Structural Insights into the Central Complement Ccomponent C3

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The complement system is a critical component of the mammalian immune defense against micro-organisms in plasma that links the innate and adaptive immune responses. It consists of >30 plasma proteins and cell-surface receptors. The three different pathways of activation converge in the activation of complement component C3. C3 is a 190 kDa plasma protein that, together with complement components C4 and C5, belongs to the α2-Macroglobulin family. C3 undergoes a series of proteolytic activation and degradation steps and interacts with several regulators of complement. Here we present the structure of a naturally occurring, proteolytic product of C3, called C3c, which constitutes ¾ of the total protein. This structure provides insight into C3 and its binding sites and provides the first insight into the core fold of the α2-Macroglobulin protein family.

The C3c structure shows a surprising domain composition and reveals that the two, β and α, polypeptide chains of mature C3 are heavily intertwined. The core of the protein consists of 8 homologous domains, which we refer to as macroglobulin (MG) domains. The domains display a fibronection type-3 (FN3) like fold but have no sequence homology and lack the FN3-motif.

The multi-domain structure, its potential domain-domain flexibility and the implications for complement activation and convertase formation will be discussed.

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