MS9-03 **Modularity and conformational changes as key features of the complement system, Bergen, 7-11 August 2012.** Federico Forneris,[a] Michael Hadders,[ab] Jin Wu,[a] Piet Gros,[a] [a]*Crystal and structural chemistry, Bijvoet centre for biomolecular research, University of Utrecht, Padualaan 8, 3584CH Utrecht, The Netherlands,* [b]*Current affiliation: Medical Research Council, Laboratory of Molecular Biology, Hills Road, Cambridge CB2 0QH, United Kingdom*
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Activation of the mammalian complement cascade induces inflammatory responses and marks pathogens and altered host cells for immune clearance. Central to complement activation is the formation of short-lived protease complexes called convertases. The C3 convertases catalyze the conversion of C3 to its activated form C3b near target surfaces, resulting in opsonisation of target cells and stimulation of the adaptive immune response. By interacting with newly generated C3b molecules, C3 convertases can change their substrate specificity, resulting in the cleavage of C5 to C5b. This process releases the potent anaphylatoxin C5a and activates the terminal pathway of complement, responsible for formation of lytic pores (membrane-attack complexes, MAC) on invading pathogens.

The interplay between formation of large multi-domain enzymes, extensive conformational changes and specific proteolytic cleavages highlights the complexity of the complement system.

Our investigation of the structural biology of the complement system allowed us to elucidate two new crucial steps of complement activation and regulation: the structures of the pro-convertase of the alternative pathway C3bB and C3bBD*, and the first assembly intermediate of the terminal pathway of complement, C5b6.

The structures of the pro-convertase complexes highlight the equilibrium between an initial (closed/loading) state and a subsequent (open/activation) state of the proenzyme factor B bound to C3b. In the transient C3bBD* complex, we show how the open state of FB provides a docking platform for the rate-limiting protease factor D distant from its catalytic site, which has been caught in an activated conformation [1].

The C5b6 complex shows marked conformational changes in the conversion from C5 to C5b, highlighting the ability of C6 to capture a labile binding site in C5b to form an assembly competent state provides the first checkpoint in MAC formation. By means of a fruitful collaboration with the laboratories of S.M. Lea in Oxford and O. Llorca in Madrid, we combined our structural data with the electron microscopy reconstruction of the so-called soluble MAC complex (an off-target assembly of the MAC in solution stabilized by specific chaperones). Taken together, these data show how the MAC is assembled and regulated in blood, providing a framework for understanding the role of complement in microbial infection and inflammatory disorders [2].

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MS9-04 **Malarial vitamin B6 biosynthesis.** Ivo Tews,[ab] Gabriela Guédez,[b] Volker Windeisen,[b] Irmgard Sinning,[b] Katharina Hipp,[c] Bettina Böttcher,[c] Martin Gengenbacher,[d] Bianca Derrer,[e] Barbara Kappes,[e] [a]*University of Southampton, Centre for Biological Sciences, Southampton SO17 1BJ, UK,* [b]*Heidelberg University Biochemistry Center, INF328, 69120 Heidelberg, Germany,* [c]*The University of Edinburgh, School of Biological Sciences, Mayfield Road, Edinburgh EH9 3JR, UK,* [d]*Max-Planck-Institute for Infection Biology, Charitéplatz 1, 10117 Berlin, Germany,* [e]*University Erlangen-Nürnberg, Paul-Gordan-Str. 3, 91052 Erlangen, Germany*
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It is perhaps surprising that the main route of vitamin B6 biosynthesis is a recent discovery [1]. The present biochemical research addresses the capability of the enzyme PLP synthase to synthesize vitamin B6 directly from two carbohydrates and the amino acid glutamine [2]. Understanding this enzyme is of relevance in anti-microbial and anti-parasitic drug discovery, particularly in the search for new strategies in anti-malarial therapy [3]. Our initial crystallisation attempts with malarial enzymes did not yield crystals suitable for 3D structure determination. When we studied the assembly of the 690 kDa protein complex by electron microscopy we realised that the PLP synthase complexes had aggregated into fibres, which hindered crystallisation [4]. These problems were obviated with the study of a chimeric complex made up of *Plasmodium falciparum* and *Plasmodium berghei* proteins that was enzymatically viable. Compared with previously determined bacterial structures [5, 6] the *Plasmodium* structure showed a different positioning of enzymatic subunits relative to each other, explaining differences in subunit association noted earlier using isothermal calorimetry. These differences may be exploitable in drug design [7]. A substrate complex at 2.4 Å resolution shows carbohydrate attachment at the pentose C1 atom through Schiff base formation. While we know that PLP synthase has a cooperative hexameric core [8, 9], our EM data now suggest that association of the glutaminase subunit with the core complex is at random.

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