The latest in signal transduction, 1999

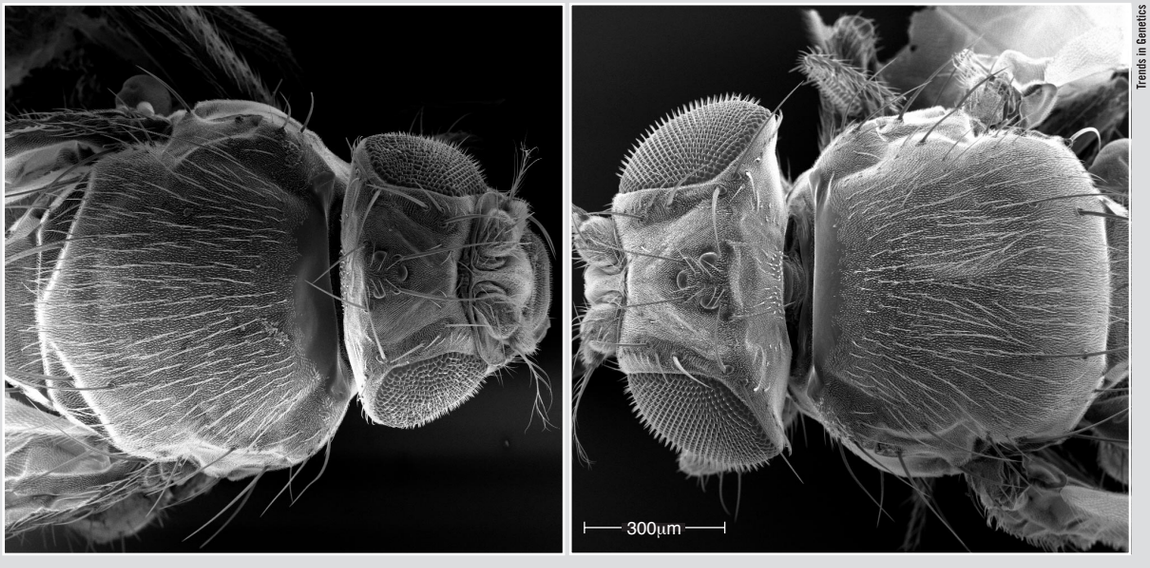
Specificity in Signal Transduction, Keystone, Colorado, USA, 9–14 April 1999

The sun smiled down on the Keystone Resort for the duration of this year's Keystone Symposia on 'Specificity in Signal Transduction', allowing the participants to enjoy the crisp mountain air outside as well as the stimulating discussion inside. The symposium, organized by Norbert Perrimon (Harvard Medical School, USA) and Tony Pawson (Mount Sinai Medical Center, USA) brought together a crowd of developmental biologists and biochemists who examine various signal-transduction pathways in different model systems. The multiple sessions were grouped by signaling pathways, such as Notch, Wnt and Hedgehog. This article examines some of the 'greatest hits' of the meeting.

In the Notch-signaling session, two presentations described the latest developments on the extracellular and intercellular transduction mechanism. Notch is a single-pass receptor that is required for cell-fate decisions; it is widely distributed throughout invertebrate and vertebrate development. Matthew Rand (Massachusetts General Hospital, USA) discussed data on the processing of the Notch ligand Delta by the metalloprotease Kuzbanian in *Drosophila*. Kuzbanian is responsible for the extracellular cleavage of Delta into a soluble extracellular, Notch-binding domain and a second fragment containing the transmembrane domain[1]. The role of Kuzbanian, previously proposed to be in the cleavage of the Notch receptor, is actually performed by the Furin protein in the trans-Golgi network. The two resulting Notch-cleavage products are then held together by a non-covalent metal-ion linkage. Following ligand binding, the Presenilin proteins, which have been implicated in the onset of Alzheimer disease, cleave Notch one more time to allow the nuclear translocation of the Notch cytoplasmic domain and its interaction with the Suppressor of Hairless DNA-binding protein. Although nuclear localization of the cytoplasmic domain of Notch has not been visualized *in vivo* under physiological conditions, Francois Schweisguth (Ecole Normale Superieure, France) described experiments that detected Notch activity in the nucleus. He achieved this by placing the yeast transcription factor GAL4 DNA-binding domain within the cytoplasmic domain of Notch. In this experiment, a UAS transgene will only be activated if the cytoplasmic domain of Notch is translocated into the nucleus. The UAS transgene was, indeed, activated in a ligand-dependent manner, demonstrating the translocation of the cytoplasmic domain of Notch into the nucleus[2].

A signal-transduction pathway that was discussed in many sessions and that appears to be extremely conserved across systems is the Insulin Receptor (IR) signaling pathway. At least three talks described work on the IR pathway, using three different model systems. The first talk, by Gary Ruvkun (Massachusetts General Hospital, USA)

FIGURE 1. *Chico* autonomously controls organ size



Eye-specific mitotic recombination of a null *P-element* insertion in the *chico* locus creates a fly with a miniscule head relative to its body (left). The small size of these 'pinheads' is the result of a reduction both in cell number and cell size. Figure provided by S. Oldham and E. Hafen.

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examined the role of IR signaling in the nematode *Caenorhabditis elegans*. Genetic analysis of dauer formation has led the Ruvkun laboratory to isolate the factors required for the transduction of a signal from the IR to the nucleus, although no ligand is known in *C. elegans* or *Drosophila* yet. The pathway signals from the IR to a protein called the Insulin Receptor Substrate (IRS). An examination of IRS function in *Drosophila* was discussed by Sean Oldham (University of Zurich, Switzerland), who reported that IR signaling in *Drosophila* controls cell size: *Drosophila* IRS mutants called Chico are about half the size of wild-type flies (Fig. 1). IRS activates the p110/p85 phosphoinositide 3 kinase (PI3K), which, in turn, activates the protein kinase AKT (also called protein kinase B, or PKB). Tony Hunter (Salk Institute, USA) discussed work on a vertebrate target of AKT called FKHR1. He found that, in serum-starved cells, AKT is found in the cytoplasm, but that upon PI3K activation, AKT translocates to the nucleus. Localization of FKHR1, a forkhead domain transcription factor, is regulated directly by AKT phosphorylation. Upon stimulation of starved cells, AKT is translocated to the nucleus, where it phosphorylates FKHR1. Phosphorylation of FKHR1 leads to its export into the cytoplasm, thereby abolishing its transcriptional-activation activity. FKHR1 is the vertebrate homolog of the nematode daf16, which was isolated in the Ruvkun laboratory screen for genes involved in dauer formation.

Two talks on specific functions of different MAP kinases were notable. Roger Davis (University of Massachusetts Medical School, USA) described the function of the Jun N-terminal kinase (JNK) in *Drosophila* and mouse. Previous work in *Drosophila* has identified a function for JNK in an embryonic developmental event called dorsal closure. Mutants lacking a functional JNK fail in this process, causing the embryos to have holes in the dorsal epidermis. The knockout phenotypes of three *Jnk* mouse genes was reported; disruption of any one of the *Jnk* genes allowed the mice to develop normally. However, the removal of *Jnk1* and *Jnk2* from the same animal causes embryonic lethality and results in defects in closure of the neural tube[3]. Stephane Noselli (Harvard Medical School, USA) has identified a function for the p38 MAP kinase in *Drosophila*, which he has called licorne. *Licorne* is required in the female germline for the correct patterning of the oocyte along the anterior–posterior and dorsal–ventral axes. This identifies a function for the third type of MAP kinase in *Drosophila*: the Erk type of MAP kinase functions downstream of Ras in receptor tyrosine-kinase signaling, the Jnk type of MAP kinase functions in dorsal closure, and the p38 type functions in the determination of oocyte polarity.

There were, of course, many excellent talks and poster presentations that we could have discussed, but we could only review a few because of space limitations. We look forward to seeing the progress in our knowledge of these signal-transduction mechanisms at next year's meeting.

Further reading

1 Qi, H. *et al.* (1999) Processing of the Notch ligand Delta by the metalloprotease Kuzbanian. *Science* 283, 91–94
2 Lecourtois, M. and Schweisguth, F. (1998) Indirect evidence for Delta-dependent intracellular processing of Notch in *Drosophila* embryos. *Curr. Biol.* 8, 771–774
3 Kuan, C-Y. *et al.* (1999) The Jnk1 and Jnk2 protein kinases are required for regional specific apoptosis during early brain development. *Neuron* 22, 667–676

The versatility of RNA structure and function

Jacques Monod Conference: New insights into the mechanism of mRNA translation: the significance of RNA structure, Aussois, France, 22–26 March 1999

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RNA is an extremely versatile and flexible molecule and not simply a long, unfolded string of ribonucleotides[1]. It has long been known that RNAs can form complex secondary and tertiary structures, but it is only relatively recently that the functional importance of RNA structure has become fully appreciated, particularly in the translational process and its control. As discussed by many of the 94 delegates at the recent CNRS-sponsored Jacques Monod meeting, held in Aussois (France), RNA structures can have positive and negative regulatory roles in post-transcriptional events. The organizers of the conference, Richard Jackson (Dept of Biochemistry, University of Cambridge, UK) and Marc Dreyfus (Ecole Normale Supérieure, Paris, France), assembled speakers who illustrated the importance of RNA structure in different biological systems, from bacteriophages to mammals.

From the beginning the focus of the meeting was established by an overview by E. Westhof (Institute de Biologie Moléculaire et Cellulaire, Strasbourg, France) of the current status of our understanding of short-range and long-range RNA interactions and the underpinning stereochemistry. Remarkably, RNA structure is not just a consequence of standard A:U and C:G Watson–Crick base pair interactions; there are now numerous examples of functionally important non-Watson–Crick base-paired structures in RNA (Ref. 2). The specificity of such base-pair interactions can be influenced by many factors, including the structure of the nucleotide and the influence of water molecules. For example, a G:U pair is not equivalent in structural terms to a U:G pair. Moreover, bifurcated interactions, ribose-backbone–base interaction and protonation of some atoms can lead to a multitude of

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