these genes alters cell size in flies and, as with Dakt1, each of them can also affect organ size. Moreover, mutations in S6K, Chico and the insulin receptor can slow the growth and dramatically reduce the size of the entire animal.

Phenotypic similarities like these are often the first leads towards the delineation of signalling pathways in model genetic systems. But in this case, regulatory connections between many of these components had already been drawn from molecular studies of vertebrate cells and yeast^{9,10}, and the requirement of insulin-like growth factors for growth *in vivo* had already been established in mammals. In the current paradigm¹⁰, extracellular insulin-like molecules activate the insulin receptor, triggering a phosphorylation cascade that ultimately leads to phosphorylation of the ribosomal protein S6 (Fig. 1). This modification of S6 is believed to increase the ribosome's ability to translate messenger RNAs containing terminal oligopyrimidine tracts (5'-TOPs)⁹. As these 5'-TOPs are ubiquitous in mRNAs encoding ribosomal proteins but rare in other types of mRNA¹¹, the insulin receptor→S6K cascade could conceivably augment ribosome biogenesis and

thereby feed back to increase general protein synthesis and cell growth.

What do the *Drosophila* studies add to this model? Although they don't radically alter our perception of the core signalling mechanism, the wealth of mutants and complexity of phenotypes in *Drosophila* do provide clues as to how the insulin-receptor pathway interfaces with cell physiology *in vivo*. The effects on cell and organ size, for instance, represent new findings. Phenotypic differences produced by mutations in the various components of the insulin-receptor 'pathway' also indicate that it is actually a complex 'web' with multiple branches and outputs. For instance, the insulin receptor, PI(3)K and Dakt1 are encoded by essential genes, whereas complete knockouts of Chico and S6K give rise to small but viable flies. PI(3)K also appears to have much stronger effects on cell size than either Dakt1 or S6K, and is capable of promoting transition from the G1 to the S phase of the cell cycle, which its known effectors cannot do. Finally, the observation that mutations in ribosomal protein genes (so-called *Minute* mutations) do not generally reduce cell size¹³ indicates that mRNAs encoding ribosomal proteins might not be

the only critical targets of activated S6K. Thus the insulin receptor, PI(3)K and S6K probably still have some unknown targets.

One wonders what the normal function of insulin receptor→PI(3)K→S6K signalling might be in the fly. Could this really be the pathway that responds to patterning cues and shapes the animal by directing differential, allometric growth? Perhaps not. One distinguishing property of the genes of the insulin-receptor pathway is that they are completely neutral with respect to patterning, cell-fate specification or cell differentiation. Although experimental manipulations that activate or suppress insulin-receptor signalling in specific regions of the fly can have striking effects on allometry (body proportions)^{2,4,7}, there is little evidence so far for patterned regulation of insulin-receptor activity during normal development. The tiny *chico*, *insulin receptor* and *dS6K* mutant flies are in fact perfectly proportioned. Given that dachshunds and Great Danes are proportioned quite differently (as are different varieties of *Drosophila*), it seems that non-insulin-like signals are responsible for modulating spatial differentials in growth. In both insects and vertebrates the most likely suspects belong to the *Wnt*, *BMP* (encoding

Lipids: defining the shape of things to come

Membrane traffic is a dynamic process that occurs in all eukaryotic cells. Intracellular transport vesicles are the universal cargo carriers, budding and pinching off from donor membranes and fusing with acceptor membranes. The process of pinching off is commonly known as membrane fission, and it takes place in many different contexts. But how do vesicles pinch off from the donor membrane, and what regulates this process? We are now several steps closer to answering these questions and it is clear that the lipid environment plays a key part.

The fission of vesicles from the plasma membrane during clathrin-coated endocytosis has perhaps received the most attention. Earlier this year, it was shown that the GTPase dynamin, which was thought to mediate the fission process directly by acting as a 'pinchase', actually uses its GTPase activity to regulate downstream effectors (*Nature* **398**,

481–486; 1999). It is these downstream effectors that are thought to be directly involved in membrane fission. Then, Huttner, Söling and colleagues identified a likely effector, endophilin I (*Nature* **401**, 133–141; 1999). They showed that endophilin I catalyses a lipid-transfer reaction, converting the substrates lysophosphatidic acid (LPA) and arachidonoyl CoA into phosphatidic acid (PA), which was necessary for the *in vitro* formation of synaptic-like microvesicles. But how does the conversion of LPA into PA trigger fission? Membrane phospholipids have different shapes and sizes, and it turns out that LPA has an inverted-cone shape while PA is cone shaped. Inverted-cone-shaped and cone-shaped lipids induce positive and negative curvature of the membrane, respectively, and it may be this change in membrane curvature that drives fission.

It is now clear that LPA/PA conversion is important in another fission reaction. Luini, Corda and colleagues have used electron microscopy to observe the fission of vesicles from Golgi membranes (*Nature* **402**, 429–433; 1999). When they incubated Golgi membranes with cytosol enriched with CtBP/BARS (a protein involved in Golgi dynamics), constrictions began to appear along the length of the Golgi tubules, causing the Golgi membranes to look like a string of butcher's sausages (see left). They propose that these constriction sites represent fission intermediates, because at later times in the incubation they see rows of aligned vesicles, which have presumably 'pinched off' from the Golgi tubules. They go on to show that CtBP/BARS catalyses the conversion of LPA to PA, and that this activity is necessary for fission. The similarity between CtBP/BARS and endophilin is particularly striking because the experiments were carried out independently of the Huttner/Söling group and without knowledge of their results. Together, these two papers provide strong evidence that the conversion of LPA to PA and the subsequent change in membrane curvature are the driving force behind membrane fission.

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