FA1-MS11-T01

Structure of the LKB1 tumour suppressor. Daan van Aalten. *College of Life Sciences, University of Dundee.*
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The LKB1 tumor suppressor kinase regulates activity of the AMPK family of kinases. LKB1 is activaty is regulated by the pseudokinase STRADa and the scaffolding protein MO25a through an unknown, phosphorylation-independent, mechanism. Here we describe the 2.65 Å structure of the heterotrimeric LKB1/STRADa/MO25a complex, revealing an unusual allosteric mechanism of LKB1 activation. STRADa adopts a closed conformation typical of active protein kinases, and binds LKB1 as a pseudosubstrate. STRADa binding, promotes the active conformation of LKB1, which is further stabilized by MO25a interacting with the LKB1 activation loop. This represents a previously undescribed mechanism of kinase activation that may be relevant to understanding the evolution of other pseudokinases. The structure also reveals how mutations found in Peutz-Jeghers syndrome and other cancers impair LKB1 function.
The body text font is Times New Roman (size 9) with single spacing and full justification. The total allowed area is 8 x 24 cm.

Keywords: tumour suppressor, kinase, cancer

FA1-MS11-T02

Angiotensinogen adjusts its shape to complex with renin and modulate blood pressure Aiwu Zhou[a], Robin W Carrell[b], Michael P Murphy[c], Zhenquan Wei[a], Yahui Yan[a], Peter L.D. Stanley[1], Penelope E Stein[b], Randy J Read[a]. [a] *Departments of Haematology and* [b]*Medicine, Cambridge Institute for Medical Research,* [c]*University of Cambridge, and MRC Mitochondrial Biology Unit*[c]*, Hills Rd, Cambridge, CB2 0XY, UK.*
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Blood pressure is critically controlled by angiotensins, vasopressor peptides specifically released by the enzyme renin from the tail of angiotensinogen, an inert member of the serpin family of protease inhibitors. Although angiotensinogen has long been regarded as a passive substrate, the crystal structures solved here to 2.1Å resolution show that the angiotensin cleavage site is inaccessibly buried in its amino-terminal tail. The co-ordinated conformational rearrangement that makes this site accessible for proteolysis and hence initiates the processes controlling blood pressure is revealed in a 4.4Å structure of the complex of human angiotensinogen with renin. The binding of renin is seen to displace a peptide loop in the body of angiotensinogen accompanied by a shift of the terminal tail of the angiotensinogen into the active cleft of renin, the two movements being linked by a labile disulphide bridge. We show that the oxidised sulphydryl-bridged form of angiotensinogen circulates in a near 1:1 ratio with a reduced unbridged form, which interacts less effectively with renin to release angiotensin. We propose that this reversible transition of angiotensinogen from the reduced to a more active oxidised form is a newly identified modulating mechanism at the commencement of the processes raising blood pressure in man. The demonstration that the transition is responsive to redox changes and potentially influenced by nitrosylation has relevance to the known, but ill-understood, association of oxidative stress with the onset of hypertension and in particular with the hypertensive crises of late pregnancy (pre-eclampsia).

Keywords: hypertension, angiotensin, renin

FA1-MS11-T03

Chemokine Binding Protein from Orf Virus Modulates Immune Function- a new twist on an old motif. Kurt L. Krause[a], Rafael Counago[a] Stephen Fleming[b], Andy Mercer[b], [a]*Biochemistry, University of Otago, Dunedin. New Zealand.* [b]*Microbiology and Immunology, University of Otago, Dunedin, New Zealand.*
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Chemokine binding proteins (CBPs) are viral proteins that modulate inflammation by interfering with host chemokine signaling. CBPs bind to their cognate partner with picomolar affinity via an extended beta sandwich structure. Here we describe the structure of a new class of CBP from the parapoxvirus, Orf virus. The crystals of this protein were challenging to produce and optimized significantly through the use of somewhat surprising additives. Crystals occupy Space Group $P6_522$ with unit cell parameters of a = b = 75.62, c = 282.49 Å,α = 90, β = 90, γ = 120 ^{o}. The structure was phased using MAD methodologies and currently the 2.1Å structure is undergoing refinement. Early analysis indicates that it is a member of the β-sandwich family but it is quite distinct from other family members when superimposed. Additionally the crystal structure is consistent with a physiologic dimer and displays a very broad β sheet on its surface containing contributions from more than 10 β strands. The dimeric nature of this CBP appears to be a unique property of its class and may be key in explaining how it is able to bind different chemokines from at least two distinct chemokine classes.

Keywords: protein crystallography, chemokine , virology

FA1-MS11-T04

Structural basis for CRM1 nuclear export complex assembly. Thomas Monecke[a], Thomas Güttler[b], Piotr Neumann[a], Nicole Doelker[c], Clement Blanchet[d], Achim Dickmanns[a], Dirk Görlich[b], Helmut Grubmüller[c], Dmitri Svergun[d], Ralf Ficner[a]. [a]*Abteilung für Molekulare Strukturbiologie, Institut für Mikrobiologie und Genetik, Georg-August-Universität Göttingen, Justus-von-Liebig-Weg 11, 37077 Göttingen, Germany.* [b]*Abteilung Zelluläre Logistik, Max-Planck-Institut für biophysikalische Chemie, Am Fassberg 11, 37077 Göttingen, Germany.* [c]*Abteilung für theoretische und computergestützte Biophysik, Max-Planck-Institut für biophysikalische Chemie, Am Fassberg 11, 37077, Göttingen, Germany.* [d]*European Molecular Biology Laboratory (EMBL), Hamburg Outstation, Notkestraße 85, 22603 Hamburg, Germany.*
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