Elsewhere in Biology

Chosen and summarized by the staff of *Chemistry & Biology*

Current Biology Ltd has launched a new journal entitled *Current Opinion in Chemical Biology*, which will be of particular interest to readers of *Chemistry & Biology*. The editors of the journal are Donald Hilvert and Steven V Ley. The second issue, on next generation therapeutics, will be published in August and is edited by John W Kozarich and Daniel H Rich.

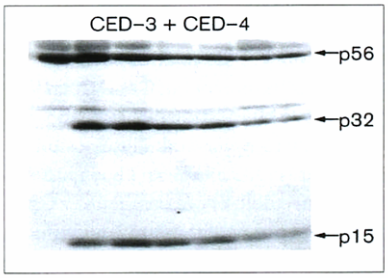
Current Opinion in Chemical Biology
Next generation therapeutics
Contents for August 1997 issue

A selection of interesting papers published last month in *Chemistry & Biology*'s sister journals, *Current Biology*, *Folding & Design* and *Structure*.

Chemistry & Biology July 1997, **4**:539–542

☐ ***Caenorhabditis elegans* CED-4 stimulates CED-3 processing and CED-3-induced apoptosis.** Somasekar Seshagiri and Lois K Miller (1997). *Curr. Biol.* **7**, 455–460.

Programmed cell death or apoptosis is a key feature of normal development, tissue homeostasis and disease progression in metazoans. Genetic studies in the nematode *C. elegans* have identified three key genes involved in apoptosis, *ced-3*, *ced-4* and *ced-9*. Expression of *ced-3* and *ced-4* is required for the induction of cell death, whereas expression of *ced-9* is necessary to inhibit cell death but the precise mechanism by which these genes influence apoptosis is not known. The authors have expressed

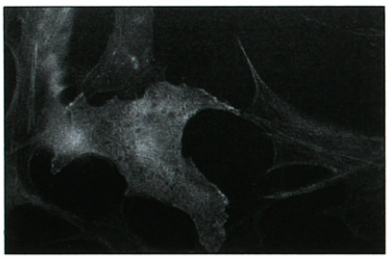


the genes in an insect cell line to explore their role in the apoptotic pathway. Co-expression of *ced-4* with *ced-3* in insect cells stimulated both the induction and the level of CED-3-mediated apoptosis. Stimulation of CED-3-dependent apoptosis by CED-4 was accompanied by accelerated processing of CED-3. Co-expression of *ced-9* with *ced-4* and *ced-3* inhibited the ability of CED-4 to stimulate CED-3 processing and CED-3-dependent apoptosis. The results indicate that CED-4 stimulates CED-3-induced apoptosis in a CED-9 regulated manner.

5 June 1997*, Research Paper, *Current Biology*

☐ **A Cdc42 target protein with homology to the non-kinase domain of FER has a potential role in regulating the actin cytoskeleton.** Pontus Aspenström (1997). *Curr. Biol.* **7**, 479–487.

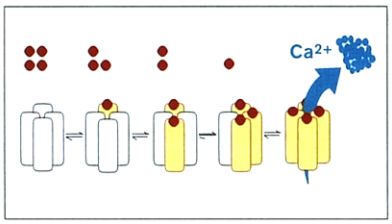
Members of the Rho family of small GTPases have been shown to have a diverse role in cell signalling events. They were originally identified as proteins that, by regulating the assembly of the actin cytoskeleton, are important determinants of cell morphology, and have recently been shown to be involved in transcriptional activation by the Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) signalling pathway. To understand the mechanisms underlying the effects of Rho GTPases on these processes, the yeast two-hybrid system has been used to identify proteins that bind to an activated mutant of Cdc42, a Rho-family member. The authors have cloned a cDNA encoding a previously unidentified Cdc42 target protein, CIP4, from a human B-cell library. The amino terminus of CIP4 resembles the non-kinase domain of the FER and Fes/Fps family of tyrosine kinases. Similarities to a number of proteins with roles in regulating the actin cytoskeleton were also noticed. CIP4 binds to activated Cdc42 *in vitro* and *in vivo* and overexpression of CIP4 in Swiss 3T3 fibroblasts causes a reduction in stress-fibre content. Moreover, coexpression of activated Cdc42 and CIP4 leads to clustering of CIP4 to a large number of foci at the dorsal side of the cells. CIP4 is a downstream target of activated GTP-bound Cdc42, and is similar in sequence to proteins involved in signalling and cytoskeletal control. Together, these findings suggest that CIP4 may act as a link between Cdc42 signalling and regulation of the actin cytoskeleton.



13 June 1997, Research Paper, *Current Biology*

☐ **Cooperative activation of IP_3 receptors by sequential binding of IP_3 and Ca^{2+} safeguards against spontaneous activity.** Jonathan S Marchant and Colin W Taylor (1997). *Curr. Biol.* **7**, 510–518.

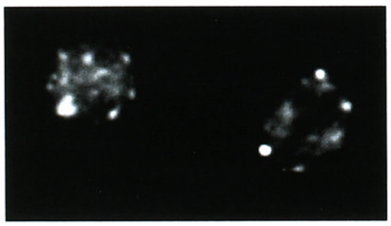
Cytosolic Ca^{2+} signals evoked by receptors linked to inositol 1,4,5-trisphosphate (IP_3) formation are complex. They give rise to Ca^{2+} waves that allow effective delivery of intracellular Ca^{2+} signals to cytosolic targets. Propagation of these regenerative Ca^{2+} signals probably results from the activation of intracellular Ca^{2+} channels by the increase in cytosolic Ca^{2+} concentration that follows the opening of these channels. Such positive feedback is potentially explosive, so mechanisms that limit the spontaneous opening of intracellular Ca^{2+} channels are therefore likely to have evolved in parallel with the mechanism of Ca^{2+}-induced Ca^{2+} release. To investigate the mechanisms, the authors have used methods that allow them to measure the rapid kinetics of $^{45}Ca^{2+}$ efflux from permeabilised hepatocytes, when stimulated by IP_3. The results indicate that channel opening does not immediately follow binding of IP_3. Although the absolute latency of Ca^{2+} release was unaffected by further increasing the IP_3 concentration, it was reduced by increased Ca^{2+} concentration. The closed conformation of the IP_3 receptor is proposed to be very stable and therefore minimally susceptible to spontaneous activation; at least three (probably four) IP_3 molecules may be required to provide enough binding energy to drive the receptor into a stable open conformation. Binding of IP_3 to each of its four receptor subunits unmasks a site to which Ca^{2+} must bind before the channel can open. This mechanism provides a safeguard against spontaneous activation.



18 June 1997, Research Paper, *Current Biology*

☐ **The complex containing actin-related proteins Arp2 and Arp3 is required for the motility and integrity of yeast actin patches.** Dirk Winter, Alexandre V Podtelejnikov, Matthias Mann and Rong Li (1997). *Curr. Biol.* **7**, 519–529.

Structural modeling and biochemical experiments *in vitro* have implicated a multi-protein complex containing two actin-related proteins, Arp2 and Arp3, as a potential actin-filament nucleation factor. This 'Arp2/3 complex' has been identified in *Acanthamoeba* and human cells and has been shown to localize to regions involved in actin-based motility, such as the leading edge of moving cells. The function of this complex *in vivo* has not been characterized, however, and the sequences of the non-actin-related subunits remain to be determined. In this paper, an Arp3 homologue from the budding yeast *Saccharomyces cerevisiae* was found to localize to cortical actin patches, highly motile structures that concentrate at sites of polarized growth during the yeast cell cycle. An *arp3-2* mutation impaired actin-patch motility. Most Arp3 protein is found in a multi-protein complex; the authors purified this complex and determined the sequences of each of the protein subunits using a high-accuracy mass peptide-mapping technique. The proteins found in the complex are similar to those in the *Acanthamoeba* and human Arp2/3 complexes except that the yeast complex lacks a 40 kDa subunit, which is therefore not required for the



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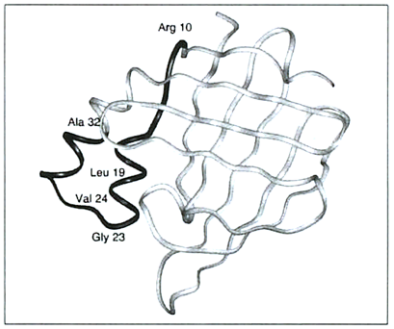
structural integrity of the complex. The authors have shown that, in yeast, the complex is required *in vivo* for the motility and integrity of cortical actin patches. They have also shown that mass spectrometric methods can be successfully used to identify complete multiprotein complexes.
18 June 1997, Research Paper, *Current Biology*

☐ **Local interactions in a Schellman motif dictate interhelical arrangement in a protein fragment.** Muppalla Sukumar and Lila M Gierasch (1997). *Fold. Des.* **2**, 211–222.

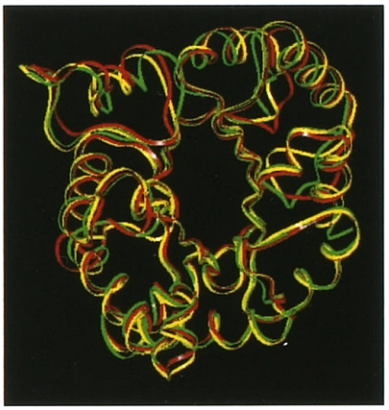
In order to understand the role a local sequence plays in determining protein tertiary structure, the authors examined the conformation of a 23-residue peptide fragment that corresponds to the structurally conserved helix–Schellman motif–helix (H–Sm–H) domain (residues 10–32) of cellular retinoic acid binding protein. They also looked at variants designed to probe the contributions of the helix-terminating Gly23 and the hydrophobic interactions between Leu19 and Val24 in stabilizing the Schellman motif and hence helix termination. In aqueous solution, NMR data for the H–Sm–H peptide showed that it samples a largely helical conformation with a break in the helix at the point of the turn in the protein. The data also established the presence of local hydrophobic interactions and intramolecular hydrogen bonds characteristic of a Schellman motif. The absence of helix termination in trifluoroethanol, a solvent known to disrupt hydrophobic interactions, along with an analysis of proton chemical shifts and NOEs in the variant peptides, suggest a major role for glycine in terminating the helix, with local hydrophobic interactions further stabilizing the Schellman motif. The presence of a Schellman motif in this isolated fragment in water is governed by local interactions and specifies the interspatial arrangement of the helices. This observation underlines the structure predictive value of folding motifs. As proposed for a Schellman motif, helix termination in this fragment is dictated by the local distribution of polar/apolar residues, which is reminiscent of the binary code for protein folding.



20 June 1997, Research Paper, *Folding & Design*

☐ **Triosephosphate isomerase from *Plasmodium falciparum*: the crystal structure provides insights into antimalarial drug design.** Sameer S Velanker, Soumya S Ray, Rajesh S Gokhale, Suma S Ray, Hemalatha Balaram, P Balaram and MRN Murthy (1997). *Structure* **5**, 751–761.

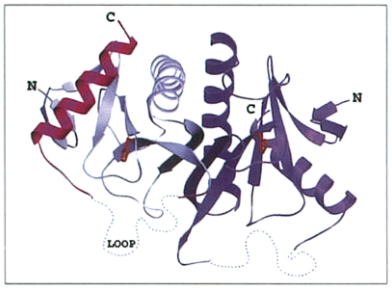
Malaria caused by the parasite *Plasmodium falciparum* is a major public health concern. The parasite lacks a functional tricarboxylic acid cycle, making glycolysis its sole energy source. Although parasite enzymes have been considered as potential antimalarial drug targets, little is known about their structural biology. In this paper, the authors report the crystal structure of triosephosphate isomerase from *P. falciparum* (PfTIM) at 2.2 Å resolution. A comparison of the crystal structure pfTIM with other triosephosphate isomerase (TIM) structures, particularly human TIM, revealed several differences. Although the human and *Plasmodium* enzymes share 42% amino acid sequence identity, several key differences suggest that PfTIM may turn out to be a potential drug target. A region has been identified which may be responsible for binding PfTIM to cytoskeletal elements or the band 3 protein of erythrocytes; attachment to the erythrocyte membrane may subsequently lead to the extracellular exposure of parts of the protein. This feature may be important in view of a recent report that patients suffering from *P. falciparum* malaria mount an antibody response to TIM leading to prolonged hemolysis. A second approach to drug design may be provided by the mutation of the largely conserved residue (Ser96) to phenylalanine in PfTIM. This difference may be of importance in designing specific active-site inhibitors against the enzyme. Finally, specific inhibition of PfTIM subunit assembly might be possible by targeting Cys13 at the dimer interface. The crystal structure of PfTIM provides a framework for new therapeutic leads.



15 June 1997, Research Article, *Structure*

☐ **MAD analysis of FHIT, a putative human tumor suppressor from the HIT protein family.** Christopher D Lima, Kevin L D'Amico, Istvan Naday, Gerold Rosenbaum, Edwin M Westbrook and Wayne A Hendrickson (1997). *Structure* **5**, 763–774.

The fragile histidine triad (FHIT) protein is a member of the large and ubiquitous histidine triad (HIT) family of proteins. It is expressed from a gene located at a fragile site on human chromosome 3, which is commonly disrupted in association with certain cancers. On the basis of the genetic evidence, it has been postulated that the FHIT protein may function as a tumor suppressor, implying a role for the FHIT protein in carcinogenesis. The FHIT protein has dinucleoside polyphosphate hydrolase activity *in vitro*, thus suggesting that its role *in vivo* may involve the hydrolysis of a phospho-anhydride bond. The three-dimensional crystal structures of free and nucleoside complexed FHIT were determined from



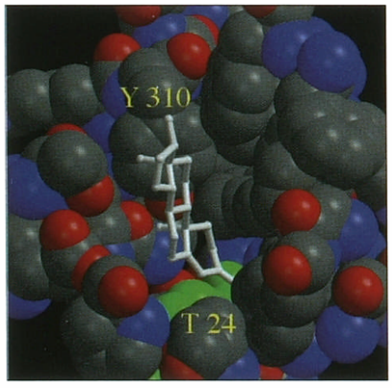
multiwavelength anomalous diffraction (MAD) data, representing some of the first successful structures to be measured with undulator radiation at the Advanced Photon Source.

The structure of FHIT, a divergent HIT protein family member, in complex with a nucleotide analog suggests a metal-independent catalytic mechanism for the HIT family of proteins. A structural comparison of FHIT with PKCI and galactose-1-phosphate uridylyltransferase (GalT) reveals additional implications for the structural and functional evolution of the ubiquitous HIT family of proteins.

15 June 1997, Research Article, *Structure*

☐ **Steroid recognition and regulation of hormone action: crystal structure of testosterone and NADP$^+$ bound to 3α-hydroxysteroid/dihydrodiol dehydrogenase.** Melanie J Bennett, Ross H Albert, Joseph M Jez, Haiching Ma, Trevor M Penning and Mitchell Lewis (1997). *Structure* **5**, 799–812.

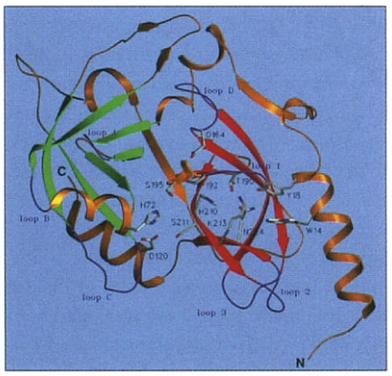
Mammalian 3α-hydroxysteroid dehydrogenases (3α-HSDs) modulate the activities of steroid hormones by reversibly reducing their C3 ketone groups. In steroid target tissues, 3α-HSDs act on 5α-dihydrotestosterone, a potent male sex hormone (androgen) implicated in benign prostate hyperplasia and prostate cancer. Rat liver 3α-HSD belongs to the aldo-keto reductase (AKR) superfamily and provides a model for mammalian 3α-HSD, 17β-HSD and 20α-HSD, which share > 65% sequence identity. The determination of the structure of 3α-HSD in complex with NADP$^+$ and testosterone (a competitive inhibitor) will help to further our understanding of steroid recognition and hormone regulation by mammalian HSDs. The active-site arrangement observed in the 3α-HSD ternary complex structure suggests that each positional-specific and stereospecific reaction catalyzed by an HSD requires a particular substrate orientation, the general features of which can be predicted. 3α-HSDs are likely to bind substrates in a similar manner to the way in which testosterone is bound in the ternary complex, that is with the A ring of the steroid substrate in the active site and the β face towards the nicotinamide ring to facilitate hydride transfer. In contrast, we predict that 17β-HSDs will bind substrates with the D ring of the steroid in the active site and with the a face towards the nicotinamide ring. The ability to bind substrates in only one or a few orientations could determine the positional-specificity and stereospecificity of each HSD. Residues lining the steroid-binding cavities are highly variable and may select these different orientations.



15 June 1997, Research Article, *Structure*

☐ **The structure of *Staphylococcus aureus* epidermolytic toxin A, an atypic serine protease, at 1.7 Å resolution.** Jean Cavarelli, Gilles Prévost, William Bourguet, Luc Moulinier, Bernard Chevrier, Bénédicte Delagoutte, Alexandrine Bilwes, Lionel Mourey, Samer Rifai, Yves Piémont and Dino Moras (1997). *Structure* **5**, 813–824.

Staphylococcal epidermolytic toxins A and B (ETA and ETB) are responsible for the staphylococcal scalded skin syndrome of newborn and young infants; this condition can appear just a few hours after birth. These toxins cause the disorganization and disruption of the region between the *stratum spinosum* and the *stratum granulosum* — two of the three cellular layers constituting the epidermis. The physiological substrate of ETA is not known and, consequently, its mode of action *in vivo* remains an unanswered question. It was thought that the determination of the structure of ETA and its comparison with other serine proteases could reveal insights into ETA's catalytic mechanism. The crystal structure of staphylococcal ETA was refined at 1.7 Å resolution. The structure of ETA reveals it to be a new and unique member of the trypsin-like serine protease family. In contrast to other serine protease folds, ETA can be characterized by ETA-specific surface loops, a lack of cysteine bridges, an oxyanion hole which is not preformed, an S1 specific pocket designed for a negatively charged amino acid and an ETA-specific amino-terminal helix which is shown to be crucial for substrate hydrolysis. Direct links can be made between the protease architecture of ETA and its biological activity.



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