the capabilities of space missions[9]. The propellants and life-support materials made in such a programme are used in space, not returned to Earth. Thus the most avidly desired products have been low-tech materials with high demand in space; the cost savings, of course, result from dramatic decreases in the mass that must be lifted (at a cost of about $20,000 per kilogram) out of the Earth's gravity well. An excellent example of this approach is the synthesis of liquid oxygen and liquid carbon monoxide out of martian atmospheric carbon dioxide to serve as the propellant for an unmanned sample return mission (or, for that matter, a manned expedition)[10].

But Kargel also turns this approach on its head: he proposes seeking a product with so high a value per kilogram that it would be profitable to return it to Earth. The NEAs are ideal targets for such exploitation, as they have both very high concentrations of valuable materials and very low energy requirements for return to Earth, much lower than for return from the Moon. Thus the 'stick' that threatens Earth is also a 'carrot' of monumental proportions. As so often happens, the line between a disaster and an opportunity is a fine one indeed. □

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SIGNAL TRANSDUCTION

Dorsal developments

Philip Ingham

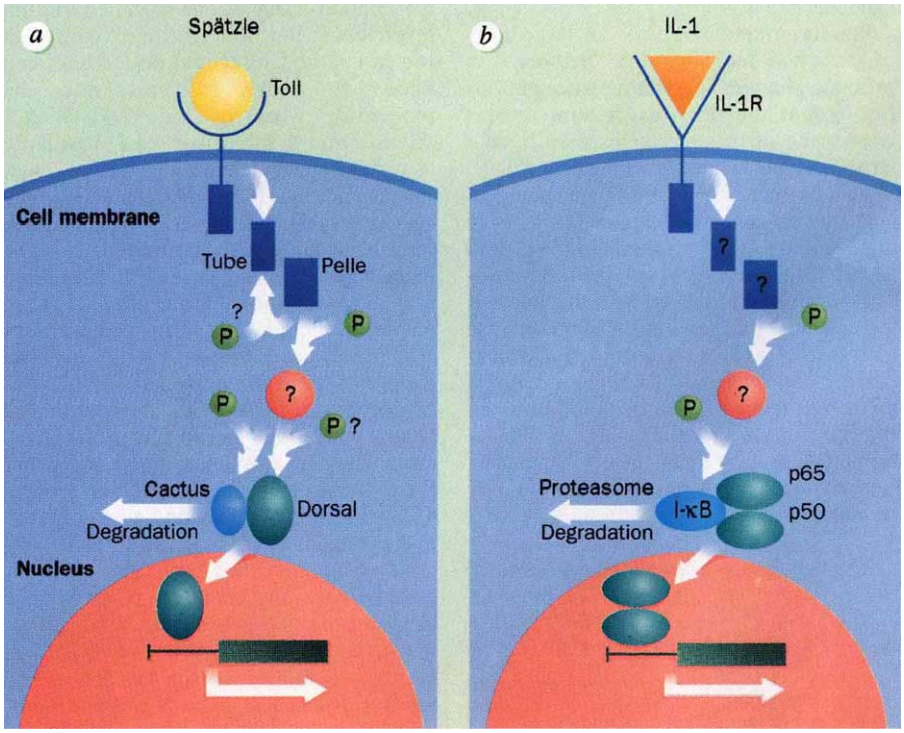
OF the many similarities and parallels between vertebrates and *Drosophila* revealed in recent years, the relationship between T-cell activation and dorsoventral patterning of the fly embryo must count as one of the more curious examples. Establishment of dorsoventral polarity is a highly complex process, beginning long before fertilization and culminating in the generation of a graded distribution of Spätzle activity, a signalling molecule found in the perivitelline fluid that surrounds the developing embryo[1,2]. The Spätzle signal is then transduced across the egg cell membrane, creating a gradient of activity of the transcription factor, Dorsal, different levels of which activate or repress various patterning genes along the dorsoventral axis[3].

Although the proteolytic cascade responsible for generating the Spätzle gradient is itself a fascinating process, it is the transduction of the Spätzle signal that has excited most interest outside the *Drosophila* community. The reason is that Toll, the putative Spätzle receptor, has significant sequence similarity in its intracellular domain to the vertebrate interleukin-1 receptor[4]; and Dorsal is a homologue of the vertebrate transcription factor NF-κB[5], activity of which is regulated by, among others, interleukin-1. Of particular interest are the downstream components of the Toll signalling pathway — for it is hoped that analysis of these components will help unravel some of the mysteries surrounding cytokine signalling and NF-κB regulation. Two such components are the products of the *pelle* and *tube* genes, and on page 563 of this issue[6] Großhans *et al.* describe a series of experiments that tell us something of how they regulate Dorsal.

In vertebrates, a major control point for NF-κB activity is its association with the protein I-κB, which acts to mask the nuclear localization signals in the NF-κB protein, inhibiting its entry into the nucleus[7]. Numerous protein kinases have been implicated in the activation of NF-κB *in vitro*, phosphorylation of I-κB leading to dissociation of the NF-κB–I-κB complex and suggesting a mechanism by which NF-κB could be released for nuclear uptake in intact cells[7].

Studies *in vivo*[8,9] have however cast doubt on the significance of this mechanism; when cells are treated with specific proteasome inhibitors, NF-κB is not activated upon stimulation, but remains associated with I-κB which is nevertheless phosphorylated. These findings suggest that phosphorylation results not in the dissociation of the inactive NF-κB–I-κB complex, but rather in the targeting of I-κB for degradation; it is the degradation of I-κB which releases NF-κB, leaving it free to enter the nucleus and activate transcription. This mechanism clearly differs from that by which various other kinases activate NF-κB *in vitro*, so the identity of the kinases that act *in vivo* remains an open question.

In *Drosophila*, the homologue of the I-κB protein is encoded by *cactus*[10,11], a genetically identified antagonist of Dorsal activity. Double-mutant analysis shows that mutations in the genes *pelle* and *tube* suppress the effects of an activated Toll receptor on Dorsal nuclear uptake; thus both genes seem to act downstream of *Toll* to regulate the Cactus–Dorsal interaction. Whereas the product of *tube* is a protein of unknown biochemical function[12], *pelle*



a, The Pelle serine/threonine kinase is activated by Spätzle activity, probably by direct interaction with the Tube protein which forms a link between Pelle and the activated Toll receptor protein. Activation of both Pelle and Tube may involve membrane association or dimerization (or both). Pelle then acts either directly, or through an intermediary, to promote the nuclear uptake of Dorsal via the phosphorylation of Dorsal and/or Cactus. *b*, An attractive hypothesis suggested by studies in mammalian systems is that phosphorylation of Cactus targets it for proteasome-dependent degradation. Degradation of the Cactus homologue I-κB has been shown to release NF-κB p65 and p50 for nuclear uptake. Whether homologues of Pelle and Tube are responsible for regulating this process in vertebrate cells remains to be seen.

encodes a serine/threonine kinase[13]; but although the implication is seductive, whether or not Pelle could act directly to phosphorylate Cactus protein has remained obscure because the sequence in which the two genes act has until now been unknown.

Großhans *et al.*[6] now describe how they have generated dominant activated forms of both proteins by fusing their coding regions with the extracellular and transmembrane regions of the Torso receptor kinase. As predicted, either of these activated forms is sufficient to activate Dorsal in the absence of activated Spätzle; but whereas Tube function depends upon Pelle activity, the reverse does not apply. This places Pelle downstream of Tube in the Toll–Dorsal pathway, the appropriate position if Pelle is the kinase responsible for phosphorylating Cactus.

Life and nature are seldom that simple, however, and *in vitro* assays show that Cactus is only feebly phosphorylated by Pelle. Dorsal protein is phosphorylated to a similar degree while — paradoxically — Tube proves to be a major substrate for Pelle activity: and, in line with this, direct association between the Pelle and Tube but not the Dorsal or Cactus proteins is demonstrated by the yeast two-hybrid assay, as well as by immunoprecipitation. The functional significance of this activity remains to be established *in vivo*, but one possibility suggested by the authors is a feedback step that regulates the signalling pathway.

These studies make a strong case that Tube acts as a direct regulator of Pelle. But, as the authors concede, the role of Pelle itself remains enigmatic — certainly, their data do not rule out the possibility that it phosphorylates Cactus — and its potential to phosphorylate Dorsal is consistent with the results of genetic analyses. Cloning the vertebrate homologues of the *tube* and *pelle* genes should help in understanding cytokine signalling pathways, but it seems certain that many other components remain to be discovered in both systems. □

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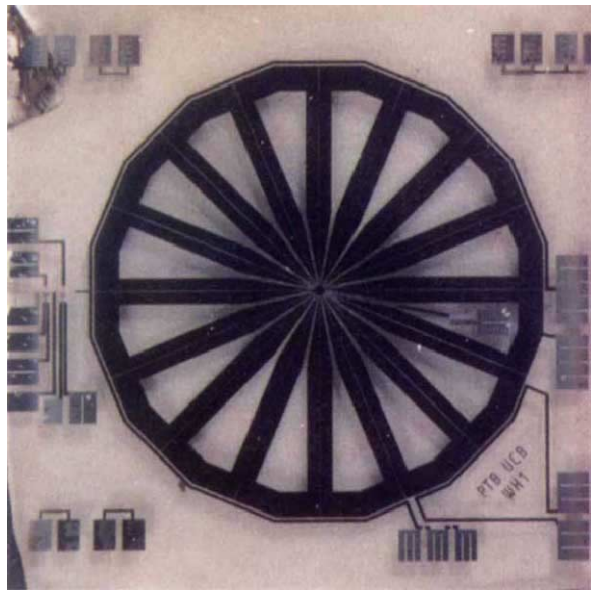
TECHNOLOGY

SQUIDs cross a watershed

John Clarke

GEOPHYSICS, magnetocardiology and magnetoencephalography — all demand sensitive measurements of magnetic field. Currently, the best bet is to use a low-transition-temperature (low-T_c) superconducting quantum interference device, or SQUID, operating in liquid helium. But such remarkable progress has been made in the technology for SQUIDs based on high-T_c superconductors that, somewhat to the amazement of those in the field, we now find ourselves with devices that are good enough for magnetocardiology and on the verge of what is needed for application to magnetoencephalography. The drive has been to produce ever quieter, more reliable SQUIDs that could be operated in liquid nitrogen; and at a meeting in Boston*, a surprisingly large number of participants reported such SQUID-based magnetometers with noise levels low enough to supplant their liquid-helium-cooled counterparts in many applications. High-T_c SQUIDs are, it seems, ready for the real world.



A 16-turn, multilayer magnetometer. Device is 7 mm across. (Berkeley, PTB Berlin, Univ. Birmingham.)

SQUIDs, which have been the most widely used low-T_c superconducting devices for almost 30 years, come in two varieties. The first and more common is the d.c. SQUID, which consists of two Josephson junctions connected in parallel on a superconducting loop and operates with a static bias current. When the magnetic flux threading the loop changes, the voltage across the device oscillates with a period of one flux quantum (Φ_0). Suitable electronics convert a small voltage change into a current which feeds back into a coil coupled to the SQUID to nullify the applied flux. In low-T_c devices, typical noise levels are $10^{-6}\Phi_0$ Hz$^{-1/2}$ ($10^{-6}\Phi_0$ in a 1-Hz bandwidth).

The second type, the radiofrequency SQUID, involves only one Josephson junction and operates with a flux bias ranging from 20 MHz to 10 GHz. Although SQUIDs are exquisitely sensitive to magnetic flux, their small area implies that they are not particularly sensitive to magnetic field (that is, flux per unit area). Generally, the effective area and hence the sensitivity are enhanced with a superconducting flux transformer, to achieve noise levels as low as a few femtotesla per square-root hertz.

To make high-T_c devices, films of the superconductor $YBa_2Cu_3O_{7-x}$ (YBCO) are grown in the presence of O_2 by an *in situ* process — usually excimer laser deposition or sputtering — so that the films grow stoichiometrically and epitaxially with their *c*-axis perpendicular to the substrate, which is heated to about 800 °C. In Boston, most authors described magnetometers with grain-boundary Josephson junctions, depositing the film across either the grain boundary of a $SrTiO_3$ bicrystal or a step edge that had been ion-milled on a single crystal of $SrTiO_3$, $LaAlO_3$, MgO or yttria-stabilized zirconia.

The magnetometers fall into two classes: those requiring a single layer of YBCO and those involving multilayers of YBCO and insulating films. Several groups reported 'directly coupled magnetometers' in which a YBCO film is patterned by photolithography to form a d.c. SQUID coupled to a large pickup loop. A magnetic field applied to the pickup loop induces a supercurrent which is directly injected into the SQUID. For instance, one such device on a 20 × 20 mm^2 bicrystal achieved 26 fT Hz$^{-1/2}$ at 1 Hz (R. Cantor, Conductus Inc., Sunnyvale). Taking a different tack, Y. Zhang (Forschungszentrum Jülich) described a radiofrequency SQUID with a large-area washer that is 'flipped' over onto a separate chip bearing a single-layer YBCO flux transformer, so that the two devices are inductively coupled. With a 40 × 40 mm^2 pickup loop, the noise of this 'flip-

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