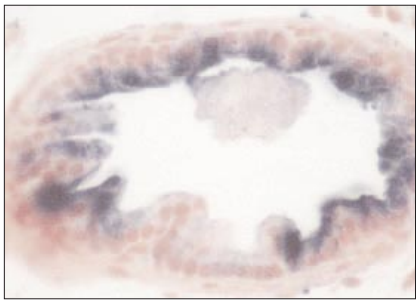
Elsewhere in biology

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**:R53–R55

☐ **The metalloproteinase matrilysin proteolytically generates active soluble Fas ligand and potentiates epithelial cell apoptosis.**
WC Powell, B Fingleton, CL Wilson, M Boothby and LM Matrisian (1999). *Curr. Biol.* **9**, 1441–1447.

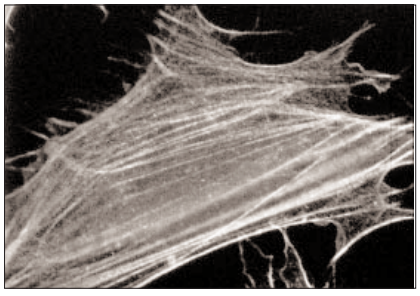
The Fas ligand/Fas receptor (FasL/Fas) system is an important mediator of apoptosis in the immune system, in which interaction with cells expressing cell-surface FasL induces the apoptotic pathway in Fas-expressing lymphocytes. The FasL/Fas system has



also been shown to be involved in apoptosis in epithelial tissues, including the involuting rodent prostate. FasL can be shed through the action of a hitherto unidentified metalloproteinase to yield soluble FasL (sFasL), although the biological activity of sFasL has been disputed. In this study, the authors report that a functional form of sFasL is generated by the action of the metalloproteinase matrilysin. The results suggest that matrilysin cleavage of FasL is an important mediator of epithelial cell apoptosis.
16 December 1999, Research Paper, *Current Biology*

☐ **Phosphatidylinositol polyphosphate binding to the mammalian septin H5 is modulated by GTP.**
J Zhang, C Kong, H Xie, PS McPherson, S Grinstein and WS Trimble (1999). *Curr. Biol.* **9**, 1458–1467.

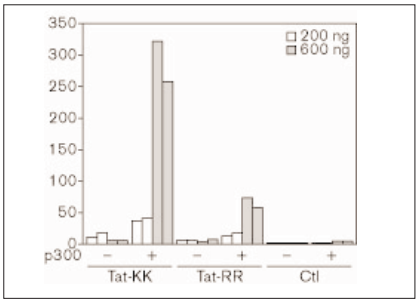
Septins are members of a conserved family of GTPases found in organisms as diverse as budding yeast and mammals. In budding yeast, septins form hetero-oligomeric filaments that lie adjacent to the membrane at the mother-bud neck. In mammals, they concentrate at the



cleavage furrow of mitotic cells. In both cases, septins provide a required function for cytokinesis. The authors show that the mammalian septin H5 is associated with the plasma membrane and specifically binds the phospholipids phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P_2) and phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P_3). This binding occurs at a site rich in basic residues that is conserved in most septins and is located adjacent to the GTP-binding motif. The results indicate that the interaction of septins with PtdInsP_2 might be an important cellular mechanism for the spatial and temporal control of septin accumulation.
16 December 1999, Research Paper, *Current Biology*

☐ **Acetylation of the HIV-1 Tat protein by p300 is important for its transcriptional activity.**
Melanie Ott, Martina Schnölzer, Jerry Garnica, Wolfgang Fischle, Stephane Emiliani, Hans-Richard Rackwitz and Eric Verdin (1999). *Curr. Biol.* **9**, 1489–1492

The human immunodeficiency virus 1 (HIV-1) Tat protein activates

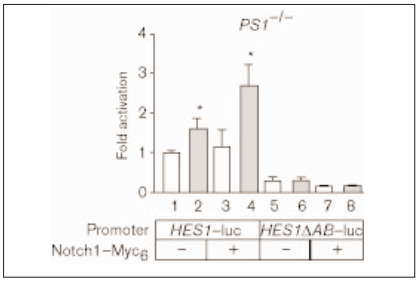


transcriptional elongation by recruiting the positive transcription elongation factor (pTEFb) complex to the TAR RNA element, which is located at the 5′ end of all viral transcripts. Tat also associates *in vitro* and *in vivo* with the transcriptional coactivator p300/CBP, an association proposed to recruit the histone acetyltransferase (HAT) activity of p300 to the integrated HIV-1 promoter. The authors have observed that the purified p300 HAT domain acetylates recombinant Tat proteins *in vitro* and that Tat is acetylated *in vivo*. The major targets of acetylation by p300 are lysine residues in the arginine-rich motif used by Tat to bind RNA and for nuclear import. Mutation of these residues in full-length recombinant Tat blocked its acetylation *in vitro*. Mutation of the lysine residues to arginine markedly decreased the synergistic activation of the HIV promoter by Tat and p300 or by Tat and cyclin T1. The results demonstrate that acetylation of Tat by p300/CBP is important for its transcriptional activation of the HIV promoter.
16 December 1999, Brief Communication, *Current Biology*

☐ **Lack of requirement for Presenilin1 in Notch1 signaling.**
BE Berechid, G Thinakaran, PC Wong, SS Sisodia and JS Nye (1999). *Curr. Biol.* **9**, 1493–1496.

Studies in invertebrates have indicated a functional requirement for presenilin (PS) genes in the Notch pathway. One model of Notch signal transduction suggests that proteolysis releases an activated Notch fragment that migrates to the nucleus and regulates gene transcription in concert with CBF1/Su(H)/lag1 (CSL) proteins.

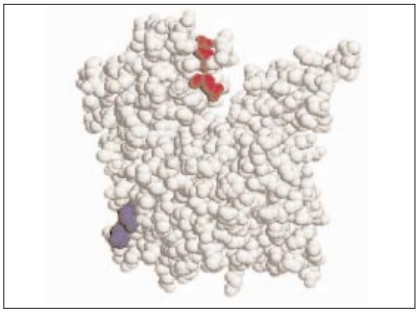
Recent studies suggest that PS genes control the proteolysis and nuclear access of the Notch intracellular



domain, offering a basis for the functional interaction of PS and Notch genes. The authors report that Notch1 signaling elicited by the ligand Delta1 was quantitatively unchanged in PS1-deficient primary embryonic fibroblasts. Although signaling through Notch1 persisted in PS1-deficient cells, there was a marked reduction in the appearance of a complex of a cleaved, intracellular Notch fragment (NICD) and a CSL protein, as previously reported. These studies reveal that PS1 is not required for ligand-dependent Notch signaling, and that PS1 and PS2 may be redundant. The data also suggest that the identified NICD fragment may not be necessary for Notch signal transduction.
16 December 1999, Brief Communication, *Current Biology*

☐ **Interaction of the p62 subunit of dynactin with Arp1 and the cortical actin cytoskeleton.**
Jorge A Garces, Imran B Clark, David I Meyer and Richard B Vallee (1999). *Curr. Biol.* **9**, 1497–1500.

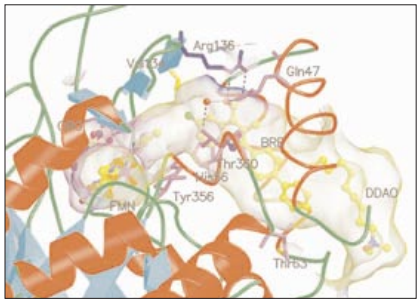
Targeting of the minus-end directed microtubule motor cytoplasmic dynein to a wide array of intracellular substrates appears to be mediated by an accessory factor known as dynactin. Dynactin is a multi-subunit complex that contains a short actin-related protein 1 (Arp 1) filament with capZ at the barbed end and p62 at the pointed end. The location of the p62 subunit and the proposed role for dynactin as a multifunctional targeting complex raise the possibility of a dual role for p62 in dynein targeting and in Arp1 pointed-end capping. To gain further insight into the role of p62 in dynactin function, the authors cloned cDNAs that encode two full-length isoforms of the protein from rat brain. They found that p62 is homologous to the nuclear migration protein Ropy-2 from *Neurospora*; both proteins contain a zinc-binding motif that resembles the LIM domain of several other cytoskeletal proteins. Overexpressing p62 in cultured mammalian cells revealed colocalization with cortical actin, stress fibers and focal adhesion sites, sites of potential interaction between microtubules and the cell cortex. The p62 protein also colocalized



with polymers of overexpressed wild-type or barbed-end-mutant Arp1, but not with a pointed-end mutant. Deletion of the LIM domain abolished targeting of p62 to focal-adhesion sites but did not interfere with binding of p62 to actin or Arp1. The data implicate p62 in Arp1 pointed-end binding and suggest additional roles in linking dynein and dynactin to the cortical cytoskeleton.
16 December 1999, Brief Communication, *Current Biology*

☐ **Structures of human dihydroorotate dehydrogenase in complex with antiproliferative agents.**
Shenping Liu, Edie A Neidhardt, Trudy H Grossman, Tim Ocain and Jon Clardy (2000). *Structure* **8**, 25–33.

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth committed step in the *de novo* biosynthesis of pyrimidines. As rapidly proliferating human T cells have an exceptional requirement for *de novo* pyrimidine biosynthesis, the use of

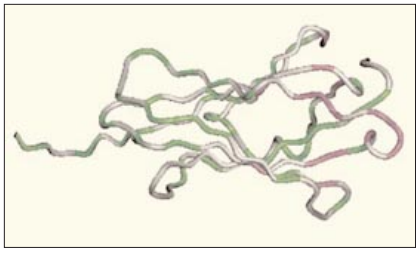


small-molecule DHODH inhibitors is an attractive therapeutic approach to autoimmune diseases, immunosuppression and cancer. The high-resolution crystal structures of human DHODH in complex with two different inhibitors (related to brequinar and leflunomide) have been solved. Human DHODH has two domains: an α/β-barrel domain containing the active site and an α-helical domain that forms the opening of a tunnel leading to the active site. Both inhibitors share a common binding site in this tunnel, and differences in the binding region govern drug sensitivity or resistance. Future therapeutic agents could be designed to explicitly exploit these differences.
20 December 1999, Research Paper, *Structure*

☐ **Mapping the binding site for the GTP-binding protein Rac-1 on its inhibitor RhoGDI-1.**
Lu-Yun Lian, Igor Barsukov, Alexander P Golovanov, Dawn I Hawkins, Ramin Badii, Kong-Hung Sze, Nicholas H Keep, Gary M Bokoch, Gordon CK Roberts (2000). *Structure* **8**, 47–56.

Members of the Rho family of small GTP-binding proteins, such as Rho, Rac and Cdc42, are involved in many cellular processes. They function as molecular switches through a conformational change between the GTP-bound (active) and GDP-bound (inactive) forms. Most members of the Rho and Rac subfamilies cycle between the cytosol and membrane. The cytosolic guanine nucleotide dissociation inhibitors, RhoGDIs, regulate both the GDP/GTP exchange cycle and the membrane association/dissociation cycle. In this paper, the regions of human

RhoGDI-1 involved in binding Rac-1 were indentified. Isoprenylated Rac-1 appears to interact with three distinct sites on RhoGDI. The isoprenyl group attached to the carboxyl terminus of Rac-1 binds in a pocket in the folded domain of RhoGDI. This is distinct

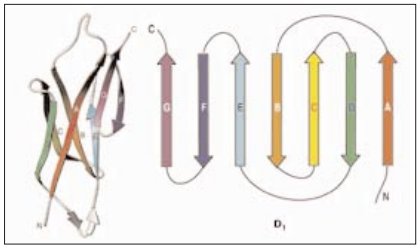


from the major site on this domain occupied by Rac-1 itself, which involves two loops at the opposite end to the isoprenyl-binding site. It is probable that the flexible carboxy-terminal region of Rac-1 extends from the site at which Rac-1 contacts the folded domain of RhoGDI to allow the isoprenyl group to bind in the pocket at the other end of the RhoGDI molecule. Finally, the flexible amino terminus of RhoGDI-1 makes a specific interaction with Rac-1 which contributes substantially to the binding affinity.

22 December 1999, Research Paper, *Structure*

☐ **Novel fold and assembly of the repetitive B region of the *Staphylococcus aureus* collagen-binding surface protein.**
Champion CS Deivanayagam, Rebecca L Rich, Mike Carson, Rick T Owens, Sita Danthuluri, Todd Bice, Magnus Höök, Sthanam VL Narayana (2000). *Structure* **8**, 67–78.

The *Staphylococcus aureus* collagen-binding protein Cna mediates bacterial adherence to collagen. The primary sequence of Cna has a nonrepetitive collagen-binding A region, followed by a repetitive B region. The B region has 1–4 23 kDa repeat units (B_1–B_4), depending on the strain of origin. The affinity of the A region for collagen is independent of the B region. The B repeat units have, however, been suggested to serve as a 'stalk' that projects the A region from the bacterial surface and therefore facilitate bacterial adherence to collagen. To understand the biological role of the B-region repeats the authors determined their three-dimensional structure. B_1 has two domains (D_1 and D_2), placed side-by-side, that have similar secondary structure and a unique fold that resembles, but is the inverse of, the immunoglobulin-like (IgG-like) domains. In the B_1B_2 crystal structure, an omission of a single glycine residue in the D_2–D_3 linker loop, compared with the D_1–D_2 and D_3–D_4 linker loops, resulted in projection of the D_3 and D_4 in a spatially new orientation. The authors also present a model for

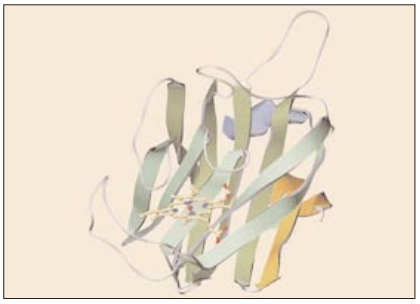


$B_1B_2B_3B_4$. The B region assembly could effectively provide the flexibility and stability required for presenting the ligand-binding A region away from the bacterial cell surface.

15 January 2000, Research Paper, *Structure*

☐ **A new scaffold for binding haem in the cytochrome domain of the extracellular flavocytochrome cellobiose dehydrogenase.**
B Martin Hallberg, Terese Bergfors, Kristina Bäckbro, Göran Pettersson, Gunnar Henriksson, Christina Divne (2000). *Structure* **8**, 79–88.

Natural recycling of lignocellulose is important for maintaining the global carbon cycle and is achieved by micro-organisms that secrete a variety of wood-degrading enzymes. Cellobiose dehydrogenase (CDH) is one of the enzymes secreted by the fungus *Phanerochaete chrysosporium* when cellulose is present as a carbon source. The enzyme is intriguing, mainly because it can degrade both cellulose and lignin and because it is the only known extracellular flavocytochrome.



This haemoflavoenzyme has a multidomain organisation with a *b*-type cytochrome domain linked to a large flavodehydrogenase domain. The two domains can be separated proteolytically to yield a functional cytochrome and a flavodehydrogenase. The authors report the crystal structure of the cytochrome domain of CDH. Three models of the cytochrome have been refined: the *in vitro* prepared cytochrome in its redox-inactive state and redox-active state, as well as the naturally occurring cytochrome fragment. The 190-residue long cytochrome domain of CDH folds as a β sandwich. The haem iron is ligated by Met65 and His163, which confirms previous results from spectroscopic studies. This is only the second example of a *b*-type cytochrome with this ligation, the first being cytochrome b_{562}. The haem-propionate groups are surface exposed and, therefore, might play a role in the association between the cytochrome and flavoprotein domain, and in interdomain electron transfer. There are no large differences in overall structure of the cytochrome at redox-active pH as compared with the inactive form, which excludes the possibility that pH-dependent redox inactivation results from partial denaturation.

15 January 2000, Research Paper, *Structure*