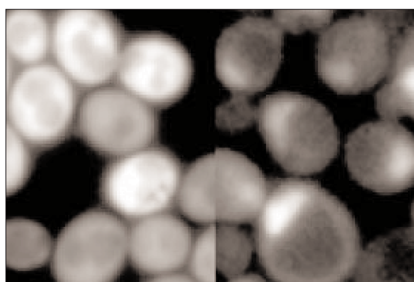
Elsewhere in biology

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

Chemistry & Biology 2000, **7**:R29–R32

☐ **The nuclear exportin Msn5 is required for nuclear export of the Mig1 glucose repressor of *Saccharomyces cerevisiae*.**
Michael J DeVit, Mark Johnston (1999). *Curr. Biol.* **9**, 1231–1241.

Mig1 is a transcriptional repressor responsible for glucose repression of many genes in the budding yeast *Saccharomyces cerevisiae*. Glucose



regulates Mig1 function by affecting its phosphorylation, which is catalyzed by the Snf1 protein kinase. Phosphorylation alters the subcellular localization of Mig1, causing it to be nuclear when glucose is present, and cytoplasmic when glucose is absent. The authors report that Msn5, a member of the importin family of nuclear transport receptors, is required to export Mig1 from the nucleus when glucose is removed. They show that Mig1 contains a new nuclear export signal that is phosphorylated by Snf1 upon glucose removal, causing it to be recognized by the nuclear exportin Msn5 and carried out of the nucleus into the cytoplasm where it contributes to derepression of glucose-repressed genes.
20 October 1999, Research Paper, *Current Biology*.

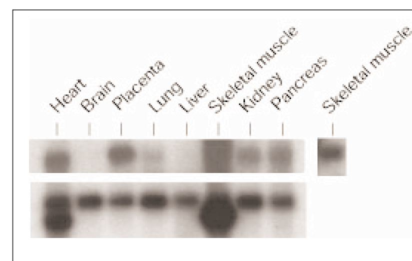
☐ **Functional interaction between the cytoplasmic leucine-zipper domain of HIV-1 gp41 and p115-RhoGEF.**
H Zhang, L Wang, S Kao, IP Whitehead, MJ Hart, B Liu, K Duus, K Burridge, CJ Der, L Su (1999). *Curr. Biol.* **9**, 1271–1274.

The long cytoplasmic tail of the HIV-1 transmembrane protein gp41 (gp41C) has been implicated in the replication and cytopathicity of HIV-1. Little is known about the specific functions of gp41C, however. HIV-1 or simian immunodeficiency virus (SIV) mutants with defective gp41C have cell-type- or species-dependent phenotypes. Host factors are therefore implicated in mediating the functions of gp41C. The authors report that gp41C interacted with the carboxy-terminal regulatory domain of p115-RhoGEF, a specific guanine nucleotide exchange factor (GEF) and activator of the RhoA GTPase, which regulates actin stress fiber formation, activation of serum response factor (SRF) and cell proliferation. gp41C inhibited p115-mediated actin stress fiber

formation and activation of SRF. An amphipathic helix region with a leucine-zipper motif in gp41C is involved in its interaction with p115. Mutations in gp41C leading to loss of interaction with p115 impaired HIV-1 replication in human T cells. The findings suggest that an important function of gp41C is to modulate the activity of p115-RhoGEF and therefore reveal a new potential anti-HIV-1 target.
25 October 1999, Brief Communication, *Current Biology*.

☐ **Human *CED-6* encodes a functional homologue of the *Caenorhabditis elegans* engulfment protein CED-6.**
Qiong A Liu, Michael O Hengartner (1999). *Curr. Biol.* **9**, 1347–1351.

The rapid engulfment of apoptotic cells is a specialized immune response used by organisms to remove apoptotic cells. In mammals, several receptors that recognize apoptotic cells have been identified; molecules that transduce

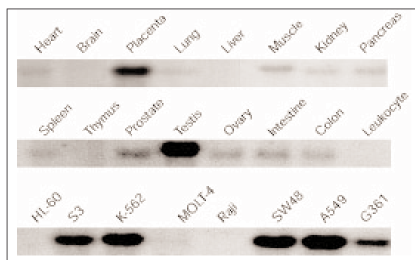


signals from these receptors to downstream cytoskeleton molecules have not been found, however. Previous analysis of the engulfment gene *ced-6* in *Caenorhabditis elegans* has suggested that CED-6 is an adaptor protein that participates in a signal transduction pathway that mediates the specific recognition and engulfment of apoptotic cells. A human cDNA encoding a protein, hCED-6, with strong sequence similarity to *C. elegans* CED-6 has been identified and characterized. The worm protein and hCED-6 share many structural similarities. Overexpression of hCED-6 rescues the engulfment defect of *ced-6* mutants in *C. elegans* significantly, suggesting that hCED-6 is a functional homologue of *C. elegans* CED-6. CED-6, and the CED-6 signal transduction pathway, might be conserved from *C. elegans* to humans.
8 November 1999, Brief Communication, *Current Biology*.

☐ **The human homologue of *Caenorhabditis elegans* CED-6 specifically promotes phagocytosis of apoptotic cells.**
Elke Smits, Wim Van Criekinge, Geert Plaetinck, Thierry Bogaert (1999). *Curr. Biol.* **9**, 1351–1354.

A key feature of the process of apoptosis is the efficiency with which the dying

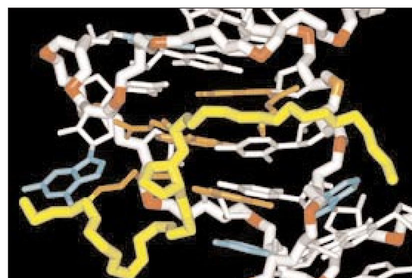
cells are recognized and engulfed by phagocytes. Apoptotic cells are rapidly cleared either by neighbouring cells acting as semi-professional phagocytes or by experts of the macrophage line, so that an inflammatory response is avoided. The *Caenorhabditis elegans* gene *ced-6* is required for efficient engulfment of apoptotic cells and is one of a group of genes that define two partially redundant parallel pathways for the engulfment process. The cloning and



characterization of human CED-6, a human homologue of *C. elegans* CED-6. The 34 kDa hCED-6 protein is expressed in most tissues, some human cancer cells, and in primary human macrophages. An assay that quantitates the phagocytic activity of mammalian macrophages has been developed: the number of apoptotic cells that have been internalized is measured by the uptake of lacZ-positive apoptotic cells by adherent transgenic macrophages. The results of this assay demonstrate that overexpression of hCED-6 promotes phagocytosis only of apoptotic cells and suggest that hCED-6 is the mammalian orthologue of *C. elegans* CED-6 and is a part of a highly conserved pathway that specifically mediates the phagocytosis of apoptotic cells.
8 November 1999, Brief Communication, *Current Biology*.

☐ **Anchoring an extended HTLV-1 Rex peptide within an RNA major groove containing junctional base triples.**
Feng Jiang, Andrey Gorin, Weidong Hu, Ananya Majumdar, Scott Baskerville, Weijun Xu, Andrew Ellington, Dinshaw J Patel (1999). *Structure* **7**, 1461–1472.

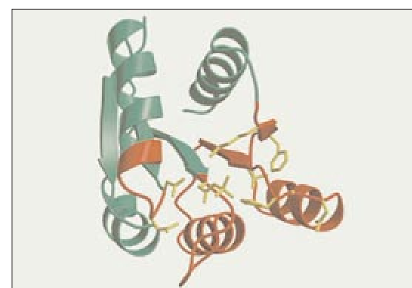
The Rex protein of the human T cell leukemia virus type 1 (HTLV-1) belongs to a family of proteins that use arginine-rich motifs (ARMs) to recognize their RNA targets. Previously, an *in vitro* selected RNA aptamer sequence was identified that mediates mRNA transport *in vivo* when placed in the primary binding site on stem-loop IID of the Rex response element. The solution structure of the HTLV-1 arginine-rich Rex peptide bound to its RNA aptamer target was determined using



multidimensional heteronuclear nuclear magnetic resonance (NMR) spectroscopy. The extended S-shaped conformation of the Rex peptide increases understanding of the strategies employed by ARMs for adaptive recognition and highlights the importance of RNA tertiary structure in accommodating minimalist elements of protein secondary structure.
17 November 1999, Research Paper, *Structure*.

☐ **Conformational changes induced by phosphorylation of the FixJ receiver domain.**
Catherine Birck, Lionel Mourey, Patrice Gouet, Béatrice Fabry, Jörg Schumacher, Philippe Rousseau, Daniel Kahn, Jean-Pierre Samama (1999). *Structure* **7**, 1505–1515.

A variety of bacterial adaptative cellular responses to environmental stimuli are mediated by two-component signal transduction pathways. In these phosphorelay cascades, histidine kinases transphosphorylate a conserved aspartate in the receiver domain, a conserved module in the response regulator superfamily. The main effect of this phosphorylation is to alter the conformation of the response regulator to modulate its biological function. The response regulator FixJ displays a typical

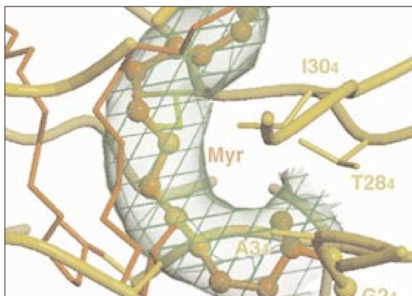


modular arrangement, with a phosphorylatable amino-terminal receiver domain and a carboxy-terminal DNA-binding domain. In the symbiotic bacterium *Sinorhizobium meliloti*, phosphorylation of this response regulator activates transcription of nitrogen-fixation genes. The crystal structures of the phosphorylated and of the unphosphorylated amino-terminal receiver domain of FixJ (FixJN) were solved. They reveal the environment of the phosphoaspartate in the active site and the specific conformational changes leading to activation of the response regulator. The cascade of phosphorylation-induced conformational changes in FixJN illustrates the role of conserved residues in stabilizing the phosphoryl group in the active site, triggering the structural transition and achieving the post-phosphorylation signaling events. These phosphorylation-induced conformational changes are proposed to underly the activation of response regulators in general.
26 November 1999, Research Paper, *Structure*.

☐ **The crystal structure of coxsackievirus A9: new insights into the uncoating mechanisms of enteroviruses.**
Elaine Hendry, Hideki Hatanaka, Elizabeth Fry, Michael Smyth, John Tate, Glyn Stanway, Juhana Santti, Marita Maaronen, Timo Hyypiä, David Stuart (1999). *Structure* **7**, 1527–1538.

Coxsackievirus A9 (CAV9), a human pathogen causing symptoms ranging from common colds to fatal infections of the central nervous system, is an icosahedral single-stranded RNA virus that belongs to the genus *Enterovirus* of the family *Picornaviridae*. One of the

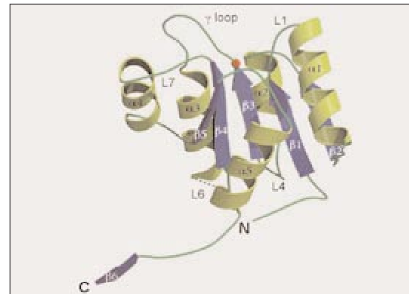
four capsid proteins, VP1, includes the Arg–Gly–Asp (RGD) motif within its carboxy-terminal extension. This region binds to integrin $\alpha_v\beta_3$, the only receptor for CAV9 to be conclusively identified to date. The crystal structure of CAV9 in complex with the antiviral compound WIN 51711 has been solved. The structures of the four capsid proteins, VP1 to VP4, resemble those of other picornaviruses. Although CAV9 resembles coxsackie B viruses (CBVs), several substitutions in the areas implicated in CBV receptor attachment suggest it may recognise a different receptor. The structure provides new



information on the uncoating mechanism of enteroviruses. CAV9 might bind a larger natural pocket factor than other picornaviruses, an observation of particular relevance to the design of new antiviral compounds.
30 November 1999, Research Paper, *Structure*.

- **The structure of the signal receiver domain of the *Arabidopsis thaliana* ethylene receptor ETR1.**
  Hans-Joachim Müller-Dieckmann, Alexander A Grantz, Sung-Hou Kim (1999). *Structure* **7**, 1547–1556.

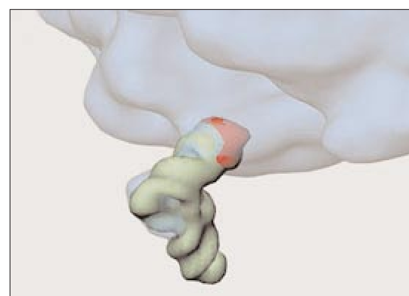
In *Arabidopsis thaliana*, ethylene perception and signal transduction into the cell are carried out by a family of membrane-bound receptors, one of which is ethylene resistant 1 (ETR1). The large cytoplasmic domain of the receptor showed significant sequence homology to the proteins of a common bacterial regulatory pathway: the two-component system. This system consists of a transmitter histidine kinase and a response regulator (or signal receiver). The crystal structures of the first plant receiver domain ETR_{RD} (residues 604–738) of ETR1 in two conformations is presented. The three-dimensional structure of ETR_{RD} shows the expected conformational conservation to prokaryotic receiver proteins, such as CheY and CheB, both of which are part of the chemotaxis



signaling pathway. Given that the dimer interface of ETR_{RD} coincides with the phosphorylation-dependent interfaces of CheY and CheB, the authors suggest that the monomerization of ETR_{RD} is phosphorylation-dependent too.
30 November 1999, Research Paper, *Structure*.

- **Direct three-dimensional localization and positive identification of RNA helices within the ribosome by means of genetic tagging and cyro-electron microscopy.**
  Christian MT Spahn, Robert A Grassucci, Pawel Penczek, Joachim Frank (1999). *Structure* **7**, 1567–1573.

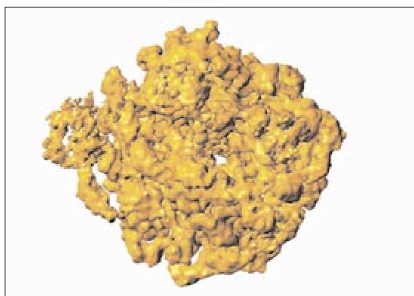
Ribosomes are complex macromolecular machines that perform the translation of the genetic message. Cryo-electron microscopic (cryo-EM) maps of the *Escherichia coli* 70S ribosome and X-ray



maps of the 30S and 50S subunits show the inner architecture of the ribosome in detail and ribosomal RNA helices are clearly visible. In the absence of further biological information, even at the higher resolution of the X-ray maps many rRNA helices can be placed only tentatively. The authors show that genetic tagging in combination with cryo-EM can place and orient double-stranded RNA helices with high accuracy. Features of a three-dimensional cryo-EM map of an asymmetric macromolecular complex can be interpreted in terms of secondary and primary structure. It is possible to model and interpret, in molecular terms, a larger portion of the ribosome. The results might be also useful in interpreting and refining the current X-ray maps.
1 December 1999, Research Paper, *Structure*.

- **The *Escherichia coli* large ribosomal subunit at 7.5 Å resolution.**
  Rishi Matadeen, Ardan Patwardhan, Brent Gowen, Elena V Orlova, Tillmann Pape, Marianne Cuff, Florian Mueller, Richard Brimacombe, Marin van Heel (1999). *Structure* **7**, 1575–1583.

The authors present the 7.5 Å solution structure of the 50S large subunit of the *Escherichia coli* ribosome, as determined using cryo-EM and angular reconstitution. The reconstruction reveals many new details, including the long α helix connecting the amino- and carboxy-terminal domains of the L9 protein, which is found wrapped like a collar around the base of the L1 stalk. A second L7/L12 dimer is now visible below the classical L7/L12 ‘stalk’, thus revealing the position of the entire L8 complex. Extensive conformational changes occur in the 50S subunit upon 30S binding; for example, the L9 protein moves by some 50 Å. Various rRNA stem-loops are found to be involved in subunit binding: helix h38, located in the A-site finger; h69, on the rim of the peptidyl transferase centre cleft; and h34, in the principal interface protrusion. Single-particle cryo-EM is



rapidly evolving towards the resolution levels required for the direct atomic interpretation of the structure of the ribosome. Structural details such as the minor and major grooves in rRNA double helices and α helices of the ribosomal proteins can already be visualised directly in cryo-EM reconstructions of ribosomes frozen in different functional states.
2 December 1999, Research Paper, *Structure*.