The central steps of the Complement System

P. Gros
Crystal and Structural Chemistry, Bijvoet Center for Biomolecular Research, Faculty of Science, Utrecht University, Utrecht, The Netherlands

The complement system is a critical component of the mammalian immune defence against micro-organisms. It recognizes and kills invading pathogens, elicits inflammatory responses and links the innate and adaptive immune responses. The system consists of 30-40 plasma proteins and cell-surface receptors. Activation and regulation of the complement system is characterized by protein-protein complex formation and proteolytic activation of large multi-domain proteins. Conformational changes are central to these activation and regulation steps.

We study the central steps of complement activation. Activation of the complement cascades by the three complement pathways converges in the proteolytic activation of the complement component C3 (1,641 res.) by the C3 convertase complex. We have determined the structures of human C3, the activated form C3b and the inactive form C3c [1, 2]. The data reveal how this 13-domain protein undergoes large rearrangements upon activation. These rearrangements results in exposure of the reactive thioester group for covalent attachment to (pathogenic and self) target surfaces; and, formation of binding sites for the multitude of regulators of complement. In addition, we published the structure of the human pro-enzyme factor B (739 res.) [3], which after binding to C3b is cleaved in to Bb yielding the C3 convertase complex C3bBb. These structural data indicate marked conformational changes that underlie the mechanisms of activation and regulation of complement activity.

One of the effects of activating the complement system is lysis of the targeted cell through the formation of membrane pores by the so-called Membrane Attack Complex. Following activation of C3 into C3b, the homologous protein C5 may be activated into C5b. The formation of C5b induces the terminal pathway of complement, in which homologous protein C6, C7, C8 and multiple copies of C9 form a complex on the target membrane forming a 100-Å wide pore. The recent structure of the central MACPF domain of human C8α revealed a surprising structural homology to bacterial cholesterol-dependent cytolysins [4]. This similarity indicates a possible mechanism of membrane attack and pore formation of these immune defence proteins.

References

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