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Structure of Human Complement Component 5. Gregers Rom Andersen[a], Nick Laursen[a], Folmer Fredslund[a], Lars Sottrup-Jensen[a]. *Department of Molecular Biology, University of Aarhus, Denmark.*
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Complement is an important component of the innate immune system, which collaborates with the adaptive antibody immune system. It is activated through three different pathways, which all trigger cleavage of the three homolgous proteins C3, C4 and C5. The latter is cleaved into the small anaphylatoxin C5a and the large C5b fragment. C5a binds to two G-protein coupled receptors and thereby elicit chemotaxis, a respiratory burst, and release of proinflammatory mediators. C5b combine with four other complement proteins to form the membrane perforating membrane attack complex. To provide the structural basis of the functions of C5, we have determined the crystal structure of human C5 at 3.1 Å resolution [1]. In addition we have studied the interaction of C5 with inhibitors. The structure of C5 will be presented and the potential for using structural data in therautic approaches to diseases involving complement will be discussed.

[1] Fredslund, F., Laursen, N.S., Roversi, P., Jenner, L., Oliveira,C.L.P., Pedersen, J.S., Nunn, M.A., Lea, S.M., Discipio, R., Sottrup-Jensen, L., Andersen, G.R. *Nature Immunology,* **2008**, *9, 753*.

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Crystal Structure of Human Spliceosomal U1 snRNP at 5.5 Å Resolution. Daniel A. Pomeranz Krummel[a,b], Chris Oubridge[a], Adelaine Leung, Jade Li[a], Kioshi Nagai[a]. *[a]MRC Laboratory of Molecular Biology, Cambridge (U.K.); [a,b] Present Address: Brandeis University, Department of Biochemistry, Waltham MA (U.S.A.)*
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Most eukaryotic protein-encoding genes contain non-coding regions (introns) that separate those encoding for protein (exons). The introns must be excised and exons spliced together from the precursor-mRNA transcript of such genes with single nucleotide precision (RNA splicing). RNA splicing is carried out by a very large and dynamic macromolecular 'machine' called the spliceosome, composed of five RNA-protein complexes or U snRNPs (U1, U2, U4, U5 and U6) as well as other associated proteins. A first step in RNA splicing involves recognition of the junction between the 5'-exon and the intron (the 5'-splice site) by the U1 snRNP. This step initiates the assembly of the spliceosome for intron excision and is highly subject to regulatory control important to alternative splicing. Human U1 snRNP (~250 kDa) is composed of one RNA (U1 snRNA) and ten distinct protein subunits (seven Sm proteins, U1-A, U1-70K, and U1-C). An experimental electron density map of its functional core at 5.5 Å resolution enabled us to build U1 snRNA and, in conjunction with site-specific labelling of individual proteins, to place the seven Sm proteins, U1-C and U1-70K into the map (1). The structure reveals a hierarchical network of intricate interactions between subunits. The seven Sm proteins interact to form a heptameric ring with a single-stranded part of U1 snRNA leafing through its center. The ring of seven Sm proteins form multiple and varied interactions, with other regions of U1 snRNA as well as the other protein subunits, to stabilize the structure of the particle overall. A striking feature is the amino (N)-terminal polypeptide of one subunit (U1-70K), which extends over a distance of ~180 Å from its RNA binding domain, wraps around the core domain consisting of the Sm protein heptameric ring and finally contacts the protein U1-C. The U1-C protein is crucial for 5'-splice-site recognition. In the crystal, the zinc-finger of U1-C interacts with an RNA duplex formed between the single-stranded 5'-end of U1 snRNA and its counterpart from an adjacent complex. This unexpected interaction provides important insight into the critical role of U1-C in recognizing the precursor-mRNA transcript 5'-splice site. (This work was funded by the Medical Research Council (U.K.) and the Human Frontier Science Program).

[1] Pomeranz Krummel, D.A., Oubridge, C., Leung, A.K., Li, J., Nagai. *Nature,* 458(7237): 475-480.

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