STRUCTURE

# The movement of activation

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C3 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=718

Three independent studies describe the crystal structure of complement component 3b (C3b), which is derived from the proteolytic activation of C3, and reveal that conformational rearrangements accompanying the conversion of C3 to C3b underlie complement activation and regulation.

C3 is a key component of the complement system and is converted to C3b (the active form of C3) by proteolytic cleavage of its anaphylatoxin domain by C3 convertase. C3b then recruits factor B and initiates formation of the alternative pathway of complement activation. However, it was previously not known how the formation of C3b exposes the sites for binding factor B and other regulators.

All three studies describe the conformational rearrangement of specific domains following cleavage of C3. This rearrangement involves the rotation of certain domains and the movement of others that contain important binding sites. Cleavage of the anaphylatoxin domain destabilizes part of the structure to expose the amino-terminal residues of the C3 α-chain (α′NT domain), which is almost completely buried in C3. The α′NT domain contains four residues that are important for binding factor B. However, both Ajees *et al.* and Janssen *et al.* suggest that there are other sites that are also involved in binding factor B.

In addition to the movement of the α′NT domain, two other domains, the CUB (complement C1r/C1s, UEGF and BMP1) domain and TED (thioester-containing domain), undergo unprecedented translocation following activation. This allows TED to 'drop down' and exposes the thioester group of TED through which C3b attaches to pathogens. In C3, the thioester group is embedded in the domains of the α-chain, but after conformational rearrangement it is completely exposed and is in the proper orientation for interaction with the target. In the structure described by Ajees *et al.* TED is dislocated farther from the main body of the protein, owing to an unfolding of the CUB domain through the loss of its β-sheet structure. Putatively, two functional states have been resolved in the three studies.

Wiesmann *et al.* examined the structure of C3b in a complex with one of its receptors that is expressed on macrophages, the complement receptor of the immunoglobulin superfamily (CRIg). Their studies show that the reorientation of the macroglobulin-like 3 domain (a domain in the β-chain of C3b), and the movement of a section in the linker region are essential for binding to CRIg. Interestingly, the binding of CRIg to C3b results in inhibition of complement activation through the alternative pathway.

Janssen *et al.* show that putative binding sites for properdin and several regulators — proteins that are involved in the formation and dissociation of C3 convertase — also become exposed on the surface of C3b, owing to domain rotations following cleavage of the anaphylatoxin domain.

Regulation of complement events can occur through several mechanisms, one involving factor I which cleaves C3b. Ajees *et al.* identified a site on CUB that is rearranged during activation to shield three scissile bonds within a cavity, thereby hindering direct access by factor I. The authors suggest that additional conformational changes are required for proteolytic cleavage by factor I.

Taken together, these studies show that the conversion of C3 to C3b results in dramatic conformational rearrangements that allow putative binding sites of key complement regulators to be made accessible, but also creates a cavity to protect target peptide bonds from access by factor I. These studies are important for therapeutic strategies to treat complement-mediated disorders.

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**ORIGINAL RESEARCH PAPERS** Ajees, A. A. *et al.* The structure of complement C3b provides insights into complement activation and regulation. *Nature* 15 Oct 2006 (doi:10.1038/nature05258) | Janssen, B. J. C. *et al.* Structure of C3b reveals conformational changes that underlie complement activity. *Nature* 15 Oct 2006 (doi:10.1038/nature05172) | Wiesmann, C. *et al.* Structure of C3b in complex with CRIg gives insights into regulation of complement activation. *Nature* 15 Oct 2006 (doi:10.1038/nature05263)