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*, *Folding & Design* and *Structure*.

Chemistry & Biology October 1996, **3**:859–861

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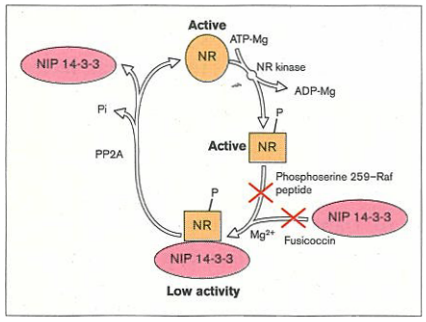
☐ **Phosphorylated nitrate reductase from spinach leaves is inhibited by 14-3-3 proteins and activated by fusicoccin.** Greg Moorhead, Pauline Douglas, Nick Morrice, Marie Scarabel, Alastair Aitken and Carol MacKintosh (1996). *Curr. Biol.* **6**, 1104–1113.

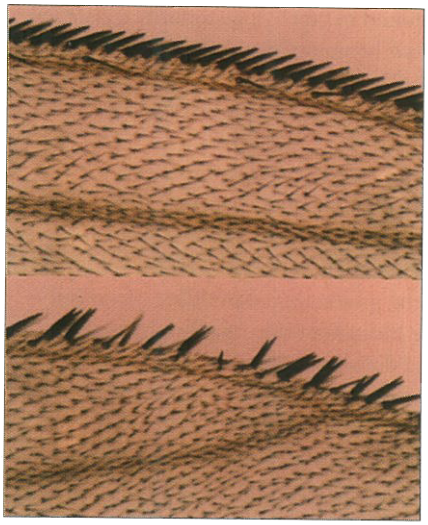
The eukaryotic 14-3-3 proteins bind to many mammalian signaling components and are implicated in many different cellular processes. Their dimeric, saddle-shaped structures support the proposal that 14-3-3 proteins are adaptors linking different signalling proteins. This study reports that the plant nitrate reductase inhibitor protein (NIP) is a mixture of 14-3-3 isoforms. When leaves are in the dark, nitrate reductase (NR) is inhibited by the two-step process of phosphorylation and binding of NIP. Mammalian and yeast 14-3-3 proteins can also inhibit phosphorylated NR, and NIP activity can be blocked by a synthetic phosphopeptide corresponding to the region of Raf that interacts with mammalian 14-3-3 proteins. These results support the idea of a common mechanism for binding of 14-3-3 to its targets in all eukaryotes, and suggest that in plants the 14-3-3 proteins provide a link between sensing the activity state of NR and signaling to other cellular processes.



1 September 1996, Research Paper, *Current Biology*

☐ **Mammalian NUMB is an evolutionarily conserved signaling adapter protein that specifies cell fate.** Joseph M. Verdi, Rosemarie Schmandt, Arash Bashirullah, Sara Jacob, Ralph Salvino, Constance G. Craig, Amgen EST Program, Howard D. Lipshitz and C. Jane McGlade (1996). *Curr. Biol.* **6**, 1134–1145.

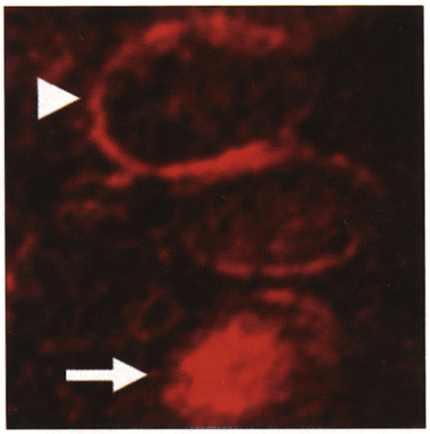
The *Drosophila numb* gene encodes an asymmetrically localized protein, dNUMB, which is required for binary cell-fate decisions during peripheral nervous system development. Part of dNUMB is homologous to phosphotyrosine-binding (PTB) domains, suggesting a potential link to tyrosine-kinase signal transduction. The cloning of the gene encoding the mammalian homologue, mNUMB, is reported here. mNUMB has a similar overall structure to dNUMB and 67 % sequence similarity. Misexpression of *mNumb* in *Drosophila* during division of sensory nervous system precursor cells causes identical cell fate transformations to those produced by ectopic *dNumb* expression. *In vitro*, the mNUMB PTB domain binds phosphotyrosine-containing proteins, and SH3 domains of SRC-family tyrosine kinases bind to mNUMB presumably through interactions with proline-rich regions in the carboxyl terminus. Overexpression of full-length mNUMB in the multipotential neural crest stem cell line MONC-1 dramatically biases its differentiation towards neurons, whereas overexpression of the mNUMB PTB domain biases differentiation away from neuronal fates. These results suggest that mNUMB and dNUMB are members of a family of signaling adapter molecules that mediate conserved cell-fate decisions during development.



1 September 1996, Research Paper, *Current Biology*

☐ **The *achaete–scute* complex proneural genes contribute to neural precursor specification in the *Drosophila* CNS.** James B. Skeath and Chris Q. Doe (1996). *Curr. Biol.* **6**, 1146–1152.

The *Drosophila* central nervous system (CNS) develops from a segmentally reiterated array of 30 neural precursors. Each precursor acquires a unique identity and goes through a stereotyped cell lineage to produce an invariant family of neurons and/or glia. The proneural genes *achaete*, *scute* and *lethal of scute* are required for neural precursor formation, but their role in specifying neural precursor identity had not been tested until now. In an *achaete–scute* double mutant, the formation of one precursor, MP2, is reduced to 11–14 %, as expected.



Suprisingly, the MP2 precursors were incorrectly specified and aquired traits of adjacent neural precursors. In rescue experiments, *achaete* or *scute*, but not *lethal of scute*, completely restored the normal MP2 identity. Given that other functions of these genes have been found to be phylogenetically conserved, it is likely that *achaete–scute* homologs may help specify neural precursor identity in other organisms.
1 September 1996, Research Paper, *Current Biology*

☐ **A role for leptin and its cognate receptor in hematopoiesis.** Brian D. Bennett, Gregg P. Solar, Jean Q. Yuan, Joanne Mathias, G. Roger Thomas and William Matthews (1996). *Curr. Biol.* **6**, 1170–1180.

Hematopoiesis entails the production of multiple blood cell lineages throughout the lifespan of the organism by the regulated expansion and differentiation of precursor cells. The cytokine family of growth factors has been implicated in this process, and, in this search for novel cytokines that influence the fate of hematopoietic stem cells, three splice variants of a novel cytokine receptor were cloned, one of which is identical to the leptin receptor. It is expressed in both human and murine hematopoietic stem cell populations, and provides a proliferative signal in multilineage hematopoietic progenitor cells. Analysis of *db/db* mice, in which the leptin receptor is trunctated, revealed that the steady-state levels of peripheral blood B cells and CD4-expressing T cells were dramatically reduced, and recovery following irradiation insult was impaired. Leptin and its receptor therefore constitute a novel hematopoietic signal acting at the level of the stem/progenitor cell that is required for normal lymphopoiesis and probably erythropoiesis. These findings offer a new perspective on the role of the fat cell in hematopoiesis.
1 September 1996, Research Paper, *Current Biology*

☐ **Design of proteins with selected thermal properties.** Michael P Morrissey and Eugene I Shakhnovich (1996). *Folding & Design* **1**, 391–405.

Methods of model protein design have until now been largely *ad hoc*, yielding sequences that are foldable only at some arbitrary simulation temperature. This works reports a method of rational sequence design that takes a target structure and generates a sequence that is predicted to be thermodynamically stable with respect to the target structure at the folding temperature. This 'cumulant design method' is based on a mean-field high temperature expansion of the molecular partition function. Folding simulations confirm the success of the approach. This method is highly successful in designing model proteins and provides some insight into the thermal properties of real proteins, illustrating how thermostable and psychrotropic (cold-loving) sequences differ from their mesophilic counterparts.
20 September 1996*, Research Paper, *Folding & Design*

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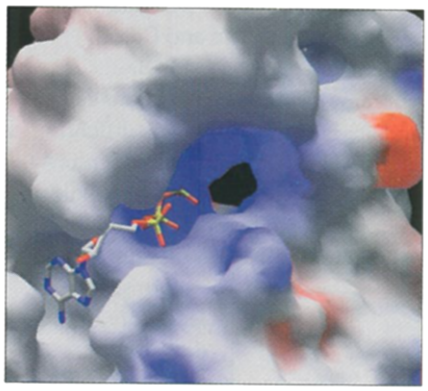
☐ **The crystal structure of the bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase reveals distinct domain homologies.** Charles A Hasemann, Eva S Istvan, Kosaku Uyeda and Johann Deisenhofer (1996). *Structure* **4**, 1017–1029.

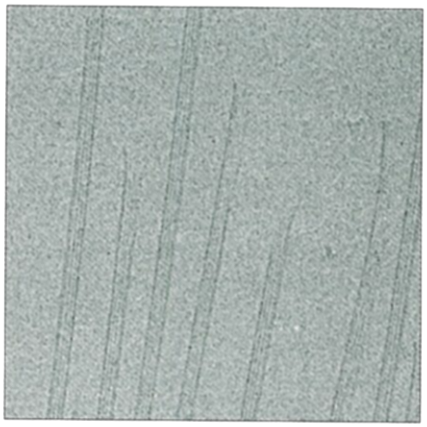
The bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase catalyzes both the synthesis and degradation of fructose-2,6-bisphosphate, a potent regulator of glycolysis. The crystal structure shows that the enzyme is a homodimer of 55-kDa subunits arranged in a head-to-head fashion, with each monomer consisting of independent kinase and phosphatase domains. The locations of ATPγS and inorganic phosphate in the kinase and phosphatase domains, respectively, allow the active sites of both domains to be defined. The kinase domain is clearly related to the superfamily of mononucleotide binding proteins, with a particularly close relationship to the adenylate kinases and the nucleotide-binding portion of G proteins. This is in disagreement with the broad speculation that this domain would resemble phosphofructokinase (PFK), and suggests that the kinase operates by transition-state stablization rather than the nucleophilic activation of the fructose-6-phosphate hydroxyl group, which characterizes the PFK mechanism. The phosphatase domain is structurally related to a family of proteins that includes the cofactor-independent phosphoglycerate mutases and acid phosphatases.



15 September 1996, Research Paper, *Structure*

☐ **Determination of microtubule polarity by cryo-electron microscopy.** Denis Chrétien, John M Kenney, Stephen D Fuller and Richard H Wade (1996). *Structure* **4**, 1031–1040.

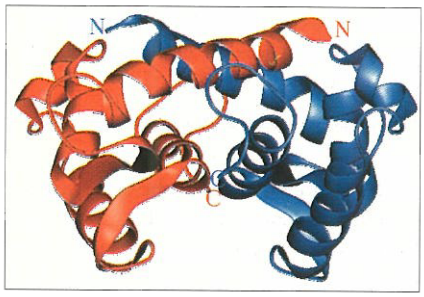
Microtubules are tubular polymers of tubulin dimers, which are arranged head-to-tail in protofilaments that run along the microtubules, giving them an overall structural polarity. Many of the processes that use microtubules, such as directed intracellular transport and chromosome



segregation, depend on this polarity. The determination of microtubule polarity by electron microscopy has not previously been possible. This work shows that, when observed in vitreous ice by cryo-electron microscopy, microtubules with skewed protofilaments show arrowhead moiré patterns. Using centrosome-nucleated microtubules, these moiré patterns can be related to microtubule polarity. The method requires knowledge of the handedness of the protofilament skew, which can be determined using two or more tilted views, or by analysis of diffraction patterns of the microtubule images. The ability to determine microtubule polarity will eliminate this ambiguity in structural studies of microtubule motors, possibly allowing the details of how different motors move in opposite directions to be determined.
15 September 1996, Research Paper, *Structure*

☐ **The solution structure of the bovine S100B protein dimer in the calcium-free state.** Peter M Kilby, Linda J Van Eldik and Gordon CK Roberts (1996). *Structure* **4**, 1041–1052.

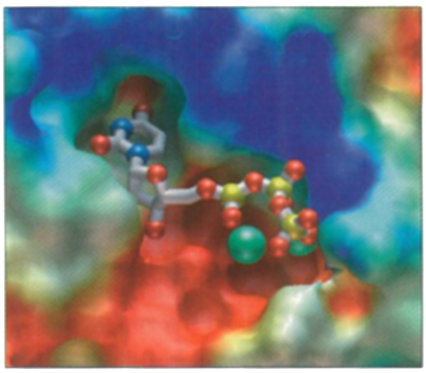
S100B is a neurite extension factor, and levels of S100B are elevated in the brains of patients with Alzheimer's disease or Down's syndrome. The pattern of S100B overexpression in Alzheimer's disease correlates with the pattern of neuritic plaque formation. S100B is a member of the S100 family of small calcium-binding proteins. Members of this family contain two helix-loop-helix calcium-binding motifs and interact with a wide range of proteins involved mainly in the cytoskeleton and cell proliferation. The NMR structure of the reduced S100B homodimer in the absence of calcium shows that each monomer is a four-helix bundle, arranged in the dimer in an antiparallel fashion. The fourth helix of each monomer runs close to the equivalent helix of the other monomer for almost its full length, extending the hydrophobic core through the interface. Calcium binding to the carboxy-terminal calcium-binding loop would be expected to require a conformational change, which might provide the signal for activation. The structure also suggests regions of the molecule that may be involved in interactions with effector molecules.



15 September 1996, Research Paper, *Structure*

☐ **Human dUTP pyrophosphatase: uracil recognition by a β hairpin and active sites formed by three separate subunits.** Clifford D Mol, Jonathan M Harris, Evan M McIntosh and John A Tainer (1996). *Structure* **4**, 1077–1092.

The essential enzyme dUTP pyrophosphatase (dUTPase) hydrolyzes dUTP to dUMP and pyrophosphate, simultaneously reducing dUMP levels to avoid uracil incorporation into DNA, and providing the dUMP for dTTP biosynthesis. The crystal structure reveals that each subunit of the trimer folds into an eight-stranded jelly-roll β barrel. Complexes with nucleotides reveal that uracil is inserted into a distorted antiparallel β hairpin, and hydrogen bonds entirely to main-chain atoms. This interaction mimics DNA base pairing, selecting uracil over cytosine and sterically precluding thymine and ribose binding. The substrate is totally enclosed, with all three subunits supplying residues that are critical to enzyme function and catalysis. As the structure is similar to that of the *Escherichia coli* enzyme, the nucleic acid base recognition motif may be ancient. The uracil–β hairpin interactions are an obvious way for peptides to become early coenzymes in an RNA world.



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