the permeability of the capillaries in addition to producing edema and the contracting smooth muscles. Increase in permeability allows WBC and more antibodies complement to enter the site of infection.

C3b binds to specific protein on macrophages and neutrophils enhancing the ability of these cells to phagocytose microbial cell to which 3b has attached. So 3b makes a crucial contribution to the diffuse against bacteria independent of complement mediated cells lysis.

Both pathways are interpreted by C3 as follows:-
REGISTRATION OF THE COMPLEMENT CASCADE IS ACHIEVED IN 2 WAYS

1. Specific inhibitor protein in blood terminate the cascade by either binding or cleaving certain components once they have been activated by proteolytic cleavage. Inhibitor protein inactivate components of C1 complex other proteins cleave C3b and inactivate it.

2. Certain components take C4b and C3b are highly unstable and unless they bind immediately to an appropriate component as the chain, they rapidly become inactive. Active form has a hydrophobic site and a reactive glutamine side chain. This side chain can form a covalent bond with a protein or polysaccharide on the nearby membrane. This has a very short half life and activate in less than 0.1 milliseconds.

<table>
<thead>
<tr>
<th>Complexes and components involved</th>
<th>Activities</th>
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<tbody>
<tr>
<td>C1,C4</td>
<td>Neutralization of herpes Simplex virus together with IgM</td>
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<tr>
<td>C1,C4,C2</td>
<td>Possible generation of benins increase in vascular permeability</td>
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<tr>
<td>C3b</td>
<td>Immune adherence, C3b on RBC, WBC, or platelets adhere to normal RBC —agglutination in vitro</td>
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<tr>
<td>C3a</td>
<td>Anaphylatoxin (Contraction of smooth muscles, increased vascular permeability and histamine release)</td>
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<tr>
<td>* C3c³</td>
<td>Mobilization of leucocytes (leucocytes promoting factor)</td>
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<tr>
<td>C3b, C5a</td>
<td>Stimulation of oxidative metabolism in phagocytes</td>
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<tr>
<td>C5a</td>
<td>leucocytes chemo taxis, Anaphylatoxin Adhere of leucocytes to vascular endothelium</td>
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<tr>
<td>C5-Ca</td>
<td>Lysis of susceptible bacterial cell</td>
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<tr>
<td>C8-C9</td>
<td>Cytotoxic effect</td>
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* C3c\(^3\) appears to be derived from C3c by proteolytic cleavage which is itself derived from C3b by action of BIH globulin and C3b inactivator.

3) **DIFFERENCE BETWEEN ALTERNATIVE/CLASSICAL PATHWAYS:**

4) **ALTERNATIVE PATHWAY OF COMPLEMENT ACTIVATION:**
Fig. The superfamily of Immunoglobulins related proteins. For each protein, the individual balls represent domains of protein structure that are derivatives of the Immunoglobulin fold. Regions of MHC proteins denoted by boxes are not Ig folds. The genes encoding the proteins all have homologies and are considered a superfamily of related genes that must have evolved over hundreds of millions of years from a common ancestor.