Elsewhere in Biology

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

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

Chemistry & Biology April 1996, 3:315–316

☐ **Sertoli cell signaling by Desert hedgehog regulates the male germline.** Mark J. Bitgood, Liya Shen and Andrew P. McMahon (1996). *Curr. Biol.* **6**, 298–304.

In mammals, testis development is initiated in the embryo in response to the expression of the sex-determining gene, *Sry*, in Sertoli-cell precursors. Sertoli cells are thought to be essential for male-specific cell interactions, including those that occur during spermatogenesis. The authors show that the Desert hedgehog gene (*Dhh*), a homolog of the *Drosophila* segment-polarity gene *hedgehog*, is expressed in Sertoli-cell precursors shortly after the activation of *Sry*, providing one of the earliest indications of male sexual differentiation, and that it persists in the testis into the adult. Female mice homozygous for a *Dhh*-null mutation show no obvious phenotype, but males are viable but infertile, and have no mature sperm. Thus *Dhh* is essential in mammalian spermatogenesis. The expression of *Patched*, a likely target of Hedgehog signaling that also displays male-specific transcription in the gonad, is also lost in *Dhh* mutants. *Patched* expression is normally restricted to Leydig cells, indicating that these cells may be the direct target of *Dhh* signaling.

1 Mar 1996, Research Paper, *Current Biology*

☐ **Codon usage limitation in the expression of HIV-1 envelope glycoprotein.** Jürgen Haas, Eun-Chung Park and Brian Seed (1996). *Curr. Biol.* **6**, 315–324.

The expression of both the *env* and *gag* gene products of human immunodeficiency virus type 1 (HIV-1) is known to be limited by *cis* elements in the viral RNA that impede exit of the RNA from the nucleus and reduce the efficiency of translation. Identifying these elements has been difficult, as they appear to be distributed throughout the viral genome. The authors observed that there is a profound bias in the codon usage of the *env*, *gag* and *pol* genes, and that the codons used are different from those used in highly expressed human proteins. They therefore constructed a synthetic gene, using the highly-expressed codons, that encodes the gp120 segment of the HIV-1 envelope protein. This synthetic gene was expressed at a very high level compared to the wild-type gp120 sequence. Re-engineering a highly-expressed human protein, Thy-1, with the codons used by HIV-1 *env* severely decreased its expression. The authors conclude that selective codon usage, not reduced nuclear export, accounts for much of the observed inefficiency of HIV-1 protein synthesis, and suggest that other proteins that are also poorly expressed in mammalian cells might benefit from codon re-engineering.

1 Mar 1996, Research Paper, *Current Biology*

☐ **The nascent polypeptide-associated complex modulates interactions between the signal recognition particle and the ribosome.** Ted Powers and Peter Walter (1996). *Curr. Biol.* **6**, 331–338.

The first step in the co-translational targeting of secretory proteins to the endoplasmic reticulum (ER) involves the capture of signal sequences emerging from the ribosome by the signal recognition particle (SRP). It has recently been proposed that SRP does not recognize the signal sequence directly, but that the nascent polypeptide-associated complex (NAC), which also interacts co-translationally with nascent polypeptides, mediates the specific interaction between SRP and a signal peptide. The authors show that, in the absence of NAC, SRP binds to a complex of the ribosome and a nascent polypeptide lacking a signal sequence, but that such binding is sensitive to salt concentration; in high salt SRP binds only to complexes with nascent polypeptides that contain the signal sequence. The non-specific, salt-sensitive binding of SRP to ribosomes with a nascent chain that lacks a signal sequence is probably due to interactions between SRP and the ribosome that are independent of the nascent polypeptide chain, and this binding is inhibited by NAC. Thus, the primary function of NAC may be to negatively modulate interactions between SRP and the ribosome.

1 Mar 1996, Research Paper, *Current Biology*

☐ **Structure of a dehydratase–isomerase from the bacterial pathway for biosynthesis of unsaturated fatty acids: two catalytic activities in one active site.** Minsun Leesong, Barry S Henderson, James R Gillig, John M Schwab and Janet L Smith (1996). *Structure* **4**, 253–264.

Escherichia coli β-hydroxydecanoyl thiol ester dehydrase is essential for the biosynthesis of unsaturated fatty acids. It shunts a 10-carbon intermediate from the saturated fatty acid pathway into the unsaturated fatty acid pathway by catalyzing two reactions on fatty acid thiol esters of acyl carrier protein (ACP). These are the dehydration of (*R*)-3-hydroxy-decanoyl-ACP to (*E*)-2-decenoyl-ACP, and the isomerization of (*E*)-2-decenoyl-ACP to (*Z*)-3-decenoyl-ACP. The authors present crystal structures of the enzyme and an enzyme–inhibitor complex at 2.0 Å resolution. The unusual bifunctional active site is found in a tunnel-shaped pocket between the two subunits of the enzyme, completely isolated from the general solvent. Side chains of histidine from one subunit and aspartic acid from the other are the only potentially reactive protein groups in the active site. A two-base mechanism in which the histidine and the aspartic acid together catalyze dehydration and isomerization reactions is consistent with the active-site structure. The enzyme has an unusual $\alpha + \beta$ fold, which is unrelated to the fold of scytalone dehydratase, the only other metal-free dehydratase whose structure is known.

15 Mar 1996, Research Paper, *Structure*

☐ **Crystal structure of firefly luciferase throws light on a superfamily of adenylate-forming enzymes.** Elena Conti, Nick P Franks and Peter Brick (1996). *Structure* **4**, 287–298.

Firefly luciferase oxidizes its substrate, firefly luciferin, in the presence of MgATP and molecular oxygen, generating an excited-state product that then decays, emitting light. The reaction proceeds through an adenylate intermediate, and firefly luciferase shows extensive sequence homology with a number of enzymes that use ATP in adenylation reactions. The crystal structure of firefly luciferase to 2.0 Å is reported in this paper. This is the first structure to be determined for a member of the adenylate-forming superfamily of homologous enzymes, which includes acyl-coenzyme A ligases and peptide synthetases (such as gramicidin S synthetase and the first enzyme of the penicillin synthetase pathway). The protein is folded into two compact domains separated by a wide cleft. The residues conserved within the superfamily are found on the surfaces of the two domains, on either side of the cleft, and are too far apart to interact simultaneously with the substrates. The authors suggest that the two domains move relative to one another in the course of the reaction, closing the cleft.
15 Mar 1996, Research Paper, *Structure*

☐ **Crystal structure of the yeast cell-cycle control protein, $p13^{suc1}$, in a strand-exchanged dimer.** N Khaszanovich, KS Bateman, M Chernaia, M Michalak and MNG James (1996). *Structure* **4**, 299–309.

$p13^{suc1}$ from fission yeast is a member of the CDC28 kinase specific (CKS) class of cell-cycle control proteins, and participates in the regulation of $p34^{cdc2}$, a cyclin-dependent kinase controlling the G_1–S and G_2–M transitions of the cell cycle. The mechanism of this regulation is not clear, but is believed to involve direct binding of the CKS protein to the kinase. The first crystal structure of $p13^{suc1}$ revealed a monomeric form of the molecule. However, the structures of the human homologs, CksHs1 and CksHs2, showed different levels of assembly; CksHs1 is a monomer, but CksHs2 forms a hexamer consisting of three dimers, with β-strand exchange participating in the formation of a tight dimer association. Two reports, this paper and a recent paper published elsewhere, now show that $p13^{suc1}$ can also form a strand-exchanged dimer in two different space groups. Thus, a switch between levels of assembly may be involved in coordinating the function of the CKS proteins with the stage of the cell cycle.
15 Mar 1996, Research Paper, *Structure*

☐ **The crystal structure of peanut peroxidase.** David J Schuller, Nenad Ban, Robert B van Huystee, Alexander McPherson and Thomas L Poulos (1996). *Structure* **4**, 311–321.

Peroxidases catalyze a wide variety of peroxide-dependent oxidations, and there is growing optimism that it will be possible to engineer peroxidases for a variety of practical applications. Crystal structures are available for peroxidases of classes I and II, but not for class III, the classical extracellular plant peroxidases. The authors present the structure of peanut peroxidase to 2.7 Å resolution. The helical fold is similar to that of other known peroxidases, and key residues around the heme, and the location of two calcium ions, are shared with class II peroxidases. Peanut peroxidase has three unique helices, however, and two of these contribute to the substrate-access channel leading to the heme edge.
15 Mar 1996, Research Paper, *Structure*

☐ **How coenzyme B_{12} radicals are generated: the crystal structure of methylmalonyl-coenzyme A mutase at 2 Å resolution.** Filippo Mancia, Nicholas H Keep, Atsushi Nakagawa, Peter F Leadlay, Sean McSweeney, Bjarne Rasmussen, Peter Bösecke, Olivier Diat and Philip R Evans (1996). *Structure* **4**, 339–350.

Methylmalonyl-coenzyme A (CoA) mutase is one of ten known enzymes that use coenzyme B_{12} (adenosylcobalamin) as a cofactor. The enzyme induces the formation of an adenosyl radical from the cofactor, and the radical then initiates a free-radical rearrangement of its substrate, succinyl-CoA, to methylmalonyl-CoA. The authors report the crystal structure of methylmalonyl-CoA mutase in complex with coenzyme B_{12} and with the partial substrate desulpho-CoA (lacking the succinyl group and the sulphur atom of the substrate) to 2 Å resolution. The active site is protected by a TIM barrel domain, so that the substrate must pass through a narrow tunnel to reach the active-site cavity, which, like the active sites of other enzymes that produce reactive radical intermediates, is protected from unwanted side reactions. The coenzyme is bound by a domain that has a similar fold to those of flavodoxin and the B_{12}-binding domain of methylcobalamin-dependent methionine synthase. The cobalt atom is coordinated to a histidine from the protein, via a long bond (2.5 Å, compared with 1.95–2.2 Å in free cobalamins), suggesting that the position of the histidine puts the cobalt into a strained position, decreasing the strength of the cobalt–carbon bond in the cofactor. This coordination also stabilizes the Co^{II} species relative to Co^{III}, favoring the formation of the adenosyl radical.
15 Mar 1996, Research Paper, *Structure*