

Classical pathway (aka Antibody-dependent):

- 1) C1q (part of a complex with C1r and C1s) binds surface of pathogen. It may bind to the surface directly or through an intermediary (either the plasma C-reactive protein which binds to phosphocholines or through an antibody-antigen complex).
- 2) C1r and C1s are zymogens (inactive forms of a protease). Binding to the pathogen induces the activity of C1r which then induces C1s.
- 3) The activated C1s cleaves C4 to C4a and C4b.
- 4) C4b binds C2 which is also cleaved by C1s to C2a and C2b. This creates the C4b2b complex, which is known as the C3 convertase.
- 5) C3 convertase cleaves C3 to C3a and C3b. C3b binds and coats the surface of the pathogen as well. C3a initiates the inflammatory response.
- 6) The C3b, C4b, C2a complex remains and is known as the C5 convertase.
- 7) The C5 convertase cleaves C5 into C5a and C5b. C5a plays a role in the inflammatory response. C5b attaches to the pathogen and recruits C6, C7, and C8 to the pathogen. Once in place, several C9 molecules form a pore in the surface of the pathogen. Contents of the pathogen leak out and the pathogen dies.

Alternative Pathway (aka Antibody-independent):

- 1) C3 is spontaneously hydrolyzed creating C3(H₂O). C3(H₂O) has a structure that enables it to bind factor B (a plasma protease).
- 2) Factor D (also a plasma protease) binds the C3(H₂O)-factor B complex and cleaves factor B to Ba and Bb.
- 3) Bb remains complexed to C3(H₂O) and is the C3 convertase for this pathway.
- 4) C3 is cleaved by the convertase into C3a and C3b. C3a acts in the inflammatory response. C3b remains in a complex with the C3 convertase (C3(H₂O)-Bb-C3b). This complex is the C5 convertase for the pathway. Some of C3b will bind to surface of pathogen as in the classical pathway.
- 5) The remainder occurs as in step 7 of the classical pathway.

Mannose-binding lectin pathway:

- 1) In this pathway, the C1q is essentially replaced by the mannose-binding lectin (MBL). MBL binds carbohydrates on bacteria or virus surfaces. Like C1q, the MBL exists in a complex with 2MBL-associated serine proteases, MASP-1 and MASP-2.
- 2) The activated MASP-2 activates C4 and C2 as in the classical pathway (steps 3-7).

Regulation of complement pathways:

- 1) Factor I is a plasma protease that cleaves C3b to an inactive form.
- 2) Factor H is a plasma protein that acts as a competitor for Bb binding to C3b.
- 3) Decay-accelerating factor (DAF) facilitates the dissociation of C3bBb complexes.
- 4) Properdin acts as a positive regulator by binding to the C3bBb complex and stabilizing it.