# 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*.**

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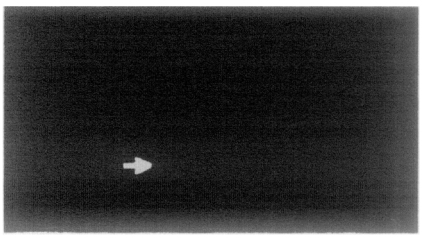
**Chemistry & Biology** February 1997, 4:159–163



☐ **Differential effect of components of the extracellular matrix on differentiation and apoptosis.** Dorit Aharoni, Iris Meiri, Ruth Atzmon, Israel Vlodavsky and Abraham Amsterdam (1996). *Curr. Biol.* **7**, 43–51.

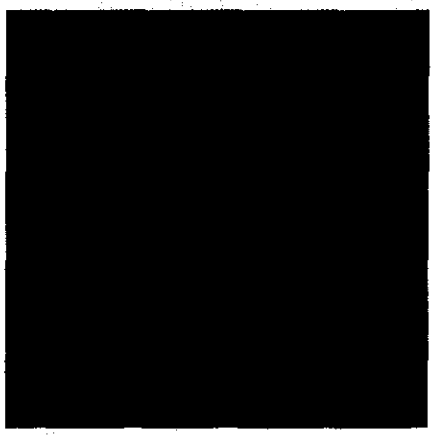
Basement membranes and extracellular matrices (ECMs) are the natural substances upon which cells migrate, proliferate and differentiate. Cellular responses to the ECM seem to be mediated by the combined action of basement membrane macromolecules, such as collagen IV, laminin, nidogen/entactin and heparan sulfate-containing proteoglycans, and regulatory molecules, such as growth factors and enzymes, that are immobilized and stored in the ECM by attachment to its macromolecular constituents, primarily to heparan sulfate proteoglycans (HSPG). To investigate the effect of the ECM on granulosa cell differentiation and death, primary granulosa cells were cultured on ECMs that lacked or contained bFGF (basic fibroblast growth factor). These otherwise identical ECMs were deposited by HR9 mouse endodermal cells, which do not synthesize bFGF, or by HR9 cells transfected with the bFGF gene. Both ECMs provided protection against apoptosis in serum-free medium, but only the bFGF-containing ECM maintained expression of the steroidogenic P450scc enzyme system and the production of progesterone. Laminin, but not fibronectin, was able to replace the ECM in protecting the cells from apoptosis; but not in maintaining steroidogenesis, whereas bFGF enhanced steroidogenesis but did not protect the cells against apoptosis. Cellular responses to ECM are therefore mediated by the combined action of macromolecular constituents and regulatory molecules, such as bFGF, that are sequestered and stored in the ECM.



18 December 1996*, Research Paper, Current Biology

☐ **Gravin, an autoantigen recognized by serum from myasthenia gravis patients, is a kinase scaffold protein.** J Brian Nauert, Theresa M Klauck, Lorene K Langeberg and John D Scott (1996). *Curr. Biol.* **7**, 52–62.

The subcellular targeting of protein kinases and phosphatases provides a mechanism for directing them to their preferred substrates. A recently identified mammalian scaffold protein, AKAP79, controls the location of two broad-specificity kinases and a phosphatase. The authors have identified and characterized another mammalian scaffold protein which coordinates the location of protein kinase A and protein kinase C. The protein turned out to be gravin, originally identified as a cytoplasmic antigen recognized by myasthenia gravis (a disease of neuromuscular transmission) sera. Residues 1526–1780 of gravin bind the regulatory subunit (RII) of protein kinase A with high affinity, and residues 265–556 bind protein kinase C. Gravin expression in human erythroleukemia cells can be induced with phorbol ester. Immunolocalization experiments show that gravin is concentrated at the cell periphery and is enriched in filopodia. These results indicate that gravin forms part of a signaling scaffold, and suggest that protein kinases A and C may participate in the coordination of signal transduction events in the filopodia of human erythroleukemia cells.



20 December 1996*, Research Paper, *Current Biology*

☐ **R-Ras can activate the phosphoinositide 3-kinase but not the MAP kinase arm of the Ras effector pathways.** Barbara M Marte, Pablo Rodriguez-Viciana, Stefan Wennström, Patricia H Warne and Julian Downward (1996). *Curr. Biol.* **7**, 63–70.

Although the small GTPase R-Ras has transforming activity, it is less potent than the closely related Ras oncogene products, and the pathways by which it exerts its effects on cellular proliferation have been unclear . The authors report that both Ras and R-Ras interact with phosphoinositide (PI) 3-kinase *in vitro*, and induce elevation of the levels of PI 3-kinase lipid products in intact cells. Unlike Ras, R-Ras does not activate Raf or mitogen-activated protein (MAP) kinase in cells. In co-transfection assays, the serine/threonine protein kinase PKB (or Akt) is effectively stimulated by R-Ras, Ras, mutants of Ras that activate PI 3-kinase but not other effectors, and activated forms

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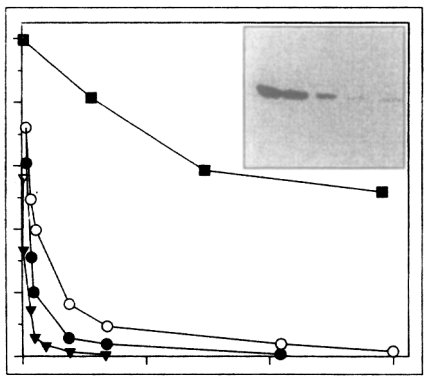
of PI 3-kinase. Ras and R-Ras thus stimulate PKB/Akt through a non-autocrine mechanism that involves PI 3-kinase. Transformation assays in fibroblasts suggest that PKB/Akt and Raf are part of distinct oncogenic signaling pathways. Both the Raf-MAP kinase and PI 3-kinase-PKB/Akt pathways are activated by Ras, but only the PI 3-kinase-PKB/Akt pathway is activated by R-Ras. PI 3-kinase, and downstream targets such as PKB/Akt, are likely to be essential mediators of transformation induced by R-Ras.
20 December 1996*, Research Paper, *Current Biology*

☐ **Cell-cycle arrest and inhibition of Cdk4 activity by small peptides based on the carboxy-terminal domain of p21$^{WAF1}$.** Kathryn L Ball, Sonia Lain, Robin Fåhraeus, Carl Smythe and David P Lane (1996). *Curr. Biol.* **7**, 71–80.

The damage-inducible cell-cycle checkpoint pathway regulated by p53 is commonly inactivated in human cancer. If the activity of key downstream effectors, such as the cyclin-dependent kinase (Cdk) inhibitor p21$^{WAF1}$, can be mimicked, it may be possible to restore growth suppression. The primary function of p21$^{WAF1}$ appears to be the inhibition of G1 cyclin–Cdk complexes. Identifying the region(s) of p21$^{WAF1}$ that contain its inhibitor activity may inform the development of novel anti-proliferative drugs for use in tumours with a defective p53 pathway. The authors report the discovery of small synthetic peptides based on the sequence of p21$^{WAF1}$ that bind to and inhibit cyclin D1–Cdk4. When introduced into cells, both a 20 amino acid and truncated 8 amino acid peptide blocked phosphorylation of the retinoblastoma protein (pRb) and induced a potent G1/S growth arrest. These data support the idea that the carboxyl terminus of p21$^{WAF1}$ is important in the inhibition of Cdk4 activity *in vivo*. The fact that a small peptide is sufficient to mimic p21$^{WAF1}$ function and produce a G1 cell-cycle arrest in tissue culture cell systems makes the cyclin D1–Cdk4 system a realistic and exciting target for the design of novel synthetic compounds that can act as anti-proliferative agents in human cells.



20 December 1996*, Research Paper, *Current Biology*

☐ **Detecting native-like properties in combinatorial libraries of *de novo* proteins.** Sushmita Roy, Kimberly J Helmer and Michael H Hecht (1996). *Folding & Design* **2**, 89–92.

Combinatorial methods based on binary patterning of polar and nonpolar residues have been used to generate large libraries of *de novo* α-helical proteins. Within such libraries, the ability to find structures that resemble natural proteins requires a rapid method to sort through large collections of proteins and detect those possessing 'native-like' features. This paper presents such a method and applies it to an initial collection of *de novo* proteins. The method identifies proteins with native-like properties from libraries of *de novo* sequences expressed *in vivo* and prepared using a novel 'rapid prep' freeze/thaw procedure; chromatographic purification was not required. The semi-crude samples were analyzed for native-like features by one-dimensional $^1$H NMR spectroscopy. The authors found native-like features for several proteins among a collection of sequences designed by binary patterning. Native-like properties can thus be detected using a method that requires neither isotopic enrichment nor chromatographic purification. The method can be used to screen for native-like properties among large collections of *de novo* sequences. The authors conclude that although the binary code strategy does not explicitly design tertiary packing, it can nonetheless generate proteins that possess native-like properties, and that the availability of a rapid assay for detecting native-like properties will facilitate the design and isolation of novel proteins with desirable properties.
29 January 1997*, Research Paper, *Folding & Design*

☐ **The molecular basis for allergen cross-reactivity: crystal structure and IgE-epitope mapping of birch pollen profilin.** Alexander A Fedorov, Tanja Ball, Nicole M Mahoney, Rudolf Valenta and Steven C Almo (1997). *Structure* **5**, 33–45.

The profilins are a group of ubiquitous actin monomer binding proteins that are responsible for regulating the normal distribution of filamentous actin networks in eukaryotic cells. Profilins can induce allergic responses in almost 20% of all pollen allergic patients. The paper describes the X-ray crystal structure of birch pollen profilin (BPP) at 2.4 Å resolution. The major IgE-reactive epitopes were mapped and found to cluster on the amino-terminal and carboxy-terminal α helices, and on a segment of the protein containing two strands of the β sheet. The prevalent epitopic areas are located in regions with conserved sequence and secondary structure and overlap the binding sites for natural profilin ligands, indicating that the native ligand-free profilin acts as the original cross-sensitizing agent. Structural homology indicates that the basic features of the G actin–profilin interaction are conserved in all eukaryotic organisms, but suggests that mechanistic differences in the binding of proline-rich ligands may